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Guidelines & Protocols Advisory Committee

Diabetes Care

Effective Date: December 9, 2015

Scope

This guideline describes the care objectives for the prevention, diagnosis and management of diabetes mellitus in adults aged ≥ 19 years. It focuses on the approaches and systems that are ideally in place to improve care for the majority of patients the majority of the time. Diabetes in pregnancy (gestational diabetes) is outside the scope of this guideline.

Key Recommendations

- Diabetes care is centred around the person living with diabetes and should include an individualized management plan developed by the patient and their primary care provider(s). **[Level 3, amended 2015]**
- The 5 R's describe the key components to consider when organizing diabetes care in the office or clinic: recognize, register, resource, relay and recall. **[Level 5, new 2015]**
- Glycosylated hemoglobin (A1C; $12.69*) or glucose testing (e.g., fasting plasma glucose (FPG; $1.46) or 2-hour plasma glucose (2hPG; $12.94)) can be used for diagnosis and screening. Best choice of test will depend on clinical circumstances. **[Level 2, new 2015]**
- Individualized glycemic targets are based on patient's age, duration of diabetes, risk of hypoglycemia, cardiovascular disease presence, and life expectancy. **[Level 5, new 2015]**
- Measure A1C every 3 months to assess glycemic goals are met. Consider testing every 6 months if targets are consistently met and treatment and lifestyle are stable. **[Level 5, new 2015]**
- There are a number of new antihyperglycemic agents available for treatment of type 2 diabetes that can be considered as part of an individualized care plan. **[Level 3, new 2015]**
- A systematic approach to vascular protection is recommended, including lifestyle management, glycemic control, blood pressure control, and pharmacological interventions. **[Level 2, new 2015]**

Epidemiology

On average, over 29,000 people are diagnosed with diabetes every year in British Columbia. In 2012/2013, over 387,000 people have diabetes in the province.† Geographic variations exist in rates of diabetes and some regions have higher or lower rates of incidence and prevalence compared to the provincial totals. To find more data on diabetes in your local community, see the interactive BC Community Health Atlas or the BC Community Health Data, at website: www.phsa.ca.

Classification and Risk Factors

Diabetes mellitus (diabetes in this guideline) is a complex chronic disease characterized by hyperglycemia due to defective insulin secretion, defective insulin action or both.[1] Diabetes is classified into four categories: type 1, type 2, gestational, and other specific types due to other causes (e.g., MODY [maturity onset diabetes of the young] after genetic defects). See Table 1, or the Canadian Diabetes Association (CDA)'s Etiologic Classification of Diabetes Mellitus at website: guidelines.diabetes.ca, for more information.

* Prices as per the Schedule of Fees – Laboratory Services Payment Schedule as of October 1, 2015.
† BC Ministry of Health's Chronic Disease Information Registries, 2012/2013, Diabetes Summary Report, created November 2013. Note: incidence uses three year moving average of 2011/2012 and prevalence uses 2012/2013 fiscal year.

Table 1. Diabetes categories

Type 1	*Type 1 Diabetes* is primarily due to beta cell destruction, usually leading to total insulin deficiency and is susceptible to ketoacidosis.[1,2] Type 1 diabetes may be due to autoimmune processes or unknown etiology. The risk for developing type 1 diabetes is influenced by family history of type 1 diabetes and other autoimmune diseases. Type 1 diabetes includes Latent Autoimmune Diabetes in Adults (LADA) a slow, progressive form of autoimmune diabetes that shares clinical characteristics of type 2 diabetes.[1, 3-5]
Type 2	*Type 2 Diabetes* is due to a combination of insulin resistance and inadequate insulin secretory response. It may range from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance.[1,2] *Risk factors* include, but are not limited to: age > 40 years; first-degree relative with type 2 diabetes; member of a high risk population (e.g., Aboriginal, Hispanic, South Asian, Asian, or African descent); history of prediabetes (impaired glucose tolerance [IGT], impaired fasting glucose [IFG], or A1C 6.0 – 6.4%); history of gestational diabetes; history of delivery of macrosomic infant; presence of end organ damage associated with diabetes; presence of vascular risk factors (e.g., dyslipidemia, hypertension, overweight, abdominal obesity, vascular disease); presence of associated diseases (e.g., polycystic ovary syndrome, acanthosis nigricans, human immunodeficiency virus-1 [HIV], psychiatric disorders [e.g., bipolar disorder, depression, schizophrenia]); and use of medications associated with diabetes (e.g., atypical antipsychotics, highly active antiretroviral therapy, glucocorticoids).[6]
Gestational	*Gestational Diabetes* is defined as glucose intolerance with onset or first recognition during pregnancy, regardless of whether the condition persists after pregnancy. Gestational diabetes does not exclude the possibility of preexisting, undiagnosed diabetes or glucose intolerance. **Note: gestational diabetes is outside the scope of this guideline.**

Prevention

Type 1 Diabetes

Safe and effective therapies for the prevention of type 1 diabetes have not yet been identified.[7]

Type 2 Diabetes

The onset and course of type 2 diabetes can be ameliorated using lifestyle modification, including regular physical activity and/or pharmacologic intervention.[8] Pharmacologic therapy with metformin or acarbose can be considered for patients with IGT.[9, 10, 11]

Screening and Diagnosis

Screening

Note: general screening for type 1 diabetes is not recommended. Screening for type 2 diabetes should be performed every 3 years in individuals ≥ 40 years of age or those at high risk. Screen more frequently in people with additional risk factors for diabetes or at very high risk according to a validated risk assessment tool and test with either A1C ($12.69‡) and/or FPG ($1.46), or 2hPG ($12.94) in a 75g oral glucose tolerance test (OGTT). Best choice of test will depend on clinical circumstances.

- See *Appendix A: Screening Algorithm for Type 2 Diabetes in Adults*.
- Canadian Diabetes Risk Assessment Questionnaire (CANRISK) is a statistically valid risk tool appropriate for use in the Canadian population, at website: www.healthycanadians.gc.ca.
- The CDA offers an interactive screening tool, at website: guidelines.diabetes.ca/ScreeningAndDiagnosis/Screening

Diagnosis (type 1 & 2)

- Diabetes can be diagnosed using any of the following criteria:
  - A FPG§ of ≥ 7.0 mmol/L.
  - A1C¶ of ≥ 6.5%.[12] See notes for contraindications.
  - 2hPG of ≥ 11.1 mmol/L in a 75g OGTT.
  - In a patient with classic symptoms of hyperglycemia (e.g., polyuria, polydipsia, and unexplained weight loss), a random plasma glucose (PG) ≥ 11.1 mmol/L.**

‡ Prices as per the Schedule of Fees – Laboratory Services Payment Schedule as of October 1, 2015.
§ Fasting = no caloric intake for at least 8 hours. Note that fasting for lipids is no caloric intake for at least 10 hours, and if both tests are requested concurrently, the higher amount should be followed
¶ Standardized, validated assay required; may be used for adults in absence of factors that might impact accuracy of A1C. **Not used for diagnosis in suspected type 1 diabetes, pregnant women, children or adolescents**.
** Random = any time of day, regardless of the interval since the last meal.

- In the absence of symptomatic hyperglycemia, if a single lab test is in diabetes range, **a repeat confirmatory test (preferably the same test) must be done another day (in a timely fashion).**
- In case of symptomatic hyperglycemia, a repeat test is not required. Diagnosis is confirmed.
- In individuals who are suspected of type 1 diabetes, confirmatory testing should not delay treatment.
- If the results of two different tests are both above diagnostic cutpoints, the diagnosis is confirmed.

Management

1. Organization of Care

Diabetes care is centred around the person living with diabetes and it includes an individualized management plan developed by the patient, their family/caregivers and primary care provider(s). The 5 R's describe the key components to consider for organizing diabetes care in the office or clinic.

Table 2. The 5 R's of diabetes care

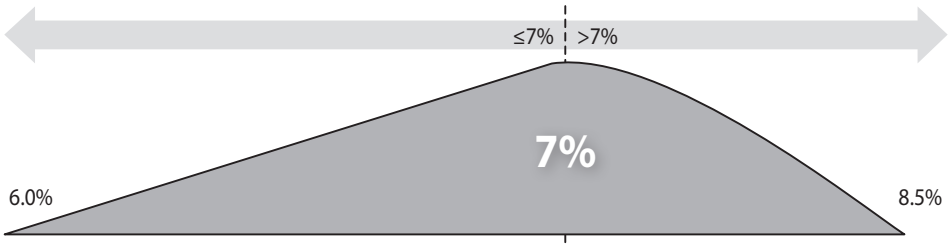
Recognize	Consider diabetes risk factors for all patients and screen appropriately. See above.
Register	Develop a list of patients with diabetes to facilitate recall and track changes in practice management. See guidelines.diabetes.ca/OrganizingCare/The5Rs/registry for more information.
Resource	Support self –management through the use of inter-professional teams, including a primary care provider, diabetes care educator, nurses, dietitian, pharmacist and specialist. Consider referral to a diabetes education clinic. A team specialized in diabetes is suggested for the following situations: • Patients with Type 1 diabetes at diagnosis and at least annually, • Women with diabetes who require pre-gestational assessment and counseling, • Women with diabetes in pregnancy (gestational/pre-gestational), • Individuals with complex type 2 diabetes or who are not reaching target. Self-management support consists of collaborative self-management education, incorporating problem solving and goal setting. Patients may require education in clinical management measurements such as blood glucose, A1C, blood pressure, and lipid profile. For further information on self-management, see *Associated Document: Patient Education and Resources* or CDA resources, at website: guidelines.diabetes.ca/SelfManagementEducation.
Relay	Facilitate information sharing between the patient with diabetes and the diabetes care team (e.g., telephone, electronic means, paper-based). See *Associated Document: Diabetes Patient Care Flow Sheet*.
Recall	Develop a system to remind patients of timely review and reassessment.

2. Individualized Targets

▶ Blood Glucose: Glycemic Targets

- The focus of glycemic goals is on achieving target A1C levels and on minimizing symptomatic hyper- and hypoglycemia. Glycemic targets are individualized based on the patient's age, duration of diabetes, risk of hypoglycemia, cardiovascular disease presence, and life expectancy. See Figure 1 for recommended targets, or to find a target for an individual patient, use the interactive CDA tool for A1C targets, at website: guidelines.diabetes.ca/BloodGlucoseLowering/A1Ctarget.

Figure 1. Recommendations for glycemic targets[††]



A target A1C ≤6.5% may be considered in some patients with type 2 diabetes to further lower risk of nephropathy and retinopathy. Must be balanced with risk of hypoglycemia

Most patients with type 1 and type 2 diabetes

Consider 7.1-8.5% A1C if:
- Limited life expectancy
- High functional dependency
- Extensive coronary artery disease at high risk of ischemic events
- Multiple co-morbidities
- History of recurrent severe hypoglycemia
- Hypoglycemia unawareness
- Longstanding diabetes for whom it is difficult to achieve A1C ≤ 7% despite effective doses of multiple antihyperglycemic agents (including insulin)

Blood Glucose: Hypoglycemia

- **Hypoglycemia can be a serious complication of therapy**. Use less stringent glycemic targets in patients at risk of hypoglycemia.
- *Risk factors for hypoglycemia:* Prior episode of severe hypoglycemia, long-term diabetes, current low A1C (< 6.0%), autonomic neuropathy, hypoglycemia unawareness, current treatment with insulin, and the elderly. Severe hypoglycemia is less common in persons with type 2 diabetes but the elderly and those on insulin, secretagogues are more vulnerable.
- *Harm reduction for patients at high risk of hypoglycemia:*
  - Educate patients and families about prevention, detection and treatment of hypoglycemia.
  - Revaluate glycemic control targets.
  - Consider education for patients and family/caregivers in glucagon administration.
  - In BC, a driver with a medical condition, like diabetes, that has the potential to affect their fitness to drive may be required to have a Driver's Medical Examination Report completed by their primary care provider.[13]
    - See the BC Driver Fitness Handbook for Medical Professionals for further information, at website: www.pssg.gov.bc.ca/osmv/medical-fitness/.
- *To reduce the risk of hypoglycemia:* increase the frequency of SMBG (including episodic assessment during sleeping hours), make glycemic targets less stringent, and consider multiple insulin injections.
- *Treatment:* See *Appendix B: Treatment of Hypoglycemia in Diabetes*.

Blood Glucose: Long-Term Control

- Studies suggest there is a long-term "legacy" benefit of glucose lowering early in the course of type 1 & 2 diabetes, in terms of reducing complications.[14,15]
- Measure A1C every 3 months to ensure that glycemic goals are being met or maintained.
- **Consider testing A1C every 6 months if treatment and lifestyle remains stable and if targets have been consistently met.**
- Focus on minimizing symptomatic hypo- and hyperglycemia, in addition to A1C levels.

[††] Reprinted from Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2013;37(Supp.1):S1-S212.

Blood Glucose: Self-Monitoring of Blood Glucose (SMBG)

- Offer to develop a SMBG schedule with the patient and review records as needed. Frequency and timing of SMGB is individualized, based on type of diabetes, treatments (e.g., use of insulin), need for information, and individual's capacity to use testing to modify behaviours or medications.
- SMBG is more important when using a drug that can cause hypoglycemia. People with low risk of hypoglycemia may need less frequent SMBG testing frequency and people at higher risk of hypoglycemia may need more frequent testing.
- For most adults with type 2 diabetes using oral antihyperglycemic agents (without insulin) or lifestyle management only to meet glycemic targets, the value of routine use of SMBG is limited.[16] In these situations, SMBG may only be needed 1 or 2 times per week.
- SMBG frequency guidance tool is available at: guidelines.diabetes.ca/bloodglucoselowering/smbgtool.
- Annual accuracy verification of glucose meter is recommended (simultaneous fasting glucose meter/lab comparison within 20%).
- Blood glucose test strips are a Pharmacare benefit for those holding a valid Certificate of Training in SMBG from a BC diabetes education centre. See *Appendix C: PharmaCare quantity limits for blood glucose test strips* for information on coverage.

3. Non-Pharmacological Management

Healthy Living and Lifestyle Management

- Patients with diabetes will benefit from health behaviour education and healthy living interventions, including regular physical activity (at least 150 minutes per week of aerobic exercise and two sessions per week of resistance training, if not contraindicated), nutrition therapy, healthy diet, maintenance of a healthy body weight, and smoking cessation.
- For more information, see BCGuidelines.ca – *Lifestyle & Self-Management Supplement*.

Bariatric Surgery

- Bariatric surgery is an emerging intervention for patients with diabetes type 2 in association with marked obesity (body mass index ≥ 35.0 kg/m^2).[17-19] Some procedures are covered by the Medical Services Plan.
- For more information on obesity management, see BCGuidelines.ca – *Overweight and Obese Adults: Diagnosis and Management*.

4. Individualized Pharmacologic Management

- Type 1 diabetes: Multiple (3 – 4) daily insulin injections or the use of Continuous Subcutaneous Insulin Infusion (insulin pump) should be considered as part of an intensive diabetes management program.
- Type 2 diabetes: please refer to *Appendix D: Management of Hyperglycemia in Type 2 Diabetes*, including details on when to initiate oral antihyperglycemic medications or insulin without a 2 – 3 month trial of lifestyle modifications alone.
- For more information, see:
  - *Appendix E: Antihyperglycemic Agents and Adjunctive Agents for Use in Type 2 Diabetes*.
  - *Appendix F: Insulin and Therapeutic Considerations*.
  - Canadian Agency for Drugs and Technologies in Health reviews of second and third-line pharmacotherapy, at website: www.cadth.ca.[20,21]

5. Preventing complications and comorbidities

Global Cardiovascular Management

- People with diabetes are at significantly increased risk of cardiovascular disease. The BCGuideline.ca – Cardiovascular Disease: Primary Prevention recommends using a risk assessment tool, medical history, physical examination, and full fasting lipid profile.[22]
  - See Controversies in Care (page 7) about use of risk calculators in the type 2 diabetes population.
  - A risk assessment calculator is not recommended for people with type 1 diabetes.
- The time interval (e.g., 1 – 5 years) for a reassessment for cardiovascular disease is based on the initial risk stratification, if the patient's risk factors change and clinical indication.
- A systematic approach to vascular protection is recommended, including lifestyle management, glycemic control, blood pressure control, and pharmacological interventions. 'Consider the **ABCDE**s' is a useful mnemonic device for vascular protection strategies and is described in table 3 below.

Table 3. Consider the ABCDEs

A – A1C and optimal glycemic control	**Glycemic control: while there is evidence to show the benefit of intensive glycemic control on microvascular complication of diabetes, the impact of hyperglycemia levels on cardiovascular disease is less clear. However, if achieved early in the disease, there might be a macrovascular benefit, particularly as part of multifactorial approach. See glycemic control section above for targets.**
B – Blood pressure	See Blood Pressure section below
C – Cholesterol	See Lipid Lowering Strategies section below
D – Drugs for vascular protection	Consider using angiotensin converting enzyme inhibitors (ACE-I) for any patient ≥ 55 years of age or with evidence of organ damage, even in absence of hypertension. In patients with diabetes and hypertension, consider an ACE-I or angiotensin receptor blockers (ARB).[1,23] Routine use of acetylsalicylic acid (ASA) in primary cardiovascular disease prevention is not recommended. ASA therapy has been recommended in the general population for primary prevention of serious vascular events, although recent studies have questioned it[24,25] and evidence for ASA therapy in persons with diabetes is even less apparent.[26-29] Risk of bleeding from ASA is higher in patients with diabetes. In patients with diabetes and established cardiovascular disease, low dose ASA (75 – 162 mg) may be considered. The decision to prescribe antiplatelet therapy for secondary prevention of cardiovascular disease events should be based on individual clinical judgement.[30]
E – Exercise/Eating	See Healthy Living and Lifestyle Management section above and BCGuidelines.ca – *Lifestyle & Self-Management Supplement*.
S – Smoking cessation	See BCGuidelines.ca – *Lifestyle & Self-Management Supplement* and www.quitnow.ca.

Blood Pressure

- Blood pressure control is a priority for patients with diabetes. Record at diagnosis and regularly thereafter.[31]
- The BCGuidelines.ca – *Hypertension: Diagnosis and Management* recommends a desirable blood pressure reading of ≤140/90 for patients with diabetes.[32] See controversies in care section below.
- If lifestyle modification is not sufficient, pharmacological treatment may be required:
  - Diabetes with moderately or severely increased albuminuria, chronic kidney disease, cardiovascular disease or cardiovascular disease risk factors:
    - First-line – ACE-I or ARB (if ACE-I intolerant).
    - Second-line – Dihydropyridine calcium channel blocker (DHP-CCB; e.g., amlodipine, felodipine, and nifedipine).
  - Diabetes (no chronic kidney disease or cardiovascular disease risk factors):
    - First-line – ACE-I or ARB or Thiazide/Thiazide-like diuretic or DHP-CCB.
    - Second-line – Combination of first line drugs (note: in combination with ACE-I, a DHP-CCB is preferable to a thiazide/thiazide-like diuretic.

Lipid Lowering Strategies

- Primary prevention: Lifestyle interventions are usual first-line strategies in vascular protection. Statin therapy is a second-line intervention, considered in an individualized discussion with the patient and after evaluation of risk and benefits.
- Recent meta-analyses and other guidelines have indicated that statin therapy in people with diabetes who are at moderate or high risk of cardiovascular disease events, may be considered.[1,2,33-38]
- The CDA recommends statin therapy to reduce cardiovascular disease risk in adults with type 1 or type 2 diabetes with any of the following features:
  - Clinical macrovascular disease;
  - Age ≥ 40 years;
  - Age < 40 years and 1 of the following: diabetes duration > 15 years and age > 30 years; microvascular complications; or other circumstances that warrant therapy based on particular risk factors according to 2012 Canadian Cardiovascular Society (CCS) guidelines.
- Treatment with a statin is expected to result in a significant reduction in elevated baseline lipids levels. Treating to a specific target is not recommended by the BCGuidelines.ca – *Cardiovascular Disease: Primary Prevention* guideline, although the CCS and CDA recommend treating high risk and intermediate risk patients to a specific low density lipoprotein cholesterol (LDL-C) target of ≤ 2.0 mmol/L.[1,22,30] The National Institute for Health and Clinical Excellence (NICE) and American College of Cardiology and American Heart Association (ACC/AHA) guidelines do not recommend target LDL-C levels, but they recommend specific target statin doses.[35,39]
- If statin therapy is decided upon, select statin based on tolerability, potential for drug interactions, and cost.[40] For information on dosages, see BCGuidelines.ca – *Cardiovascular Disease: Primary Prevention*.

Retinopathy

- Early recognition and treatment of retinopathy can prevent vision loss.[1,2]
- Ensure patient receives dilated pupil retinal examination at diagnosis, then every 1 – 2 years or as indicated (for patient with type 1 diabetes the first follow-up pupil retinal exam can start at 5 years post-diagnosis, then every 1 – 2 years). Annual referral to optometrist/ophthalmologist recommended.
- Retinopathy can worsen during pregnancy. Women with existing diabetes considering pregnancy or in early pregnancy should be assessed by an ophthalmologist.

Nephropathy and Chronic Kidney Disease

- Optimize blood pressure and glucose control to prevent or slow progression of nephropathy.
- Screen for macroscopic proteinuria and non-renal disease with urine dipstick.
- Measure albumin/creatinine ratio (ACR), creatinine/estimated glomerular filtration rate (eGFR), and urinalysis annually: If tests are normal, screen and monitor annually. [41] If tests are abnormal, repeat within 3 months in a well hydrated state to confirm, unless there is deteriorating renal function which requires urgent investigation, management and referral.
- See BCGuidelines.ca – *Chronic Kidney Disease – Identification, Evaluation and Management of Adult Patients* for further information.

Neuropathy

- The best way to prevent diabetic neuropathy is to achieve long-term glycemic control.[1]
- Screening can be performed via 10-g monofilament or 128-Hz tuning fork during foot exam.
- Check at least annually for symptoms or findings such as peripheral anesthesic neuropathy or pain, or autonomic neuropathy (e.g., erectile dysfunction, gastrointestinal disturbance, orthostatic hypotension).

Foot Examination

- Examine feet annually, and more frequently for those at high risk (e.g., neuropathy, macrovascular complications, smokers, patient with foot or leg abnormalities).
- Management of foot ulceration requires interdisciplinary care approach to address infection, wound care, glycemic control, lower-extremity vascular status, and off-loading of high pressure areas.
- Encourage regular self-examination of feet. A foot care patient's checklist is available, at website: guidelines.diabetes.ca/Browse/Appendices/Appendix9

Psychosocial Aspects of Diabetes

- Psychosocial factors affect many aspects of diabetes management and glycemic control.
- Screen for depression, anxiety and eating disorders. Treatment of these conditions may improve outcomes.[7]
- Cognitive behaviour therapy (CBT) based techniques such as stress management strategies and coping skills can be implemented to improve outcomes.[42]

Communicable Diseases

- Annual influenza vaccination is recommended.
- In adults with diabetes, pneumococcal vaccination is recommended. Note: re-vaccination is not routinely recommended. Once-only revaccination 5 years after the initial dose is suggested for specific medical conditions (e.g. chronic kidney disease, chronic liver disease, sickle cell disease, immunosuppression due to disease). For further information, see the BC Centre for Disease Control Immunization Manual, at website: www.bccdc.ca.[43]

Sick Days

- Patients who experience illness and are unable to maintain adequate fluid intake, or have acute decline in renal function (e.g., gastrointestinal upset or dehydration) should increase the frequency of SMBG and they may need to adjust doses of insulin, oral antihyperglycemic agents and/or other medications.[1] See the Sick Day medication list, at website: guidelines.diabetes.ca/Browse/Appendices/Appendix7.
- Encourage individuals with type 1 diabetes to perform ketone testing during acute illness accompanied by elevated blood glucose. Blood ketone testing may be preferred over urine ketone testing.

6. Special Populations

Geriatric Population

In frail elderly people with diabetes:

- Pay attention to potential for polypharmacy. Review medication list periodically, particularly if patient presents with depression, falls, cognitive impairment, perceptual difficulties, or urinary incontinence.
- Use sulfonylureas (especially glyburide) with caution as the risk of hypoglycemia increases with age. Generally, initial doses can be half of those for younger people and increased more slowly.
- Monitor postural blood pressure.
- Consider less strict glycemic targets (7.1 – 8.5% A1C) if the individual has limited life expectancy, high functional dependency, extensive disease or multiple co-morbidities etc.
- Consider a cognitive assessment before initiating insulin. See the BCGuidelines.ca – *Cognitive Impairment: Recognition, Diagnosis and Management in Primary Care* for assessment tests.[44]

Pregnancy

- Contraception and pre-pregnancy planning in all patients with diabetes is encouraged.
- Identify patients with previous gestational diabetes. These patients can develop type 2 diabetes and special attention prior to next pregnancy and in later life, is necessary.
- See the CDA guide on women of child-bearing age, at website: guidelines.diabetes.ca/SpecialPopulations/WomenPregnancyRefGuide

7. Controversies in Care

Controversies in Care: Cardiovascular Risk Calculators

Some controversy exists around the use of risk calculator tools with the type 2 diabetes population. Risk calculators generally predict an individual's proximate (5 – 10 year) risk for a cardiovascular event. The CDA guideline does not promote use of a cardiovascular disease risk calculator to assess risk and notes that lifetime risk is generally very high in all people with diabetes, even if as a younger individual, they can have a low proximate risk. Very high lifetime risk may justify early interventions. Alternatively, the CCS and the BCGuidelines.ca – *Cardiovascular Disease: Primary Prevention* recommends using a risk calculator tool to assess cardiovascular disease risk.[22,45] Two tools that can be used for the type 2 diabetes population are:

- Cardiovascular Risk/Benefit Calculator, at website: chd.bestsciencemedicine.com/calc2.html
- United Kingdom Prospective Diabetes (UKPDS) risk engine, at website: www.dtu.ox.ac.uk/riskengine

Some recent validation studies have shown conflicting results about effectiveness of cardiovascular risk calculator tools (including UKPDS) and more evidence is needed.[46,47] It is also important to note that cardiovascular disease risk scores were developed mainly with caucasian populations and there may be variability in predictive ability with different populations.[48]

Controversies in Care: Blood Pressure

This guideline aligns with the BCGuidelines.ca – *Hypertension: Diagnosis and Management* guideline in recommending a desirable blood pressure reading of 140/90 for the diabetes population. This does not match the CDA or Canadian Hypertension Education Program (CHEP)'s targets of 130/80 but is consistent with 2014 Eight Joint National Committee (JNC 8) and 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines and is similar to NICE (140/80 in type 2 and 135/85 type 1) and ADA (140/80) guidelines.[1,31,49-53] A recent Cochrane review and other systematic review and meta analyses have indicated there is no evidence to support blood pressure targets lower than standard targets in people with hypertension and diabetes, although there may be a small reduction in risk for stroke.[54,55] Due to the lack of convincing evidence to support more intensive blood pressure control, this guideline recommends the same desirable blood pressure reading in adults with diabetes and hypertension as the general population.

Controversies in Care: Sulfonylureas

There is some conflicting evidence about the cardiovascular safety of sulfonylureas. Some studies suggest that sulfonylureas may be associated with poorer outcomes after a myocardial infarction.[56] Cohort studies have found higher risks of death and cardiovascular outcomes, though it is unclear if these results demonstrate the protective effect of the metformin comparator rather than harm from the sulfonylurea, and observational studies cannot establish causality. In addition, older agents, higher historical doses and tighter glucose targets were used which may have contributed to seen differences, and cohort populations were highly heterogeneous. This potential harm does not appear to be as well associated with gliclazide. Cardiovascular safety of sulfonylureas is supported by a meta-analysis and the ADVANCE trial.[57, 58] In addition, the UKPDS trial reported long term mortality and cardiovascular benefit in patients given a sulfonylurea.[59] At present, there is a lack of evidence clearly demonstrating cardiovascular harm, and clinicians should interpret this data cautiously.

Resources

References

1. Canadian Diabetes Association (CDA) Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes. 2013;37 Suppl.1:S1-S212.
2. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2014;37 Suppl. 1:S14-80.
3. Groop L, Tuomi T, Rowley M, et al. Latent autoimmune diabetes in adults (LADA) – more than a name. Diabetologia. 2006;49:1996-8.
4. Redondo, MJ. LADA: Time for a new definition. Diabetes. 2013 Feb;62:339-40.
5. Cernea, S, Buzzetti, R, Pozzilli, P. β-cell protection and therapy for latent autoimmune diabetes in adults. Diabetes Care. 2009;32 Suppl.2:S246-52.
6. CDA Clinical Practice Guidelines Expert Committee. Screening for type 1 and type 2 diabetes. Can J Diabetes. 2008;32 Suppl.1:S14-S16.
7. CDA Clinical Practice Guidelines Expert Committee. Prevention of Diabetes. Can J Diabetes. 2008;32 Suppl.1:S17-S19.
8. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403.
9. Chiasson JL, Josse RG, Gomis R et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDdiabetes randomised trial. Lancet. 2002;359(9323):2072-7.
10. Chiasson JL, Rabasa-Lhoret R. Prevention of type 2 diabetes insulin resistance and β-cell function. Diabetes. 2004;53(S3):S34-S38.
11. Lindstrom J, Ilane-Parikka P, Aunola S, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet. 2006;368:1674-69.
12. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care. 2009;32:1327-1334.
13. British Columbia. Ministry of Justice, Office of the Superintendent of Motor Vehicles. British Columbia Driver Fitness Handbook for Medical Professionals. Victoria, BC: 2014 [cited 2015 Apr 20]. Available from www.pssg.gov.bc.ca.
14. Nathan diabetes, Zinman B, Cleary PA. Diabetes control and complications trial/epidemiology of diabetes interventions and complications (DCCT/EDIC) research group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration. Arch Intern Med. 2009;169(14):1307-1316.
15. Chalmers J, Cooper ME. UKPDS and the legacy effect. N Engl J Med. 2008;395(15)5:1618-1620.
16. Canadian Agency for Drugs and Technologies in Health (CADTH). Optimal therapy recommendations for the prescribing and use of blood glucose test strips. COMPUS. 2009;3(6). [cited Apr 20 2015]. Available from www.cadth.ca.
17. Colquitt JL, Pickett K, Loveman E, et al. Surgery for weight loss in adults (Cochrane Collaboration Review). The Cochrane Database of Systematic Reviews. 2014. Issue 8. No. CD003641.
18. Schauer PR, Kashyap SR, Wolski K. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366:1567-76.
19. Canadian Institute for Health Information (CIHI). Bariatric Surgery in Canada. Ottawa, ON: CIHI; 2014.
20. CADTH. Second-line pharmacotherapy for type 2 diabetes – update. CADTH Optimal Use Report. 2013;3(1A): 1-94. Available from www.cadth.ca/media/pdf/OP0512_DiabetesUpdate_Second-line_e.pdf
21. CADTH. Third-line pharmacotherapy for type 2 diabetes – update. CADTH Optimal Use Report. 2013;3(1B):1-85. Available from www.cadth.ca/media/pdf/OP0512_Diabetes%20Update_Third-line_e.pdf
22. Guidelines and Protocols Advisory Committee, Medical Services Commission of British Columbia. Cardiovascular Disease - Primary Prevention. c2014 [Cited 2015 Apr 20]. Available from www.bcguidelines.ca
23. McAlister FA, Renin Angiotensin System Modulator Meta-Analysis Investigators. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are beneficial in normotensive atherosclerotic patients: a collaborative meta-analysis of randomized trials. Eur Heart J. 2012;33:505e14.
24. Bell AD, Roussin A, Cartier R, et al. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society guidelines. Can J Cardiol. 2011;27:S1-S59.
25. Antithrombotic Trialists' Collaboration. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849-60.
26. De Barardis G, Sacco M, Strippoli GF, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: Meta-analysis of randomized controlled trials. BMJ. 2009;339:b4531.
27. ETDRS Investigators Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. JAMA. 1992;268:1292-1300.
28. Ogawa M, Nakayama M, Morimoto, T. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial JAMA;2008;300: 2134-41.
29. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008; 337:a1840.
30. Bell AD, Roussin A, Cartier R, et al. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society Guidelines. Can J Cardiol. 2011 Mar-Apr;27(2)208-21.
31. Canadian Hypertension Education Program (CHEP). 2015 CHEP recommendations for the management of hypertension. 2015. Available from www.hypertension.ca/chep
32. Guidelines and Protocols Advisory Committee, Medical Services Commission of British Columbia. Hypertension - Diagnosis and Management. c2015 [Cited 2015 Apr 20]. Available from www.bcguidelines.ca
33. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: A meta-analysis. Lancet. 2008;371:117-25.
34. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease (Cochrane Collaboration Review). The Cochrane Database of Systematic Reviews. 2013. Issue 1. Art. No.: CD004816.
35. National Institute for Health and Clinical Excellence (NICE). Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 181. C2014 [modified Sept 2014; cited 2015 Apr 20]. Available from www.nice.org.uk
36. Chen YH, Feng B, Chen ZW. Statins for primary prevention in diabetic patients without established cardiovascular diseases: A meta-analysis. Exp Clin Endocrinol Diabetes. 2012;120:116-120.
37. Reiner, Z, Catapano, AL, De Bracker, G, et al. ESC/EAS guidelines for the management of dyslipidemias. European Heart J. 2011;32(14):1769-1818.
38. Chang YH, Hsieh MC, Wang CY, et al. Reassessing the benefits of statins in the prevention of cardiovascular disease in diabetic patients – A systematic review and meta-analysis. Rev of Diabet Studies. 2013;10(2-3): 157-170.
39. Stone NJ, Robinson J, Lichtenstein AH. 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology /American Heart Association task force on practice guidelines. Circulation. 2013. pii:S0735-1097(13)06028-2.

40. BC Provincial Academic Detailing Service. Statins and coronary heart disease. 2012.
41. Guidelines and Protocols Advisory Committee, Medical Services Commission of British Columbia. Chronic Kidney Disease - Identification, Evaluation and Management of Adult Patients. C2014 [Cited 2015 Apr 20]. Available from www.bcguidelines.ca
42. Ismail K, Winkley K, Rabe-Hesketh S. Systematic review and meta-analysis of randomized controlled trials of psychological interventions to improve glycemic control in patients with type 2 diabetes. Lancet. 2004;363:1589-1597.
43. BC Centre for Disease Control. Communicable disease control manual. 2011. British Columbia [cited 2015 Apr 20]. Available from www.bccdc.ca
44. Guidelines and Protocols Advisory Committee, Medical Services Commission of British Columbia. Cognitive Impairment - Recognition, Diagnosis and Management in Primary Care. C2014 [Cited 2015 Apr 20]. Available from www.bcguidelines.ca
45. Anderson TJ, Grégoire J, Hegele RA, et al. 2012 update of the Canadian cardiovascular society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. 2013;29(2):151-67.
46. Collins GS, Altman DG. An independent and external validation of QRISK2 cardiovascular disease risk score: a prospective open cohort study. BMJ. 2010;340:c2442.
47. Bannister CA, Poole CD, Jenkins-Jones S, et al. External validation of the UKPDS risk engine in incident type 2 diabetes: A need for new type 2 diabetes–specific risk equations. Diabetes Care. 2014;37:537-45.
48. Chamnan P, Simmons RK, Sharp S, et al. Cardiovascular risk assessment scores for people with diabetes: A systematic review. Diabetologia. 2009;52(10):2001-14.
49. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-520.
50. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension. Journal of Hypertension 2013, 31:1281–1357.
51. NICE. Type 2 diabetes: The management of type 2 diabetes. NICE clinical guideline 87. C2009 [modified December 2014; cited 2015 Apr 20]. Available from www.nice.org.uk
52. NICE. Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults. NICE clinical guideline 15. C2004 [modified December 2014; cited 2015 Apr 20]. Available from www.nice.org.uk
53. American Diabetes Association. Standards of Medical Care in Diabetes—2015: Summary of revisions. Diabetes Care. 2015;38 Suppl. 1:S4.
54. Arguedas JA, Leiva V, Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus (Cochrane Collaboration Review). The Cochrane Database of Systematic Reviews. 2013. Issue 10. Art. No.: CD008277.
55. McBrien K, Rabi DM, Campbell N, et al. Intensive and standard blood pressure targets in patients with type 2 diabetes mellitus: Systematic review and meta-analysis. Arch Intern Med. 2012;172(17):1296-1303.
56. Garratt KN, Brady PA, Hassinger NL, et al. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. J Am Coll Cardiol. 1999;33(1):119.
57. Hemmingsen B, Schroll JB, Lund SS, et al. Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2013;4:CD009008
58. Heller, SR, on behalf of the ADVANCE Group. A summary of the ADVANCE trial. Diabetes Care. 2009;32 Suppl. 2:S357-61.
59. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577.

Diagnostic code: 250 – Diabetes mellitus

Appendices

- Appendix A: Screening Algorithm for Type 2 Diabetes in Adults
- Appendix B: Treatment of Hypoglycemia in Diabetes
- Appendix C: PharmaCare quantity limits for blood glucose test strips
- Appendix D: Management of Hyperglycemia in Type 2 Diabetes
- Appendix E: Antihyperglycemic Agents and Adjunctive Agents for Use in Type 2 Diabetes
- Appendix F: Insulin and Therapeutic Considerations

Associated Documents

The following documents accompany this guideline:

- Diabetes Patient Care Flow Sheet
- Patient Education and Resources

This guideline is based on scientific evidence current as of the Effective Date.

This guideline was developed by the Guidelines and Protocols Advisory Committee, approved by the British Columbia Medical Association, and adopted by the Medical Services Commission.

THE GUIDELINES AND PROTOCOLS ADVISORY COMMITTEE

The principles of the Guidelines and Protocols Advisory Committee are to:

- encourage appropriate responses to common medical situations
- recommend actions that are sufficient and efficient, neither excessive nor deficient
- permit exceptions when justified by clinical circumstances

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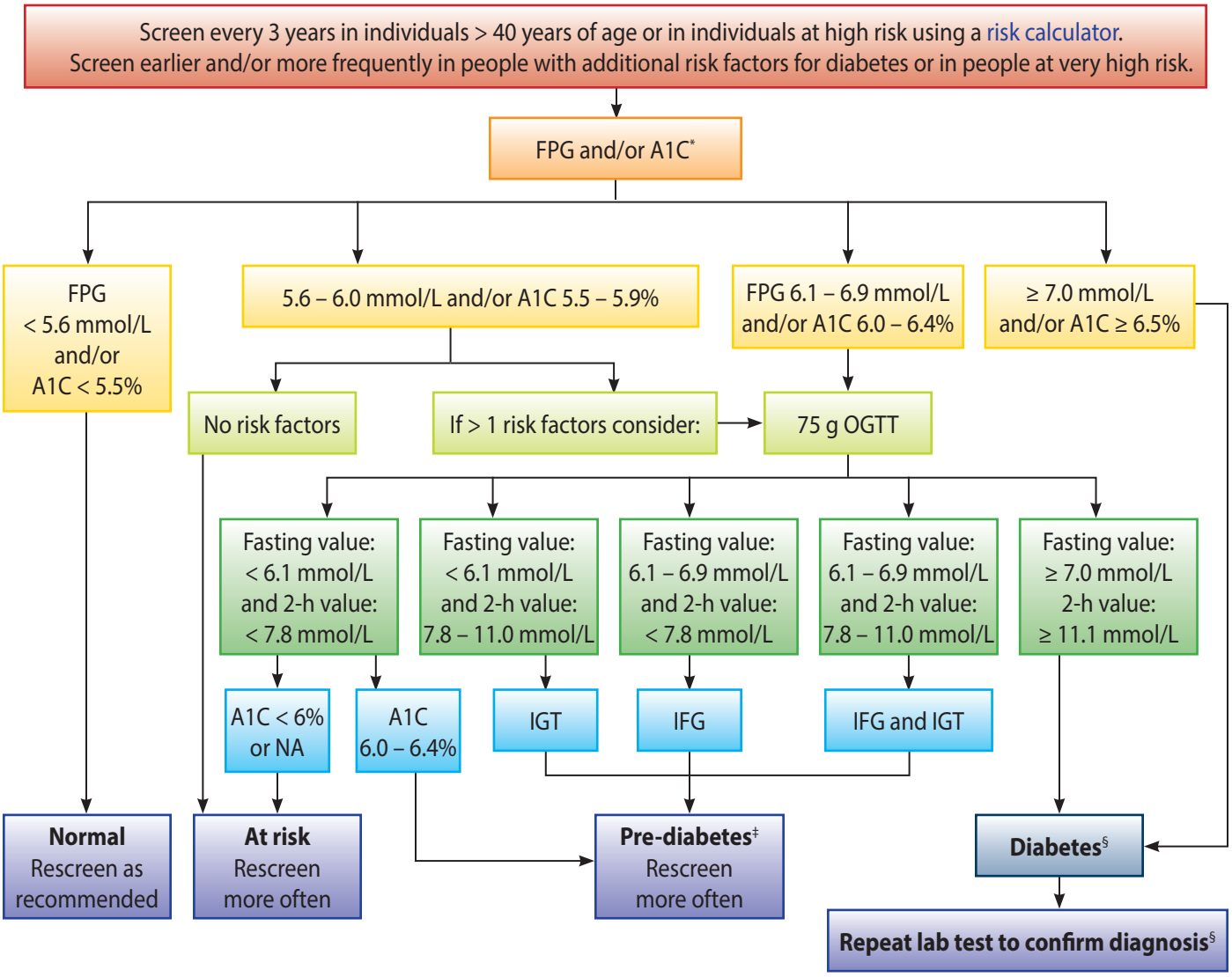
Disclaimer

Appendix A: Screening Algorithm for Type 2 Diabetes in Adults

Note: an interactive form of this tool is available at website: guidelines.diabetes.ca/ScreeningAndDiagnosis/Screening



Abbreviations: A1C= glycated hemoglobin; FPG= fasting blood glucose; 75-g OGTT= 75 gram oral glucose tolerance test; 2hPG= 2-hour plasma glucose; IFG= impaired fasting glucose; IGT= impaired glucose tolerance; NA = Not available; PG= plasma glucose.

* If both FPG and A1C are available but conflict, use the test that appears to the furthest to the right of the algorithm.

‡ The term "prediabetes" refers to IFG and/or IGT, or A1C 6.0-6.4%. These individuals are at risk of developing diabetes, should be monitored regularly, and benefit from cardiovascular disease risk factor modification.

§ If a single lab test is in the diabetes range, then a **confirmatory laboratory test** (FPG, A1C or a 2hPG in a 75 g OGTT) must be done on another day (in timely fashion) in all cases in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation. It is preferable the same test is repeated. If two lab tests are available and both are above cutoff points, then diagnosis is confirmed.

Adapted from: Ekoe, J-M, Punthakee, Z, et al. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Screening for Type 1 and Type 2 Diabetes. Can J Diabetes. 2013 Apr;37 (Suppl 1):S12-15.

Appendix B: Treatment of Hypoglycemia in Diabetes

Severity	Definition	Initial Treatment	Follow-up
Mild	Autonomic symptoms present. Individual able to self-treat.	Oral ingestion of 15 g of carbohydrate, preferably as glucose or sucrose tablets or solution: • 15 g glucose as glucose tablets • 15 mL (3 teaspoons) or 3 packets of table sugar (sucrose) dissolved in water • 175 ml (3/4) of juice or regular soft drink • 6 LifeSavers (1 = 2.5 g carbohydrate) • 15 mL (1 tablespoon) honey • Following initial treatment, retest blood glucose in 15 minutes and re-treat with another 15 g carbohydrate if the BG level remains < 4.0 mmol/L.	Once the hypoglycemia has been reversed, the person should have the usual meal or snack that is due at that time of the day to prevent repeated hypoglycemia. If a meal is > 1 hour away, a snack (including 15 g carbohydrate and a protein source) should be consumed. Discuss episode with the diabetes healthcare team as soon as possible. Individuals (and their families/ caregivers) at high risk of severe hypoglycemia should be taught to administer glucagon by injection.
Moderate	Autonomic and neuroglycopenic symptoms present. Individual able to self-treat.		
Severe	Individual requires assistance. Unconsciousness may occur. Plasma glucose (PG) typically < 2.8 mmol/L.	• Conscious: Oral ingestion of 20 g carbohydrate, preferably glucose tablets. • Retest blood glucose in 15 minutes and re-treat with another 15 g carbohydrate if the BG level remains < 4.0 mmol/L.	
		• Unconscious: ◦ Seek emergency assistance ◦ 1 mg glucagon subcutaneously or intramuscularly ◦ Discuss with the diabetes healthcare team as soon as possible	
Patients on Acarbose (GlucoBay™)		• Glucose (dextrose) or if unavailable honey or milk • Avoid table sugar (sucrose)	

Appendix C: PharmaCare quantity limits for blood glucose test strips

TREATMENT CATEGORY	NOTES – For combination therapy, the highest eligible quantity limit applies. (e.g., If a patient takes insulin, this higher limit applies, regardless of other diabetes medications.)	ANNUAL QUANTITY LIMIT
Managing diabetes with insulin		3,000
Managing diabetes with anti-diabetes medications with a high risk of causing hypoglycemia	Drugs with a higher risk of hypoglycemia (insulin secretagogues-sulfonylureas, meglitinides).	400
Managing diabetes with anti-diabetes medications with a low risk of causing hypoglycemia	Drugs with a lower risk of hypoglycemia (acarbose, metformin, Dipeptidyl Peptidase-4 Inhibitors (DPP4I's), incretin mimetics/ glucagon-like peptide (GLP-1) agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors and thiazolidinediones (TZDs).	200
Managing diabetes through diet/lifestyle		200

SPECIAL AUTHORITY ADDITIONAL STRIP COVERAGE
If a patient meets one of the criteria below and is not on insulin, BC PharmaCare will cover 100 extra strips per year on receipt of a Special Authority Request from a physician or from a health professional at a Diabetes Education Centre recognized by the BC Ministry of Health. BGTS Limited Coverage Form: www.health.gov.bc.ca/pharmacare/sa/criteria/restricted/bgts.html
For patients requiring 100 additional blood glucose test strips **AND** who are not using insulin **AND** Are experiencing at least one of the following: • Not meeting glycemic targets, as determined by a physician, for 3 months or more **OR** • Acute illness or comorbidities that may impact blood glucose control **OR** • Changes in drug therapy that may impact blood glucose control (e.g., starting or stopping hypo- or hyperglycemic inducing medications, or drug-to-drug or drug-to-disease interactions) **OR** • Occupations where hypoglycemia presents a significant safety risk (e.g., pilots, air traffic controllers, commercial drivers) **OR** • Gestational diabetes

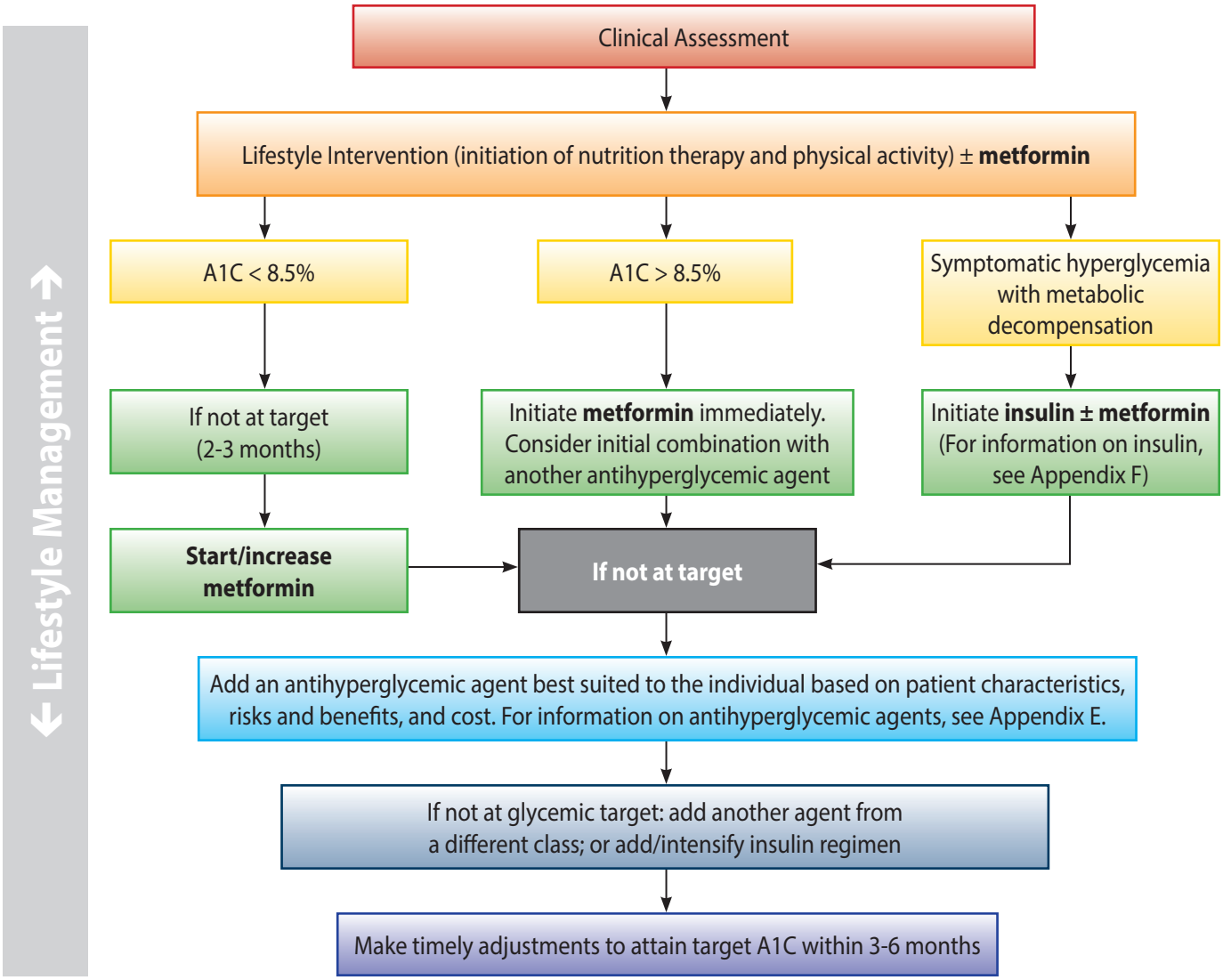
For more information on BC PharmaCare coverage of test strips, please see their website at www.health.gov.bc.ca/pharmacare/bgts-pro.html.

Note: In the rare case that a patient has a medical need for even more frequent testing, or when a **patient on insulin** needs to test more frequently, an endocrinologist may submit a **written request** to PharmaCare for additional strips. Requests will be considered on a case-by-case basis. The letter should outline the need for the additional strips and the quantity required.

References:

1. Optimal Therapy Recommendations for the Prescribing and Use of Blood Glucose Test Strips. From *CADTH Technology Overviews*, Volume 1, Issue 2, e0109. June 2010. Available at: www.cadth.ca/en/products/cadth-overviews/vol-1-issue-2/vol-1-issue-2-09
2. BC Ministry of Health, Blood Glucose Testing. Available at: www.health.gov.bc.ca/pharmacare/bgts-pro.html

Appendix D: Management of Hyperglycemia in Type 2 Diabetes



Adapted from: Harper W, Clement M, Goldenberg R, et al. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: pharmacologic management of type 2 diabetes. Can J Diabetes 2013;37 (Supp.1): S61-68

Appendix E: Antihyperglycemic Agents and Adjunctive Agents for Use in Type 2 Diabetes

Generic Name (Trade Name), Dosages	Adult Dose[1,2,3]	Cost/30 days (usual dose)	PharmaCare Coverage (definitions under resources)	Therapeutic Considerations
Biguanides				
Metformin (generic) 500, 850 mg tablets Glumetza: 500, 1000 mg SR tablets	Initial: 250 or 500 mg PO BID Usual: 1000 mg BID (Glumetza-daily dose) Max: 2550 mg/day.[1]	$6.50 (3x500 mg) $40 – Glumetza	Regular benefit Glumetza- no coverage	**Pro:** Usual first line drug for type 2 diabetes; low rates of hypoglycemia; weight neutral to modest weight loss (2-3 kg).[5,6] **Con:** GI side effects, Vitamin B12 deficiency. Use with caution / reduce dose if eGFR < 60 mL/min. **Contraindicated:** eGFR < 30 mL/min, hepatic or cardiac failure. **Effect:** lowers A1C 1.5%, decreases micro and macrovascular endpoints events.[7,8]
Insulin Secretagogues, Sulfonylureas				
Gliclazide (Diamicron®, Diamicron MR®, generic) 80 mg, 30 mg ER, 60 mg ER tablets	Initial: 80-160 mg PO daily Usual: 80-320 mg daily (≥160 mg divide BID) Diamicron MR. Initial: 30 mg PO daily at breakfast to a Max of 120 mg daily.	$6 (2x80 mg) $9 (2x30 mg ER)	Limited Coverage* (Requires Special Authority). Criteria: Treatment failure or intolerance to at least one other sulfonylurea drug at adequate doses. See Pharmacare website: gliclazide.	**Pro:** Extensive clinical experience. **Con:** Hypoglycemia variable based on drug (more with glyburide), dose, patient, modest weight gain[9,10,11] (2-3 kg). Use with caution / reduce dose if eGFR < 50 mL/min (glyburide), eGFR < 30 mL/min (glimepiride, gliclazide). **Not recommended:** eGFR < 30 mL/min (glyburide), eGFR < 15 (glimepiride, gliclazide). **Effect:** lowers A1C 1-2%.[12,13,14]
Glimepiride (Amaryl™, generic) 1, 2, 4 mg tablets	Initial: 1 mg PO daily Usual: 1-4 mg daily Max: 8mg daily	$16 (1x4 mg daily)	No Coverage	
Glyburide (Diabeta®, generic) 2.5, 5 mg tablets	Initial: 5 mg PO daily Usual: 2.5-20 mg (divide BID if >10 mg) Max: 20 mg daily	$2 (2x5 mg)	Regular Coverage	
Insulin Secretagogues, Meglitinides				
Repaglinide (GlucoNorm®) 0.5, 1, 2 mg tablets	Initial: 0.5mg (treatment-naïve) or 1 mg PO TID AC Max: 16 mg daily.[3]	$32 (4x2 mg)	No Coverage	**Pro:** No risk sulfa allergy, no dosage adjustment for decreased eGFR. **Con:** some hypoglycemia and weight gain, TID dosing. **Contraindicated:** pregnancy. **Effect:** lowers A1C 0.5-1%.[15,16,17]
Nateglinide (Starlix) 60, 120 mg tablets	Initial and maintenance: 60-120 mg PO TID AC.[3]	$55 (any dose TID)	No Coverage	

Generic Name (Trade Name), Dosages	Adult Dose[1,2,3]	Cost/30 days (usual dose)	PharmaCare Coverage (definitions under resources)	Therapeutic Considerations
Alpha-glucosidase inhibitor				
Acarbose (Glucobay®) 50, 100 mg tablets	Slowly titrate (every 1-2 weeks) from 50mg daily to 50 mg TID. Max 100 mg TID. AC meals.	$27 (3x50 mg)	No Coverage	**Pro:** low risk hypoglycemia, weight neutral to modest weight loss. **Con:** frequent GI side effects. Not recommended if eGFR < 25 mL/min. **Contraindicated:** IBS and IBD. **Note:** Must use glucose (dextrose) for hypoglycemia, not sucrose as complex sugars are ineffective.
Thiazolidinediones (TZDs)				
Pioglitazone (Actos®, generic) 15, 30 mg tablets	Initial: 15-30 mg PO daily Max: 45 mg daily	$29 (1x30 mg)	Limited Coverage* (Requires Special Authority). Criteria: part of a combination treatment for type 2 diabetes: 1. When insulin NPH is not an option **AND** 2. After inadequate glycemic control on maximum tolerated doses of dual therapy of metformin **AND** a sulfonylurea. See Pharmacare website: pioglitazone.	**Pro:** low risk of hypoglycemia, increase HDL. **Con:** weight gain (4-6 lbs, fluid retention contributes)[4], fluid retention, can precipitate heart failure, increased risk fractures, cardiovascular risk-benefit unclear. **Use with caution:** if eGFR < 30 mL/min. **Contraindicated:** pregnancy, metabolic bone disease, NYHA III/IV heart failure. **Effect:** Lowers A1C 1-1.5%. Pioglitazone may reduce cardiovascular harm.[18] Pioglitazone can cause significant fluid retention, particularly in heart failure. Contraindicated in active bladder cancer or history of bladder cancer. Risk of bladder cancer may increase with high dose and duration of use.
Rosiglitazone (Avandia®) 2, 4, 8 mg tablets *Use of rosiglitazone is not recommended.*	4 mg PO daily in 1-2 doses Max: 8 mg daily (4 mg if taking sulfonylurea)	$70 (1x4 mg)	No Coverage	Rosiglitazone can cause fluid retention, heart failure, and may be associated with an increased risk of cardiac ischemia.[19] Use of rosiglitazone is not recommended.

Generic Name (Trade Name), Dosages	Adult Dose[1,2,3]	Cost/30 days (usual dose)	PharmaCare Coverage (definitions under resources)	Therapeutic Considerations
Dipeptidyl Peptidase-4 Inhibitors (DPP4Is)				
Sitagliptin (Januvia™) 25, 50, 100 mg Tabs	100 mg PO daily	$96 (all doses)	No Coverage	**Pro:** weight neutral. **Con:** rare reports of pancreatitis, emerging concerns about HF (saxagliptin), modest lowering effect on A1C, may cause severe joint pain. Dosage reduction required if eGFR < 50 mL/min (sitagliptin, saxagliptin). **Contraindicated:** pregnancy, hepatic failure, previous lactic acidosis. **Effect:** Lowers A1C 0.75%.[20] Trials up to 3 years in length show no cardiovascular disease benefit over placebo.[20-22]
Saxagliptin (Onglyza™) 2.5, 5mg tablets	5 mg PO daily	$77 – 2.5 mg $92 – 5 mg	Limited Coverage* (Requires Special Authority). Criteria: part of a combination treatment for type 2 diabetes: 1. When insulin NPH is not an option **AND** 2. After inadequate glycemic control on maximum tolerated doses of dual therapy of metformin **AND** a sulfonylurea. See Pharmacare website: saxagliptin.	
Linagliptin (Trajenta) 5 mg tablets	5 mg PO daily	$73	Limited Coverage* (Requires Special Authority). Criteria: As saxagliptin above See Pharmacare website: linagliptin	
Alogliptin (Nesina) 6.25 mg, 12.5 mg, 25 mg	25 mg daily	$85 (1x25 mg)	No Coverage	
Glucagon-Like-Peptide 1 (GLP-1) Agonists				
Albiglutide (Eperzan)	30mg SC once weekly, may increase to 50 mg SC once weekly after 4 weeks if needed.	Not available in BC as of 2015/09/28	Not available in BC as of 2015/09/28	**Pro:** modest weight loss (up to 2-3 kg)[23], low hypoglycemia. **Con:** GI side effects, rare reports of pancreatitis, increased heart rate, injectable. Use with caution / not recommended if eGFR < 50 mL/min. **Contraindicated:** pregnancy, history of pancreatitis, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. **Effect:** lowers A1C 1%. [24]
liraglutide (Victoza®) pre-filled pen (0.6 mg/0.1 ml) Pack size: 2x3 ml, 3x3 ml (3 ml=15 doses of 1.2 mg/ml)	Initial: 0.6 mg SC once daily x 1 week Increase to 1.2-1.8 mg SC once daily (1.8 is more expensive, similar A1C effect)	$175 (1.2 mg)	No Coverage	
Exenatide (Byetta) Pre-filled pen. 5 mcg/0.02 ml Pack size: 1.2 ml (60 doses of 5 mcg/dose) and 2.4 ml (60 doses of 10 mcg/dose)	Initial: 5 mcg SC BID within 60-minute period before the two main meals of the day, at least 6 hours apart. Increase to 10 mcg BID as tolerated	$150 (all doses)	No Coverage	

Generic Name (Trade Name), Dosages	Adult Dose[1,2,3]	Cost/30 days (usual dose)	PharmaCare Coverage (definitions under resources)	Therapeutic Considerations
Sodium-Glucose Cotransporter 2 Inhibitors				
Canagliflozin (Invokana) 100, 300 mg tablets	100 mg PO daily prior to first meal. May increase to a maximum of 300 mg daily. Use only 100 mg dose if eGFR 45-60 mL/min.	$84 (all doses)	Under Review	**Pro:** weight loss (2-3 kg), low rates of hypoglycemia, blood pressure lowering (unknown clinical significance). **Con:** decreased bone mineral density and increased risk of bone fractures (canagliflozin), reports of euglycemic diabetic ketoacidosis, volume depletion (more in age > 65 years), genital mycotic infections, UTI, increased LDL, glucose lowering is independent of beta cell function and insulin sensitivity. **Contraindicated:** pregnancy, eGFR < 45 mL/min (< 60 mL/min if dapagliflozin), renal disease, dialysis, bladder cancer imbalance (dapagliflozin). **Effect:** lowers A1C 0.5 – 0.7%.[25,26] limited by filtered load of glucose, osmotic diuresis and kidney function.
Dapagliflozin (Forxiga) 5, 10 mg tablets	Initial: 5 mg once daily; may increase to 10 mg once daily	$84 (all doses)	Under Review	
Empagliflozin (Jardiance) 10, 25 mg tablets	10 mg once daily; may increase to 25 mg once daily	Under review	Under Review	
Combinations				
Rosiglitazone plus metformin (Avandamet™) 2/500, 2/1000, 4/500, 4/1000 mg tablets *Rosiglitazone not recommended*	2 mg/500 mg PO BID with meals, max 8 mg/1000 mg BID	$52 (4 mg/500 mg)	No Coverage	See individual drug components. Rosiglitazone not recommended.
Sitagliptin plus metformin (Janumet™) 50 mg/500, 50/1000 mg tablets	50 mg/500 mg PO BID, Max: 50 mg/1000 mg BID	$104 (all doses)	No Coverage	
Alogliptin-metformin (Kazano) 12.5/500 mg, 12.5/850 mg 12.5 mg/1000 mg	One tablet BID	$89 (all doses)	No Coverage	
Linagliptin plus metformin (Jentadueto) 2.5/500 mg, 2.5/850 mg, 2.5/1000 mg Tablets	Max: 2.5 mg/1000 mg BID	$77 (all doses)	Limited Coverage* (Requires Special Authority). Criteria: As saxagliptin and linagliptin above.	
Saxagliptin plus metformin (Komboglyze) 2.5/500 mg, 2.5/850 mg, 2.5/1000 mg Tablets	Max: 2.5 mg/1000 mg BID	$82 (all doses)		

Abbreviations: AC=before meals; A1C=glycosylated hemoglobin; BID= twice a day; BC=British Columbia; eGFR= estimated glomerular filtration rate; ER= extended release; GI=gastrointestinal; HDL= high density lipoprotein; IBD= inflammatory bowel disease; IBS= Irritable bowel syndrome; LDL = low density lipoprotein; mg=milligram; NPH= Neutral protamine hagedorn (e.g., Humulin N); NYHA= New York Heart Association Functional Classification; PO=orally; SC=subcutaneous; TID= three times a day; URTI=upper respiratory tract infection; UTI=urinary tract infection

- Limited Coverage Criteria are current as per Pharmacare 2014/12/01 and are subject to change. Refer to Pharmacare website for updated criteria.
- Pricing is approximate as per PharmaNet 2014/08/26 and does not include dispensing fee and retail markup.
- For information on the current costs, please visit BC PharmaCare Formulary Search, website: pcbl.hlth.gov.bc.ca/pharmacare/benefitslookup/

PharmaCare Coverage Definitions:

Regular coverage: also known as regular benefit; does not require Special Authority; patients may receive full coverage*

Partial coverage: Some types of regular benefits are only partially covered* because they are included in the Low Cost Alternative (LCA) program or Reference Drug Program (RDP) as follows: LCA: When multiple medications contain the same active ingredient (usually generic products), patients receive full coverage* for the drug with the lowest average PharmaCare claimed price. The remaining products get partial coverage. RDP: When a number of products contain different active ingredients but are in the same therapeutic class, patients receive full coverage* for the drug that is medically effective and most cost-effective. This drug is designated as the Reference Drug. Remaining products get partial coverage.

Special Authority: requires Special Authority for coverage. Patients may receive full or partial coverage* depending on LCA or RDP status. These drugs are not normally regarded as first-line therapies or there are drugs for which a more cost-effective alternative exists. Pharmacare coverage period is indefinite, 3rd party payers may require re-confirmation.

No coverage: does not fit any of the above categories

* coverage is subject to drug price limits set by PharmaCare and to the patient's PharmaCare plan rules and deductibles. See www.health.gov.bc.ca/pharmacare/ for further information.

References:

1. Canadian Pharmacists Association. e-CPS [Internet]. Ottawa (ON): Author; c2007 [cited 2007 Jul 30]. Available from: www.e-cps.ca.
2. Harper W, Clement M, Goldenberg R, et al. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: pharmacologic management of type 2 diabetes. Can J Diabetes 2013;37 (Supp.1): S61-68
3. Mann E. Diabetes mellitus. e-Therapeutics+ [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2007 [updated Sep 2006; cited 2007 Jul 30]. Available from: www.e-therapeutics.ca.ezproxy.library.ubc.ca
4. McCulloch, DK. Management of persistent hyperglycemia in type 2 diabetes mellitus. In: UpToDate, Waltham, MA.
5. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355(23):2427.
6. Umpierrez G, Tofé-Povedano S, Pérez Manghi F, et al. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). Diabetes Care. 2014 Aug;37(8):2168-76.
7. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352(9131):854.
8. Saenz A, Fernandez-Esteban I, et al. Metformin monotherapy for type 2 diabetes mellitus (Cochrane Collaboration Review). The Cochrane Database of Systematic Reviews. 2005. Issue 3. Art. No.: CD002966.
9. Yki-Jarvinen H, Ryysy L, Nikkila K, et al. Comparison of bedtime insulin regimens in patients with Type 2 diabetes mellitus: a randomized controlled trial. Ann. Intern. Med. 1999;130:389–96.
10. Belcher, Glyn, et al. Safety and tolerability of pioglitazone, metformin, and gliclazide in the treatment of type 2 diabetes. Diabetes Research and Clinical Practice. 2005;70(1): 53-62.
11. Gangji AS, Cukierman T, Gerstein HC, et al. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: A comparison of glyburide with other secretagogues and with insulin. Diabetes Care. 2007;30(2): 389-394.
12. Bressler R, and Johnson DG. Pharmacological regulation of blood glucose levels in non-insulin-dependent diabetes mellitus. Archives of Internal Medicine. 1997;157(8): 836-48.
13. Hermann LS, Scherstén B, Bitzén PO, et al. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations: a double-blind controlled study. Diabetes Care. 1994;17(10): 1100-9.
14. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). The Lancet. 1998;352(9131): 837-853.
15. Jovanovic L, Dailey G, Huang WC, et al. Repaglinide in type 2 diabetes: a 24-week, fixed dose efficacy and safety study. J of Clin Pharm, 2000;40(1):49-57.
16. Moses RG, Gomis R, Frandsen KB, et al. Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive type 2 diabetes. Diabetes Care. 2001 Jan;24(1):11-5.
17. Rosenstock J, Hassman DR, Madder RD, et al. Repaglinide versus nateglinide monotherapy: a randomized multicenter study. Diabetes Care. 2004; 17(6):1265-70.
18. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study: a randomised controlled trial. The Lancet. 2005;366(9493): 1279-89.
19. Home PD, Kahn, SE, Jones NP, et al. Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT and RECORD clinical trials. Diabetologia. 2010;53(9):1838-45.
20. Scirica BM, Braunwald E, Raz I, et al. Heart failure, saxagliptin and diabetes mellitus: Observations from the SAVOR-TIMI 53 randomized trial. Circulation (2014): CIRCULATIONAHA-114. Published online before print.
21. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. New Engl J Med. 2013;369(14): 1327-35.
22. Green JB, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;373(3):232-42.
23. Shyangdan DS et al. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2011;
24. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA. 2007;298(2):194.
25. Clar C, Gill JA, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. *BMJ* open 2.5 (2012): e001007.
26. Musso, Giovanni, et al. A novel approach to control hyperglycemia in type 2 diabetes: Sodium glucose co-transport (SGLT) inhibitors. Systematic review and meta-analysis of randomized trials. Annals of medicine. 2012;44(4): 375-93.

Appendix F: Insulins and Therapeutic Considerations

Also see guidelines.diabetes.ca/CDACPG_resources/Insulin_Prescription_May_5_2014.pdf

Insulin Action	Insulin Name Trade Name– Supplied as either Vials (1x10 ml), Cartridges (5x3 ml) and/or Prefilled Pens (5x3 ml)	Cost per 100 IU of insulin (Cost per supply – 10 ml vial or 5x3 ml Pen/Cartridge)	Pharmacare Coverage	Therapeutic Considerations
RAPID	Insulin aspart NovoRapid(Vial, Pen/Flex Touch Pen) Insulin glulisine Apidra (Vial, Cartridge, Solostar pen) insulin lispro Humalog (Vial, Cartridge, Kwikpen)	Aspart $3 ($31)-Vial $4.25 ($65)-Pen Glulisine $2.70 ($27)-Vial $3.60 ($54)-Pen/Cartridge lispro $2.9 ($29)-Vial $4 ($60)-Pen/Cartridge	Partial Benefit	Bolus Insulin Onset: 10-15min. Peak 60-90min. Duration 4-5h
SHORT	Insulin regular Humulin R (Vial, Cartridge) Novolin ge Toronto (Vial, Pen)	Humulin R $2.40 ($24)-Vial $3.2 ($48)-Cartridge Novolin Toronto $2.30 ($23)-Vial $3 ($45)-Pen	Regular benefit	Bolus Onset: 0.5-1h. Peak 2-4h. Duration 5-8h.
INTERMED	Insulin NPH Humulin N (Vial, Cartridge, Kwikpen) Novolin ge NPH (Vial, Pen)	Humulin N $2.5 ($25)-Pen $3.2 ($48)-Vial Novolin NPH $2.3 ($23)-Vial $3.1 ($46)-Pen	Regular benefit	Basal Insulin Onset: 1-2h. Peak: 5-8h. Duration 14-18h.
LONG	Insulin glargine Lantus (Vial, Cartridge, Pen) Insulin detemir Levemir (Cartridge, Pen)	Insulin glargine $6.6 ($66)-Vial $6.6 ($100)-Pen Insulin detemir $7.3 ($110)-Cartridge $7.7 ($116)-Pen	Limited Coverage for insulin glargine and insulin determir (Requires Special Authority or prescription written by endocrinologist). See Pharmacare website on insulin determir or insulin glargine	Basal Insulin Onset: 1.5h. Peak: Flat. Duration: 24h (6-24h Levemir) Do not mix with other insulins. Levemir: at low dose may require BID administration Lantus: SC only
	Long-acting Basal Analogue Insulin Glargine U300 Toujeo SoloSTAR 4504/1.5 mL	Note: Insulin Glargine U300 solution is 300U/mL Toujeo SoloSTAR is 1.5 mL pen 3-pack/4.5 mL $80 5-pack/7.5 mL $135	To be determined	Basal Analogue Onset: Up to 6h. Peak: Not applicable. Duration: Up to 30h. SC only. Must not be mixed with any other insulin or diluted with any other solution
PREMIXED	**Premixed (% short (regular) to % intermediate (NPH))** Humulin 30/70 (Vial, Cartridge) Novolin ge 30/70, 40/60, 50/50 (Pen, Vial (30/70 only))	Humulin 30/70 $2.40 ($24)-Vial $3.2 ($48)-Cartridge Novolin 30/70, 40/60, 50/50 $2.3 ($23)-Vial $3 ($45)-Pen	Regular benefit	Action is combination of individual components.
PREMIXED	**Premixed Insulin Analogues** insulin lispro/lispro protamine Humalog Mix25, Humalog Mix 50 (Cartridge, Pen) insulin aspart/aspart protamine (NovoMix 30) (Cartridge)	Lispro/Lispro Protamine and aspart/aspart protamine $4 ($60)-Cartridge, Pen	Partial benefit – covered to cost of short-acting insulin, no SA coverage	Humalog-Onset: 10-15 min, Peak and Duration unavailable. Novomix 30-Onset: 10-15min Peak: 60-90min Duration: 15-18h

- Limited Coverage Criteria are current as per Pharmacare 2014/12/01 and are subject to change. Refer to Pharmacare website for updated criteria.
- Pricing is approximate as per PharmaNet 2014/08/26 and does not include dispensing fee and retail markup.
- For information on the current costs, please visit BC PharmaCare Formulary Search, website: pcbl.hlth.gov.bc.ca/pharmacare/benefitslookup/

PharmaCare Coverage Definitions

regular coverage: also known as regular benefit; does not require Special Authority; patients may receive full coverage*

partial coverage: Some types of regular benefits are only partially covered* because they are included in the Low Cost Alternative (LCA) program or Reference Drug Program (RDP) as follows:

- **LCA:** When multiple medications contain the same active ingredient (usually generic products), patients receive full coverage* for the drug with the lowest average PharmaCare claimed price. The remaining products get *partial coverage*.
- **RDP:** When a number of products contain different active ingredients but are in the same therapeutic class, patients receive full coverage* for the drug that is medically effective and the most cost-effective. This drug is designated as the Reference Drug. The remaining products get *partial coverage*.

Special Authority: requires Special Authority for coverage. Patients may receive full or partial coverage* depending on LCA or RDP status. These drugs are not normally regarded as first-line therapies or there are drugs for which a more cost-effective alternative exists. Pharmacare coverage period is indefinite, 3rd party payers may require re-confirmation.

No coverage: does not fit any of the above categories

* coverage is subject to drug price limits set by PharmaCare and to the patient's PharmaCare plan rules and deductibles. See www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmacare-for-bc-residents for further information.

References:

1. e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2007 [cited 2007 Jul 30]. Available from: www.e-cps.ca.
2. Harper W, Clement M, Goldenberg R, et al. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: pharmacologic management of type 2 diabetes. Can J Diabetes 2013;37 (Supp.1): S61-68
3. Mann E. Diabetes mellitus. In: Gray Jean, editor. e-Therapeutics+ [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2007 [updated Sep 2006; cited 2007 Jul 30]. Available from: www.e-therapeutics.ca.ezproxy.library.ubc.ca.