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Individualizing Glycemic Targets for the Frail Elderly with T2DM

General Considerations

- Healthy, active elderly without significant comorbidities (those with a life expectancy >10yrs), may aim for the same glycemic targets as younger adults (e.g. A1C ≤7%).[1,2] However, consideration for individualization of approach is recommended based on various patient factors.[3, 4]
- Frail elderly require a cautious approach to A1C targets!
  - Frailty is associated with multiple illnesses such as dementia, functional decline, predisposition to falls, impaired mobility & polypharmacy.
  - The evidence base is limited by lack of studies in this population & there are ↑ risk of harms (e.g. falls, death) from glycemic lowering treatment. Harms may outweigh benefits especially when the *time to benefit* (more than 5-10yrs) exceeds *life expectancy*.
- Key Goals – ***Treat the patient, not the target***
  - Avoid the acute complications of poor glycemic control (hypoglycemia & hyperglycemia).
  - Consider factors that impact how stringent of a target should be set (e.g. life expectancy, comorbidity & duration of diabetes; see the VA/DoD Guidelines Appendix B)[3,4].

Hypoglycemia (e.g. BG <4mmol/L with symptoms)

- Hypoglycemia is a serious risk documented in both clinical trials & anecdotally. Avoiding hypoglycemia is key to decreasing falls, fractures, seizures & death.

Link: Diabetes Guidelines for Elderly in Long-Term Care (LTC), Nova Scotia[5]
⇨ http://diabetescareprogram.ns.ca/pdf/LTC/GuideBackground.pdf

Hyperglycemia

- Hyperglycemia is associated with increased risk of infections, falls, etc. It is defined differently for a frail elderly population. A random BG of 7-14$_{mmol/L}$ (or even higher) may be acceptable if the patient has no reversible symptoms such as polyuria & nocturia. {Of interest, the threshold at which glucose spills into the urine increases with age.}

Monitoring Blood Glucose (BG)[6]

- If only on metformin, may not need BG monitoring.
- If on a drug associated with hypoglycemia (eg. glyburide, gliclazide, insulin), monitor with drug initiation, changes & sick days. Long-term monitoring can be less frequent if no hypoglycemia or medication changes. See also SMBG chart.[7]
- Maintaining hydration helps to avoid acute hypoglycemia.

Summary of Trials Related to T2DM Glycemic Targets in Table 1

⇨Intensive A1C lowering in trials offers modest benefit, mostly microvascular over 5+ yrs. There is some evidence for macrovascular benefit over the long-term (>10-20yrs) UKPDS-80.

⇨Intensive A1C lowering may increase risk of harms including major hypoglycemia[8] & increased all-cause death[9] in some.

⇨In studies with A1Cs as high as 7.9% and 8.4% in the less intensive Tx arms, there were only marginal clinical outcome differences, but much less hypoglycemia in the less intensive Tx arms. Since frail elderly patients are even more likely to experience potential harms, these A1Cs provide some insight as to potentially reasonable A1C targets/ranges.

⇨The cohort study in aging found that the mortality risk is a U-shaped curve which increases for A1Cs <6% and >9%.[10] Risk of any complication increased with A1Cs >8%. A similar study of patients with diabetes and CKD found a similar U-curve where mortality was increased with A1C <6.5% and >8.0%.[11]

⇨Some guidelines have provided specific recommendations on how to individualize glycemic control in the elderly. (Table 2)

Table 1: RCT Trials - Intensive vs Less-Intensive BG Lowering#

RCT Trial mean age; duration & **A1C Attained**	Benefits or Harms in More Intensive Glucose Lowering (Lower A1C) Arm vs Less Intensive Tx
UKPDS-33[12] age 54; 10yrs ***A1C: 7 vs 7.9***	⇨ no difference in major clinical outcomes* at 10yrs ⇨ benefits on surrogate outcomes ↓ microvascular disease after 6+ yrs ⇨ ↑ major hypoglycemia
UKPDS-34[13]	(follow-up study @20yrs, saw ↓ MI & all-cause death) UKPDS-80,81
[Note: UKPDS-34 found ↓ death NNT=14/10.7yrs, ↓stroke NNT=48/**10.7 yrs**, when metformin specifically was used vs standard Tx in obese T2DM; A1C achieved was 7.4% vs 8%]	
ADVANCE[14] age 66; 5yrs ***A1C: 6.5 vs7.3***	⇨ no difference in major clinical outcomes* at 5yrs ⇨ ↓ microvascular endpoints NNT=67/5yrs, mostly nephropathy surrogates ⇨ ↑ major hypoglycemia NNH=83/5yrs
VADT[15] most had CV hx age 60; 5.6yrs ***A1C: 6.9 vs 8.4***	⇨ no difference in major clinical outcomes* at 5.6yrs ⇨ ↑serious adverse events NNH=15/5.6yrs⇨ e.g. dyspnea, hypoglycemia, edema, weakness, N&V, infection… ⇨ ↑ major hypoglycemia NNH=83/5.6yrs
ACCORD[9] 35% CV hx age 62; 3.5yrs ***A1C: 6.4 vs 7.5***	⇨↑ all-cause death with intensive Tx NNH=95/3.5yrs (some macrovascular benefit but outweighed by↑death) ⇨↑ major hypoglycemia NNH=9/3.5yrs

no RCTs studying the effect of intensive glycemic control have included frail elderly
* major clinical outcomes include CV death, MI, stroke, end-stage renal disease, blindness
A1C=Hemaglobin A1C, BG=Blood glucose, CKD=Chronic kidney disease, CV=Cardiovascular, FBG=fasting BG, HF=Heart failure, hx=History, LTC=Long-term care, MI=Myocardial infarction, NNH=NNT for 1 extra person to be harmed, NNT=Number needed to treat for 1 additional person to benefit, PP=Postprandial, RCT=Randomized controlled trial, T2DM=Type 2 diabetes mellitus, Tx=Treatment, yrs=Years

Table 2: Comparison Of Guidelines/Reviews for Glycemic Targets in the Frail Elderly & Key Observations

	FBG	PPBG	A1C %
1) AGS[2,16] American Geriatric Society	-	-	<8
2) VA[4] Veterans Affairs (USA)	-	-	8-9
3) BGS British Geriatric Society	-	-	<8.5
4) European[17] Diabetes Working Party for Older People	7.6-9$_{mmol/L}$		7.6-8.5
5) Meneilly[18] **Canadian** Journal of Diabetes	<10$_{mmol/L}$	<14$_{mmol/L}$	<8.5
CDA[1] Canadian Diabetes Association -targets for healthy adults (General comment re "elderly" in text box)	4-7 $_{mmol/L}$	5-10$_{mmol/L}$	≤7

Also note need for less stringent targets in elderly to avoid hypoglycemia & symptoms of hyperglycemia.

- **Individualize glycemic targets for the frail elderly**
  - ⇨ Consider life expectancy, comorbidity, other therapy, etc.[3,4]
  - ⇨ Avoid hypoglycemic episodes (*do no harm*).
  - ⇨ An A1C of <8% - 8.5% (& even up to 9%) may be suitable for most frail elderly with comorbidities & limited life expectancy.
  - ⇨ Avoid random BG <7$_{mmol/L}$ if high hypoglycemia risk.
  - ⇨ Random BG of 7-14$_{mmol/L}$ may be reasonable, but individualize.

{CDA guidelines lack adequate guidance on glycemic targets for the frail elderly. For guidance on individualization, see Appendix A, B & reference 3.[3]}

Table 3: Drug Selection Considerations in Elderly Patients with T2DM see also related charts in RxFiles in RxFiles Drug Comparison Charts book.

Metformin (MF)	◆MF is suitable for most elderly with reasonable renal function (except possibly with very lean older adult where insulin resistance is not an issue). Adjust dose for renal function! Current Canadian and American Guidelines suggest to avoid if CrCl <30$_{ml/min}$ due to risk of lactic acidosis; however, it is rational to have some flexibility with this suggested cut-off. [1,2,20] Given the outcome benefits seen with metformin, and the rare and controversial concern of its association with lactic acidosis, it is sometimes used cautiously in patients with even lower renal function. [See RxFiles Metformin Q&A.][20] Alternative drugs carry their own risks (hypoglycemia with SUs; edema, weight gain, HF & fractures with TZDs) and often less evidence of benefit and safety in this population.
Sulfonylurea (SU) - gliclazide DIAMICRON - glyburide DIABETA - tolbutamide ORINASE	◆May be used but increase risk of hypoglycemia. Start with low dose, titrate carefully & avoid max doses. ◆Often have limited usefulness in those with long history T2DM due to limited β-cell function ◆Gliclazide may be a preferred SU for elderly.[1] It may cause less hypoglycemia than glyburide although this evidence is derived from studies with the regular formulation. It is unknown if this advantage applies if using the long acting (MR) form, or when glycemic lowering is being less aggressively pursued. ◆Repaglinide may be useful for patients who have varying appetite/meal consumption as the dose may be held or delayed if necessary. However, for most long-term care facilities, food and activity are usually predictable.
Insulin - lispro HUMALOG - aspart NOVORAPID - glulisine APIDRA - regular HUM R, NOVOLIN TORONTO - intermediate HUM N, NOVOLIN NPH - premixed NOVOLINs, HUMALOGs, NOVOMIX 30 - detemir LEVEMIR - glargine LANTUS	◆Basal & premixed insulin is often useful due to the predictable mealtimes and activity levels common in LTC. However, if patient is ill or not eating, will need to adjust dose or use only basal insulin. ◆Multiple daily injection regimens may be OK in some, but need to consider ability of patient or caregivers to administer 4-5 injections daily. ◆Insulin glargine potentially associated with less nocturnal and less severe hypoglycemia. ◆Avoid sliding scale insulin given reactive approach & high risk of hypoglycemia. Use of a basal/bolus regimen has the advantage of being proactive, yet allowing for flexibility.
Incretin related - DPP-4 inhibitors - GLP-1 agonists	◆These agents have limited usefulness due to limited β-cell function, high cost, and lack of outcome data. However, some long-term safety concerns (e.g. association with cancer) are not an issue in those with limited life expectancy. Hypoglycemia risk is less than that seen with a SU or insulin.
Pioglitazone a TZD	◆Less useful due to concerns (↑ HF, edema, weight gain, fractures); but can be used in renal dysfunction.

Appendices

A) ADA 2012 statements regarding less stringent A1C goals for some.[2,21]

1) Less stringent A1C goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and extensive comorbid conditions and for those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. 2) New Release April 2012: …"<8 or even slightly higher…"[21]

B) The VA/DoD (Veterans Affairs $_{USA}$) approach to individualizing A1C targets [4]

Adapted directly from the VA/DoD Guidelines [4]

VA/DoD Approach to the Determination of Target HbA_1c Level for VA Sites [(A)(B)]

Major Comorbidity (d) Or Physiologic Age	Microvascular Complications		
	Absent or Mild (a)	Moderate (b)	Advanced (c)
Absent >10 years of life expectancy	<7%	<8%	8-9%*
Present (e) 5 to 10 years of life expectancy	<8%	<8%	8-9%*
Marked (f) <5 years of life expectancy	8-9%*	8-9%*	8-9%*

A. Based upon the DCCT referent standard. Clinicians need to evaluate the methodology used at their site.

B. Reflects a "goal" over time. Intensification of therapy should be undertaken based upon individual clinical circumstances and treatment option.

(a) Mild microvascular disease is defined by early background retinopathy, and/or microalbuminuria, and/or mild neuropathy.

(b) Moderate microvascular disease is defined by pre-proliferative (without severe hemorrhage, intra-retinal microvascular anomalies [IRMA], or venous bleeding) retinopathy or persistent, fixed proteinuria (macroalbuminuria) and/or demonstrable peripheral neuropathy (sensory loss).

(c) Advanced microvascular disease is defined by severe non-proliferative (with severe hemorrhage, IRMA, or venous bleeding), or proliferative retinopathy and/or renal insufficiency (serum creatinine level > 2.0 mg/dL $_{or\ 176.8umol/L\ in\ SI\ units}$), and/or insensate extremities or autonomic neuropathy (e.g., gastroparesis, impaired sweating, or orthostatic hypotension).

(d) Major co-morbidity includes, but is not limited to, any or several of the following active conditions: significant cardiovascular disease, severe chronic kidney disease, severe chronic obstructive pulmonary disease, severe chronic liver disease, recent stroke, and life-threatening malignancy.

(e) Major co-morbidity is present, but is not end-stage and management achievable.

(f) Major co-morbidity is present and is either end-stage or management is significantly challenging.

* Further reductions may be appropriate, balancing safety and tolerability of therapy.

Remember, A1C accuracy is diminished by factors such as anemia (accuracy ↑ with Hg >100; accuracy ↓↓ with Hg <80).
See: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Diabetes-Insulin-Managment(Tool.pdf

References available next page, or online at www.RxFiles.ca

[1] Canadian 2008 Guidelines (Sept 2008): http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
(Bhattacharyya OK, Estey EA, Cheng AY; Canadian Diabetes Association 2008. Update on the Canadian Diabetes Association 2008 clinical practice guidelines. Can Fam Physician. 2009 Jan;55(1):39-43.)

[2] American Diabetes Association. Executive Summary: Standards of medical care in diabetes – 2012. Diabetes Care 2012;35:S4-S10. http://care.diabetesjournals.org/content/35/Supplement_1/S4.full

[3] Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. Ann Intern Med. 2011 Apr 19;154(8):554-9. Accessed 28 March 2012 online at http://www.annals.org/content/154/8/554.full.

[4] VA/DoD Clinical Practice Guideline for the Management of Diabetes Mellitus. August 2010. Accessed online at: http://www.healthquality.va.gov/diabetes/DM2010_FUL-v4e.pdf

[5] Diabetes Guidelines for Elderly Residents in Long Term Care in Nova Scotia - 2010. Accessed online at http://diabetescareprogram.ns.ca/pdf/LTC/GuideBackground.pdf

[6] COMPUS Optimal Therapy Report: Systematic Review of Use of Blood Glucose Test Strips for the Management of Diabetes Mellitus. May 2009. Accessed Feb 04, 2010 at http://www.cadth.ca/media/pdf/BGTS_SR_Report_of_Clinical_Outcomes.pdf

[7] RxFiles Group. Self-Monitoring of Blood Glucose (SMBG) in Type 2 Diabetes (T2DM). Accessed Apr 03, 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-SMBG.pdf.

[8] Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, Wetterslev J. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2011 Jun 15;(6):CD008143.

[9] **ACCORD** Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2545-59.

[10] Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. Diabetes Care. 2011 Jun;34(6):1329-36.

[11] Shurraw S, Hemmelgarn B, Lin M, Majumdar SR, Klarenbach S, Manns B, Bello A, James M, Turin TC, Tonelli M; Alberta Kidney Disease Network. Association between glycemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease: a population-based cohort study. Arch Intern Med. 2011 Nov 28;171(21):1920-7.

[12] UKPDS-33 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (**UKPDS 33**). (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53.

[13] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (**UKPDS 34**). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65.

[14] **ADVANCE** Patel A; **ADVANCE** Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40.

[15] **VADT** Duckworth W, Abraira C, Moritz T, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. N Engl J Med. 2008 Dec 17.

[16] Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc. 2003 May;51(5 Suppl Guidelines):S265-80.

[17] Sinclair AJ, Paolisso G, Castro M, Bourdel-Marchasson I, Gadsby R, Rodriguez Mañas L; European Diabetes Working Party for Older People. European Diabetes Working Party for Older People 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. Diabetes Metab. 2011 Nov;37 Suppl 3:S27-38.

[18] Meneilly G. Diabetes in the Elderly. Canadian J of Diabetes. March 2011. Accessed 02 Apr 2012 online at http://www.diabetes.ca/documents/for-professionals/CJD--March_2011--GMeneilly.pdf

[19] RxFiles Drug Comparison Charts. Saskatoon Health Region. Editors: Jensen B, Regier L. Accessible by subscription online at www.RxFiles.ca (or in book form – 8th Ed.)

[20] Breault R, Regier L, Jensen B. Metformin: Precautions with Renal Impairment, Hepatic Disease and Heart Failure. RxFiles Q&A, Oct 2008. Accessed online at: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Metformin-LacticAcidosis-QandA.pdf

[21] Inzucchi S, Bergenstal R, Buse J, Diamant M, Ferrannini E, Nauch M, et al. Management of Hyperglycemia in Type 2 Diabetes: a patient-centred approach. Diabetes Care, Accessed April 19, 2012 online at http://care.diabetesjournals.org/content/early/2012/04/17/dc12-0413.full.pdf.