Treating the elderly patients with type 2 diabetes mellitus

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Declaration of interest

- Associate Editor of *Angiology*
- Associate Editor of *Clinical Lipidology*
- Associate Editor of the *Hellenic College of Treatment of Atherosclerosis for The Open Cardiovascular Medicine Journal*
- Section Editor of *Archives of Medical Science*
- Book Review and News and Views Editor of *Current Vascular Pharmacology*
- Editorial Board Member of *Metabolism Clinical and Experimental* and *Current Medical Research and Opinion*
Declaration of interest

- NK has given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, Astra-Zeneca, Boehringer Ingelheim, Galenica, MSD, Novartis, Novo Nordisk, Sanofi and WinMedica
Why discuss treatment in the elderly?
Elderly?

- Oxford dictionary: following middle-age, the age of pension (!)

- «The span of time between retirement and the beginning of age-imposed physical, emotional, and cognitive limitations»

- Clinical trials: > 65 years
Aging of the population

Number of people aged 60 or over:
World, developed and developing countries, 1950-2050


Note: The group of "developed countries" corresponds to the "more developed regions" of the World Population Prospects: The 2010 Revision, and the group "developing countries" corresponds to the "less developed regions" of the same publication.
An aging world
Fertility rates projected to go down and life expectancy on the rise, ageing populations will become a future challenge.

Population by age group and sex
Millions

Regional life expectancy

Median age of world population

Source: UN Population Aging Development 2009
Figure 2.3
Changes in the Population Pyramid

1950

- 4.9% 65 and over
- 59.6 15-64
- 35.4 0-14

2010*

- Males 23.1%
  - 63.7
- Females
  - 39.6%
  - 51.8

2050 (Projection)

- 8.6

Source: Statistics Bureau, MIC; Ministry of Health, Labour and Welfare.
Why discuss T2DM in the elderly?
T2DM: A Worldwide Epidemic

Prevalence estimates of diabetes mellitus 2025

IDF
- Diabetes currently affects 371 million people worldwide
- It is expected to affect 552 million by 2030

IDF = International Diabetes Federation; T2DM = type 2 diabetes mellitus

The prevalence of Diabetes increases with age

<table>
<thead>
<tr>
<th>Age</th>
<th>% of Canadians with diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 - 44 years</td>
<td>4%</td>
</tr>
<tr>
<td>50-54 years</td>
<td>8.40%</td>
</tr>
<tr>
<td>60-64 years</td>
<td>14.20%</td>
</tr>
<tr>
<td>70-74 years</td>
<td>21.30%</td>
</tr>
</tbody>
</table>

The proportion of people diagnosed with diabetes generally increases with age. The sharpest increase in the prevalence occurs after the age of 40. The above table shows figures from 2008/2009 provided by PHAC.
Prevalence of T2DM in Canada

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>1-19</th>
<th>20-24</th>
<th>25-29</th>
<th>30-34</th>
<th>35-39</th>
<th>40-44</th>
<th>45-49</th>
<th>50-54</th>
<th>55-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70-74</th>
<th>75-79</th>
<th>80-84</th>
<th>≥85 Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>0.3</td>
<td>0.7</td>
<td>1.1</td>
<td>1.8</td>
<td>2.7</td>
<td>3.7</td>
<td>5.1</td>
<td>7.4</td>
<td>10.7</td>
<td>14.2</td>
<td>17.8</td>
<td>21.3</td>
<td>23.1</td>
<td>23.4</td>
<td>19.9  6.4</td>
</tr>
<tr>
<td>Males</td>
<td>0.3</td>
<td>0.7</td>
<td>0.9</td>
<td>1.5</td>
<td>2.6</td>
<td>4.1</td>
<td>6.2</td>
<td>9.5</td>
<td>14.0</td>
<td>19.1</td>
<td>23.7</td>
<td>27.1</td>
<td>28.5</td>
<td>27.8</td>
<td>23.2  7.2</td>
</tr>
<tr>
<td>Total</td>
<td>0.3</td>
<td>0.7</td>
<td>1.0</td>
<td>1.6</td>
<td>2.6</td>
<td>4.0</td>
<td>5.6</td>
<td>8.4</td>
<td>12.3</td>
<td>16.6</td>
<td>20.7</td>
<td>24.1</td>
<td>25.5</td>
<td>25.2</td>
<td>21.0  6.8</td>
</tr>
</tbody>
</table>
Postprandial glucose values are higher in the elderly, as both phases of insulin secretion decrease with age. Therefore, we rather underestimate T2DM prevalence with almost one third of the elderly with diabetes being undiagnosed.
Pathophysiology of T2DM in the elderly
Glucose Intolerance of Aging

**Diabetes Risk Factors in Aging**

- Decreased physical activity
- Increased adiposity
- Age effects on insulin action
- Medications
  - antihypertensive (diuretics, beta-blockers, CCB)
  - antipsychotics (olanzapine and clozapine)
  - antidepressants, steroids and statins
- Genetics
- Coexisting illness
- Age effects on β cells

**Diagram Flow**

1. Insulin resistance
2. Decreased insulin secretion
3. Impaired adaptation: No ↑ insulin
4. Progression to IGT and type 2 diabetes

Chang AM et al. Am J Physiol Endocrinol Metab 2003; E7-12
Type 2 Diabetes Mellitus and the Elderly: An Update on Drugs Used to Treat Glycaemia

Asimina Mitrakou, Niki Katsiki and Nebojsa M Lalic

Graphical abstract: Pathophysiology of type 2 diabetes mellitus in the elderly

- Menopause
- Leptin resistance
- Physical inactivity
- Drugs that adversely affect glucose metabolism (i.e. antipsychotics, antihypertensive, steroids and statins)
- Increased insulin resistance
- Decreased insulin secretion (both first and second phase)
- Lipotoxicity due to ectopic fat distribution in the liver, muscle and pancreas in overweight individuals
- Sarcopenia in lean individuals
- Impaired pancreatic islet function
Glucose increases gradually after the age of 30-40 years

- Every 10 years:
  - FBG increases by about 1 mg/dl
  - PPG increase by 6-13 mg/dl

Davidson MB. Metabolism 1979
Other characteristics of the elderly...

- More frequent complications

**Table 1**

<table>
<thead>
<tr>
<th>Complication of Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Complications</strong></td>
</tr>
<tr>
<td>- Presenting Symptoms:</td>
</tr>
<tr>
<td>Fatigue, polyuria, blurry vision, polydipsia</td>
</tr>
<tr>
<td>- Infection(s)</td>
</tr>
<tr>
<td>- Diabetic ketoacidosis (DKA)</td>
</tr>
<tr>
<td>- Hyperglycemic, hyperosmolar, non-ketotic coma (HHNKC)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

[www.healthplexus.net/article/medication-use-geriatric-population](http://www.healthplexus.net/article/medication-use-geriatric-population)
Other characteristics of the elderly...

- Increased all-cause mortality

Verona Study

Figure 8.2 Mortality rates from all causes in the Verona Type 2 diabetic population, as compared with the general population of Verona, according to sex and age

Muggeo M et al 2001
### Epidemiology of geriatric syndromes among older adults with diabetes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Prevalence or Incidence</th>
<th>Risk Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls</td>
<td>Incidence of recurrent falls over 3 years among persons age &gt;65 years: 30.6% diabetes group vs. 19.4% non diabetes group (25).</td>
<td>Incidence: HR 1.67 (1.11–2.51) (25).</td>
</tr>
<tr>
<td>Vision Loss</td>
<td>Prevalence of self-reported vision impairment among persons age &gt; 60 years: 34.2% diabetes group vs. 21.4% non diabetes group (12).</td>
<td>Prevalence: OR 1.44 (1.11–2.17) (31).</td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>Prevalence of hearing loss among cohort with mean age 70 years: 50% diabetes group vs. 38.2% non diabetes group (31).</td>
<td>Prevalence: OR 1.28 (1.11–1.48) (37).</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td>Prevalence of weekly incontinence among women: 35.4% diabetes group vs. 25.7% non diabetes group (33). Prevalence of incontinence among men with a mean age 76 years: 21.7% diabetes group vs. 13.9% non diabetes group (35).</td>
<td>Incidence: HR 2.05 (1.41–2.97) (63).</td>
</tr>
<tr>
<td>Cognitive impairment and Dementia</td>
<td>Prevalence of cognitive impairment in cohort age &gt;65 years: 3.4% diabetes group vs. 2.8% non diabetes group (38). Prevalence combined cognitive impairment and dementia in a cohort age &gt;75 years with diabetes: 24.1% (37). Incidence of cognitive impairment and dementia in a cohort age &gt;60 years with 6.5 years mean follow up: 13.6% treated diabetes group vs. 8% non diabetes group (63).</td>
<td>Incidence: HR 3.63 (1.41–9.33) for developing frailty among women with baseline A1C &gt;8% compared to A1C&lt;5.5% (55). Incidence: HR 1.15 (1.02–1.31) for incident frailty per SD increase in HOMA-IR (56).</td>
</tr>
<tr>
<td>Depression</td>
<td>Incidence of depression among persons age 70-79 years over mean 5.9 years: 23.5% diabetes group vs. 19% non diabetes group (42). Prevalence depression in cohort age &gt;65 years: 12.2% diabetes group vs. 9.3% non diabetes group (37).</td>
<td>Prevalence: OR 1.35 (1.25–1.46) (37).</td>
</tr>
<tr>
<td>Frailty</td>
<td>Prevalence of frailty among women aged 70–79 years: 16.1% for group with A1C ≥ 6.5% vs. 9.4% for group with A1C &lt; 6.5% (64)</td>
<td>Incidence: HR 3.63 (1.41–9.33) for developing frailty among women with baseline A1C &gt;8% compared to A1C&lt;5.5% (55). Incidence: HR 1.15 (1.02–1.31) for incident frailty per SD increase in HOMA-IR (56).</td>
</tr>
</tbody>
</table>

COMPLEX INTERACTIONS in ELDERLY PATIENTS with T2DM

↑ Morbidity and Functional Disability

↓ COMPLIANCE

↓ QUALITY of LIFE

↑ HYPOGLYCEMIA

↑ MORBIDITY
↑ MORTALITY

CAD
CVD
PVD
NEUROPATHY
RETINOPATHY
NEUROPATHY

COGNITIVE DYSFUNCTION
DEPRESSION
POLYPHARMACY
FALLS
URINARY INCONTINENCE
PHYSICAL DISABILITY

T2DM
Clinical features of T2DM in the elderly
Clinical presentation of T2DM in the elderly

Type 2 DM may present to the clinician in one of 4 ways:
- Classical symptoms;
- Incidental diagnosis;
- Complications of diabetes mellitus;
- Hyperosmolar nonketotic coma.

Symptoms of type 2 DM that may be seen at diagnosis are thirst, polyuria, fatigue and malaise, infections (especially genital candidiasis), and blurred vision.

Campbell IW Value Health 2000;3:3-6
Treatment of T2DM in the elderly
Why treat T2DM in the elderly?

- Prevention of micro- and macrovascular diabetic complications
- Improvement of quality of life
- Increase survival
**Table 2**
Areas of clinical importance and targets for concerted action: type 2 diabetes mellitus in older people.

| Importance of functional and vascular risk assessment |
| Relationship between functional outcome and metabolic control |
| Management of diabetes in primary care |
| Detection of cognitive impairment and depression |
| Management of specific major complications: e.g. foot disease, visual loss, hypoglycaemia, pain |
| Care Home diabetes |
| Ethical and moral aspects of treatment |
Hypoglycaemia
Hypoglycaemia in the elderly

- **Elderly T2DM patients are prone to hypoglycaemia** due to old age (characterized by defective mechanisms of response to hypoglycaemia and lack of hypoglycaemia awareness), polypharmacy and co-morbidities (such as renal impairment).

- **Malnutrition** and the use of insulin and/or sulfonylureas (SUs), and especially glyburide, further increase the risk of hypoglycaemia.

- Hypoglycaemia may present with **non-specific symptoms** in the elderly, thus hampering the early diagnosis of a hypoglycaemic episode.

- **Strict glycaemic control** in older patients with T2DM on SUs or insulin may lead to **severe hypoglycaemic episodes** requiring hospitalization. In contrast, other antidiabetic drugs have a low risk of hypoglycaemia such as **metformin, pioglitazone and incretin-based therapies**.

Older patients have less perception of hypos

**WHY??????**

1. Attention to hypoglycemic symptoms may be reduced by depression, cognitive dysfunction or other chronic conditions.

2. Many elderly patients have limited knowledge about the symptoms of hypoglycemia; knowledge of diabetes is essential for symptom recognition.

Severe hypoglycemia accounts for almost 20% of all hospitalizations for T2DM in the elderly.

- Severe hypoglycaemia: 17%
- Chronic complications of diabetes: 17%
- Acute cardiovascular events: 13%
- Intercurrent illness: 14%
- Decompensated diabetes: 39%

T2DM = type 2 diabetes mellitus.
Hypoglycaemia has been linked to:

- **increased morbidity** (e.g. CVD, falls and dementia) and **mortality**, especially in the elderly; potential mechanisms include electrophysiological and proinflammatory changes as well as increased oxygen demand and myocardial workload (due to the activation of the sympathoadrenal nervous system)

Large DM outcome trials suggested that severe hypoglycaemia may predict CVD events

- **worse outcomes** after a fall (i.e. head injuries and fractures) and a higher rate of use of emergency and long-term health care settings
- **cognitive and physical dysfunction, poor quality of life, less adherence to drug therapy** and increased frailty with poor long-term outcomes
- **worsening of glycaemic control**
Hypoglycaemia in the elderly

- **Strongest predictors** of severe hypoglycaemia in the elderly are *advanced age, recent hospitalisation and polypharmacy*

- **Lifestyle measures and careful selection of antidiabetic drugs** to prevent hypoglycaemia

- **Education** *is the key to preventing recurrent or severe hypoglycaemia* (close coordination of care between the patient, physician and all other healthcare providers in identifying the cause of hypoglycaemia in elderly patients, treating hypoglycaemia and preventing further episodes)

- **Prevention of hypoglycaemia** has the potential *to improve psychosocial aspects* of elderly health, including enhanced quality of life, boosted confidence, *improved compliance* with antidiabetic regimens and avoidance of long-term complications

Chelliah A et al Drugs Aging 2004; 21: 511 - 30
Standards of Medical Care in Diabetes
Older Adults

- 26% of patients aged >65 have diabetes
- Older adults have higher rates of premature death, functional disability & coexisting illnesses
- At greater risk for polypharmacy, cognitive impairment, urinary incontinence, injurious falls & persistent pain
- Screening for complications should be individualized and periodically revisited
- At higher risk for depression
Glycemic goals for some older adults might be relaxed but hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all patients.

Hypoglycemia should be avoided in older adults with diabetes.

It should be screened for and managed by adjusting glycemic targets and pharmacologic interventions.

Recommendations: Older Adults

American Diabetes Association Standards of Medical Care in Diabetes. Older adults. Diabetes Care 2016; 39 (Suppl. 1): S81-S85
Recommendations: Older Adults

- Patients with DM in long-term care facilities need careful assessment to establish a glycemic goal & to make appropriate choices of glucose-lowering agents

- Other CV risk factors should be treated in older adults with consideration of the time frame of benefit and the individual patient
  - Treatment of HTN is indicated in virtually all older adults
  - Lipid-lowering and aspirin therapy may benefit those with life expectancy at least equal to the time frame of primary or secondary prevention trials
Recommendations: Older Adults

- When palliative care is needed, strict BP control may not be necessary and withdrawal of therapy may be appropriate.

- Intensity of lipid management can be relaxed and withdrawal of lipid-lowering therapy may be appropriate.

- Screening for complications should be individualized, but attention should be paid to complications that would lead to functional impairment.
Recommendations: Older Adults

- Screening for geriatric syndromes may be appropriate in older adults with limitations in basic and instrumental activities of daily living.

- Older adults with DM should be considered a high-priority population for depression screening and treatment.

- Overall comfort, prevention of distressing symptoms & preservation of quality of life and dignity are primary goals for diabetes management at the end of life.
Recommendations: Hypertension/Blood Pressure Control

- Patients with confirmed BP >140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals.

- In older adults, pharmacological therapy to achieve treatment goals of <130/70 are not recommended.

- Lifestyle intervention including:
  - Weight loss if overweight
  - DASH-style diet including reduced sodium, increased potassium
  - Moderation of alcohol intake
  - Increased physical activity
Treatment:

- Pharmacological therapy for patients with diabetes and HTN includes:
  - either an **ACE inhibitor or angiotensin II receptor blocker**
  - if one class is not tolerated, substitute the other

- **Multiple drug therapy** (two or more agents at maximal doses) generally required to achieve BP targets
# Recommendations for Statin Treatment in People with Diabetes

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk Factors</th>
<th>Statin Intensity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factor(s)**</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td>40–75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ACS &amp; LDL &gt;50 who can’t tolerate high dose statin</td>
<td>Moderate + ezetimibe</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ACS &amp; LDL &gt;50 who can’t tolerate high dose statin</td>
<td>Moderate + ezetimibe</td>
</tr>
</tbody>
</table>

* In addition to lifestyle therapy. ** ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71
Consider therapy with statin and fenofibrate for men with both trigs $\geq 204 \text{ mg/dL (2.3 mmol/L)}$ and HDL $\leq 34 \text{ mg/dL (0.9 mmol/L)}$.

Combination therapy (statin/niacin) hasn’t demonstrated additional CV benefit over statins alone, may raise risk of stroke & is not generally recommended.
Consider aspirin therapy (75–162 mg/day)

- As a **primary prevention** strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%)
- Includes **most men or women with diabetes age ≥50 years** who have **at least one additional major risk factor**, including:
  - Family history of premature ASCVD
  - Hypertension
  - Smoking
  - Dyslipidemia
  - Albuminuria
Recommendations: Antiplatelet Agents

- Use aspirin therapy (75–162 mg/day) as secondary prevention in those with diabetes and history of ASCVD

- For patients w/ ASCVD & aspirin allergy, clopidogrel (75 mg/day) should be used

- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome
## Approach to the Management of Hyperglycemia

### Patient/Disease Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low</th>
<th>High</th>
<th>More Stringent</th>
<th>A1C 7%</th>
<th>Less Stringent</th>
<th>Usually Not Modifiable</th>
<th>Potentially Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks associated with hypoglycemia &amp; other drug adverse effects</td>
<td>low</td>
<td>high</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Duration</td>
<td>newly diagnosed</td>
<td>long-standing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>short</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>absent</td>
<td>Few/mild</td>
<td>severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>Few/mild</td>
<td>severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient attitude &amp; expected treatment efforts</td>
<td>highly motivated, adherent, excellent self-care capabilities</td>
<td>less motivated, nonadherent, poor self-care capabilities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resources &amp; support system</td>
<td>readily available</td>
<td>limited</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# Treatment targets for the elderly

## Table 10.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

<table>
<thead>
<tr>
<th>Patient characteristics/health status</th>
<th>Rationale</th>
<th>Reasonable A1C goal†</th>
<th>Fasting or preprandial glucose (mg/dL)</th>
<th>Bedtime glucose (mg/dL)</th>
<th>Blood pressure (mmHg)</th>
<th>Lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (few coexisting chronic illnesses, intact cognitive and functional status)</td>
<td>Longer remaining life expectancy</td>
<td>&lt;7.5%</td>
<td>90–130</td>
<td>90–150</td>
<td>&lt;140/90</td>
<td>Statin unless contraindicated or not tolerated</td>
</tr>
<tr>
<td>Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)</td>
<td>Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk</td>
<td>&lt;8.0%</td>
<td>90–150</td>
<td>100–180</td>
<td>&lt;140/90</td>
<td>Statin unless contraindicated or not tolerated</td>
</tr>
<tr>
<td>Very complex/poor health (long-term care or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)</td>
<td>Limited remaining life expectancy makes benefit uncertain</td>
<td>&lt;8.5%†</td>
<td>100–180</td>
<td>110–200</td>
<td>&lt;150/90</td>
<td>Consider likelihood of benefit with statin (secondary prevention more so than primary)</td>
</tr>
</tbody>
</table>
Multiple Classes of Medications for T2DM

- Insulin Sulfonylureas Meglitinides
- GLP-1 RA DPP-4 inhibitors
- SGLT-2 inhibitors
- Metformin

Hyperglycemia

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased HGP
- Decreased Glucagon Secretion
- Decreased Glucose Reabsorption
- Decreased Glucose Uptake

Decreased Incretin Effect

Increased Lipolysis

Increased Glucose Reabsorption
**Start With Monotherapy Unless:**

- HbA1c level is \(\geq 9\%\), consider dual therapy.
- HbA1c level is \(\geq 10\%\), blood glucose level is \(\geq 300\ \text{mg/dL}\), or patient is markedly symptomatic, consider combination injectable therapy.

### Monotherapy

<table>
<thead>
<tr>
<th></th>
<th><strong>Metformin</strong></th>
<th><strong>Lifestyle Management</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY</strong></td>
<td>High</td>
<td></td>
</tr>
<tr>
<td><strong>Hypoglycemia Risk</strong></td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Neutral/loss</td>
<td></td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>Gl/lactic acidosis</td>
<td></td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after approximately 3 mo of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference; choice dependent on a variety of patient- and disease-specific factors).

### Dual Therapy

<table>
<thead>
<tr>
<th></th>
<th><strong>Metformin +</strong></th>
<th><strong>Lifestyle Management</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylurea</strong></td>
<td>High</td>
<td>Highest</td>
</tr>
<tr>
<td><strong>Thiazolidinedione</strong></td>
<td>High</td>
<td>Highest</td>
</tr>
<tr>
<td><strong>DPP-4-i</strong></td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td><strong>SGLT-2-i</strong></td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td><strong>GLP-1-RA</strong></td>
<td>High</td>
<td>Gain</td>
</tr>
<tr>
<td><strong>Insulin (basal)</strong></td>
<td>Highest</td>
<td>Hypoglycemia</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after approximately 3 mo of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference; choice dependent on a variety of patient- and disease-specific factors).

### Triple Therapy

<table>
<thead>
<tr>
<th></th>
<th><strong>Metformin +</strong></th>
<th><strong>Lifestyle Management</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylurea +</strong></td>
<td>High</td>
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If HbA1c target not achieved after approximately 3 mo of triple therapy and patient on oral combination, move to basal insulin or GLP-1-RA; if the patient is on GLP-1-RA, add basal insulin; or if the patient is on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. Metformin therapy should be maintained, whereas other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).
**Start With Monotherapy Unless:**

- HbA1c level is ≥9%, consider dual therapy.
- HbA1c level is ≥10%, blood glucose level is ≥300 mg/dL, or patient is markedly symptomatic, consider combination injectable therapy.

### Monotherapy

<table>
<thead>
<tr>
<th><strong>Metformin</strong></th>
<th><strong>Lifestyle Management</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>High</td>
</tr>
<tr>
<td><strong>Hypoglycemia Risk</strong></td>
<td>Low</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Neutral/loss</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>GI/lactic acidosis</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>Low</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after approximately 3 mo of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference; choice dependent on a variety of patient- and disease-specific factors):

### Dual Therapy

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<thead>
<tr>
<th><strong>Metformin +</strong></th>
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<tbody>
<tr>
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</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>High</td>
</tr>
<tr>
<td><strong>Hypoglycemia Risk</strong></td>
<td>Moderate risk</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Gain</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
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<tr>
<th><strong>DPP-4-I</strong></th>
<th><strong>SGLT-2-I</strong></th>
<th><strong>GLP-1-RA</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>Hypoglycemia Risk</strong></td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Gain</td>
<td>Gain</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>GI, dehydration, and fractures</td>
<td>GI</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after approximately 3 mo of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference; choice dependent on a variety of patient- and disease-specific factors):

### Triple Therapy

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If HbA1c target not achieved after approximately 3 mo of triple therapy and patient on oral combination, move to basal insulin or GLP-1-RA; if the patient is on GLP-1-RA, add basal insulin; or if the patient is on optimally titrated basal insulin, add GLP-1-RA or mealttime insulin. Metformin therapy should be maintained, whereas other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).
**Initiate Basal Insulin**
*Usually with metformin +/- other noninsulin agent*

- **Start**: 10 U/day or 0.1–0.2 U/kg/day
- **Adjust**: 10–15% or 2–4 units once or twice weekly to reach FBG target
- **For hypo**: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10–20%  

### If A1C not controlled, consider combination injectable therapy

#### Add 1 rapid-acting insulin injection before largest meal

- **Start**: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount
- **Adjust**: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
- **For hypo**: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

- **If A1C not controlled, advance to basal-bolus**

#### Add GLP-1 RA

- **If not tolerated or A1C target not reached, change to 2 injection insulin regimen**

#### Change to premixed insulin twice daily (before breakfast and supper)

- **Start**: Divide current basal dose into ½ AM, ½ PM or ⅛ AM, ⅛ PM
- **Adjust**: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
- **For hypo**: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

- **If A1C not controlled, advance to 3rd injection**

#### Add ≥2 rapid-acting insulin injections before meals (‘basal-bolus’)  

- **Start**: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount
- **Adjust**: ↑ dose(s) by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
- **For hypo**: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

- **If goals not met, consider changing to alternative insulin regimen**

#### Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)

- **Start**: Add additional injection before lunch
- **Adjust**: ↑ doses by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
- **For hypo**: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

- **If goals not met, consider changing to alternative insulin regimen**
European Diabetes Working Party for Older People 2011
Clinical Guidelines for Type 2 Diabetes Mellitus. Executive Summary

A Report of the European Diabetes Working Party for Older People (EDWPOP) Revision Group
on Clinical Practice Guidelines for Type 2 Diabetes Mellitus

Recommended glucose targets:
- Fasting glucose range = 7.6-9.0 mmol/L
- HbA1c range = 7.6-8.5%

Frailty criteria:
- Care home residency
- Significant cognitive decline
- Major lower limb mobility disorder
- History of disabling stroke

3-6 months dietary and lifestyle advice

Not achieving agreed glucose targets

Metformin contraindicated in renal/hepatic dysfunction, respiratory/heart failure, anorexia, gastrointestinal disease

Metformin

Failure to achieve glucose targets

Further weight loss with a GLP-1 agonist may have adverse consequences in a frail patient

Metformin + DPPIV inhibitor

Failure to achieve glucose targets

Frailty associated with increased hypoglycaemia risk: caution when using insulin or sulphonylurea therapy

Metformin + insulin

Alternative treatments:
- Metformin + lower-risk SU
- Metformin + GLP-1 agonist

Alternative treatments:
- DPPIV inhibitors, or
- Lower risk sulphonylureas (SU)
- Glinides

Alternative treatments:
- Low risk SU + insulin
Metformin

**HbA1c reduction: 1-2%**

- **Advantages**
  - Weight neutral
  - Low cost
  - No hypos

- **Disadvantages**
  - GI side effects
  - Lactic acidosis
  - **Contraindications:** heart, liver and renal failure (GFR < 30 ml/min)
Acarbose

HbA1c reduction: 0.5-0.8%

- **Advantages**
  - Weight neutral
  - Improvement in PPG
  - No hypos

- **Disadvantages**
  - GI side effects
  - Contraindications: renal failure (GFR < 25 ml/min)
SUs

HbA1c reduction: 1-2%

- **Advantages**
  - High efficacy
  - Low cost

- **Disadvantages**
  - Weight gain
  - Hypos
  - Ischemic preconditioning
  - **Contraindications:** renal failure (GFR < 30 ml/min)
Meglitinides

HbA1c reduction: 0.5-1.5%

- **Advantages**
  - Improvement in PPG
  - Flexibility

- **Disadvantages**
  - Hypos
  - Weight gain
  - **Contraindications**: renal failure (GFR < 15 ml/min)
Pioglitazone

HbA1c reduction: 0.5-1.4%

- **Advantages**
  - CV benefits (PROActive trial)
  - Low cost
  - No hypos

- **Disadvantages**
  - Weight gain/edema
  - Bone fractures
  - Contraindications: heart and renal failure (GFR < 5 ml/min)
DPP-4 inhibitors

HbA1c reduction: 0.5-0.8%

- **Advantages**
  - Weight neutral
  - No hypos
  - CV safety (TECOS, EXAMINE and SAVOR-TIMI trials)

- **Disadvantages**
  - Cost
  - Weight gain
  - Dose adjustment in renal failure (GFR < 50 ml/min), except for linagliptin
  - Heart failure (saxagliptin)
GLP-1 receptor agonists

HbA1c reduction: 0.5-1.0%

- **Advantages**
  - Weight reduction
  - No hypos
  - Metabolic effects
  - CV reduction (LEADER and SUSTAIN trials) - safety (EXCSEL trial)

- **Disadvantages**
  - Cost
  - Injectable
  - GI side effects
  - **Contraindications**: renal failure (GFR < 30 ml/min)
SGLT2 inhibitors

HbA1c reduction: 0.5-0.8%

- **Advantages**
  - Weight reduction
  - No hypos
  - Metabolic effects: BP, lipids, uric acid
  - CV reduction (EMPA-REG OUTCOME and CANVAS Program trials)

- **Disadvantages**
  - Cost
  - Genital infections
  - **Contraindications:** renal failure (GFR < 60 ml/min)
  - Caution: diuretics, dehydration
Insulin therapy

Basal, basal-plus, basal-bolus, premixed

- Advantages
  - Efficacy
  - Can be used in heart, liver and renal failure

- Disadvantages
  - Hypos
  - Education of the patient + care provider
  - Fear of the needle/hypos
  - Follow-up
1. Self Management Education
2. Nutrition
3. Counseling
4. Physical Activity
5. Smoking Cessation
6. Immunizations
7. Psychosocial Care
8. Medications

Effectiveness of the Mediterranean diet in the elderly

Blanca Roman¹
Laura Carta²
Miguel Ángel Martínez-González³
Lluís Serra-Majem⁴

¹Mediterranean Diet Foundation, University of Barcelona Science Park, Spain; ²Department of Biosystems and Applied Sciences, Unit of Physiology and Human Nutrition, University of Cagliari, Italy; ³Department of Epidemiology and Public Health, University of Navarra, Spain; ⁴Department of Clinical Sciences, University of Las Palmas de Gran Canaria, Spain

Abstract: The Mediterranean diet is known to be one of the healthiest dietary patterns in the world due to its relation with a low morbidity and mortality for some chronic diseases. The purpose of this study was to review literature regarding the relationship between Mediterranean diet and healthy aging. A MEDLINE search was conducted looking for literature regarding the relationship between Mediterranean diet and cardiovascular disease (or risk factors for cardiovascular disease), cancer, mental health and longevity and quality of life in the elderly population (65 years or older). A selection of 36 articles met the criteria of selection. Twenty of the studies were about Mediterranean diets and cardiovascular disease, 2 about Mediterranean diets and cancer, 3 about Mediterranean diets and mental health and 11 about longevity (overall survival) or mental health. The results showed that Mediterranean diets had benefits on risks factors for cardiovascular disease such as lipoprotein levels, endothelium vasodilatation, insulin resistance, the prevalence of the metabolic syndrome, antioxidant capacity, the incidence of acute myocardial infarction, and cardiovascular mortality. Some positive associations with quality of life and inverse associations with the risk of certain cancers and with overall mortality were also reported.
## Physical Activity Recommendations

### Adults with diabetes

**Exercise recommendations**
- \( \geq 150 \text{ min/wk} \) moderate-intensity aerobic activity (50%–70% max heart rate), spread over \( \geq 3 \text{ days/wk} \) with no more than 2 consecutive days without exercise
- **Resistance training \( \geq 2 \text{ times/wk} \) (in absence of contraindications)**
- **Reduce sedentary time**: break up \( >90 \text{ mins} \) spent sitting

**Evaluate patients for contraindications prohibiting certain types of exercise before recommending exercise program**

**Consider age and previous level of physical activity**

### Children with diabetes, prediabetes

\( \geq 60 \text{ min physical activity/day} \)

*Adults with type 2 diabetes  
†Eg. uncontrolled hypertension, severe autonomic or peripheral neuropathy, history of foot lesions, unstable proliferative retinopathy

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Type 2 Diabetes Mellitus and the Elderly: An Update on Drugs Used to Treat Glycaemia

Asimina Mitrakou, Niki Katsiki and Nebojsa M Lalic

Abstract: Type 2 Diabetes Mellitus (T2DM) and its complications are more prevalent in the elderly. As the general population worldwide is ageing, effective and safe treatment of older T2DM patients is becoming more important in clinical practice. Elderly T2DM patients should be carefully evaluated for functional, mental, geriatric and medical disorders before the initiation of antidiabetic drug therapy and regularly monitored thereafter. Treatment strategy and goals should be individualized based on patient co-morbidities and drug pharmacokinetic and pharmacodynamic properties. This narrative review discusses the use of antidiabetic drugs in the elderly T2DM population.
# Diabetes treatment considerations with aging

<table>
<thead>
<tr>
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<th>ENVIRONMENT</th>
</tr>
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<tbody>
<tr>
<td>Postprandial Hyperglycemia</td>
<td>Meal planning</td>
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<tr>
<td>Increased risk of Hypoglycemia</td>
<td>Physical activity</td>
</tr>
<tr>
<td>Age related PK and PD changes</td>
<td>Safety</td>
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<tr>
<td><strong>SELF MANAGEMENT ABILITY</strong></td>
<td><strong>DIABETES TREATMENT</strong></td>
</tr>
<tr>
<td>Competing priorities</td>
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<td>Hypoglycemia affects cognition</td>
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<td>Benefit of treatment over lifespan</td>
</tr>
<tr>
<td>Physical limitations</td>
<td>Risks of treatment</td>
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“The good physician treats the disease; the great physician treats the patient who has the disease”

William Osler