Test Focus
Diabetes in Cardiovascular Care

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The Diabetes Epidemic

A killer disease—and how diet and lifestyle can help beat it
Metabolic Syndrome

How to predict the future……...

….. of premature cardiovascular disease in your patients……..

…..and PREVENT it BEFORE it happens.
Impact of Diabetes: Mortality in US

- Mortality: 69,000 deaths directly attributable to diabetes — #7 cause
- Mortality: 254,000 deaths linked to diabetes — #3 cause
- Diabetes may be underreported as a cause of death. Studies have found that only about 35-40% of people with diabetes who died had diabetes listed anywhere on the death certificate.

Impact of Diabetes Morbidity in US

- Diabetic Retinopathy
- Diabetic Nephropathy
- Diabetic Amputations
- Diabetic Vascular Disease

Impact of Diabetes Morbidity in US

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- Diabetic Nephropathy
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- Diabetic Vascular Disease

Disease Burden of Type 2 Diabetes

- **Macrovascular disease**
  - 2- to 4-fold more likely to have heart disease or stroke
  - 2- to 8-fold more likely to have heart failure
  - Accounts for 60% to 70% of all diabetes-related deaths
  - Lower extremity amputations

- **Microvascular disease**
  - Up to 24,000 new cases of blindness annually
  - Leading cause of end-stage renal disease
  - Neuropathy (including erectile dysfunction)

Atherosclerosis in Diabetes

- ~65% of all diabetic mortality
  - 75% from coronary atherosclerosis
  - 25% from cerebral or peripheral vascular disease
- >75% of all hospitalizations for diabetic complications
- >50% of patients with newly diagnosed type 2 diabetes have CHD

HbA$_1c$ Predicts Coronary Heart Disease in Type II Diabetes

Kuusisto et al., Diabetes, 1994; 43:960-967

* P<.01 vs. lowest tertile
** P<.05 vs. lowest tertile
Cholesterol predicts CHD mortality rate in men with and without diabetes

Multiple Risk Factor Intervention Trial (MRFIT)

Rate/1000

1                2                3              4                5

Diabetic
Nondiabetic

Serum Cholesterol Quintile

Bierman EL, Arterioscler Thromb, June 1992
Based on data from J. Stamler
Increasing Cholesterol with Other Risk Factors

Coronary Risk Handbook: American Heart Association; 1973
Type II Diabetes & Coronary Heart Disease
Seven Year Incidence of Fatal/Nonfatal MI (East West Study)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence Rate</th>
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<tbody>
<tr>
<td>No DM, No MI</td>
<td>3.5%</td>
</tr>
<tr>
<td>No DM, MI</td>
<td>18.8%</td>
</tr>
<tr>
<td>DM, No MI</td>
<td>20.2%</td>
</tr>
<tr>
<td>DM, MI</td>
<td>45.0%</td>
</tr>
</tbody>
</table>


DM - diabetes mellitus
MI - myocardial infarction
The risk of a **FIRST** myocardial infarction in a person with diabetes is equal to the risk of a second myocardial infarction in a person without diabetes who has **ALREADY HAD** a myocardial infarction.
Diabetes is a cardiac risk equivalent

Every diabetic patient is at high risk for coronary heart disease
Natural History of Type 2 Diabetes

Glucose (mg/dL)

- Obesity
- IFG*
- Diabetes
- Uncontrolled hyperglycemia

Relative Function (%)

- Post-meal Glucose
- Fasting Glucose
- Insulin Resistance
- Beta-cell failure
- Insulin Level

*IFG = impaired fasting glucose

Adapted from International Diabetes Center (IDC) Minneapolis, Minnesota
Natural History of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Obesity</th>
<th>IFG*</th>
<th>Diabetes</th>
<th>Uncontrolled hyperglycemia</th>
</tr>
</thead>
</table>

Glucose (mg/dL)

- Post-meal Glucose
- Fasting Glucose

Relative Function (%)

- Insulin Resistance
- Beta-cell failure
- Microvascular disease

*IFG = impaired fasting glucose

Adapted from International Diabetes Center (IDC)
Minneapolis, Minnesota
Natural History of Type 2 Diabetes

Glucose (mg/dL) | Obesity | IFG* | Diabetes | Uncontrolled hyperglycemia
---|---|---|---|---
0 | 50 | 100 | 150 | 200
100 | 150 | 200 | 250 | 300
350

Fasting Glucose
Post-meal Glucose

Microvascular disease
Macrovascular disease

Beta-cell failure
Insulin Resistance
Insulin Level

*IFG = impaired fasting glucose

Adapted from International Diabetes Center (IDC)
Minneapolis, Minnesota
Natural History of Type 2 Diabetes

*IFG = impaired fasting glucose

Adapted from International Diabetes Center (IDC)
Minneapolis, Minnesota
Type 2 Diabetes: Insulin Resistance & Impaired β-Cell Function

- Insulin resistance
  - Normal β-cell function
    - Compensatory hyperinsulinemia
    - Normoglycemia
    - Insulin Resistance Syndrome
  - Abnormal β-cell function
    - Relative insulin deficiency
    - Hyperglycemia
    - Type 2 diabetes
Insulin Resistance Syndrome

Insulin resistance
plus compensatory hyperinsulinemia
which prevents the evolution of diabetes mellitus
Insulin Resistance Syndrome

Many of the manifestations are not due to the manifestations of insulin resistance per se, but to the fact that certain tissues remain normally insulin sensitive in the same individual who has muscle and liver insulin resistance.
Metabolic Syndrome

Genetic Influences

Insulin Resistance

Environmental Influences

50%

Hyperinsulinemia

Glucose Metabolism

Glucose Intolerance

Uric Acid Metabolism

↑ Uric Acid
↓ Uric Acid Clearance

Dyslipidemia

↑ TG
↑ PP Lipemia
↓ HDL Cholesterol
↓ Post heparin Lipolytic Activity
Small, dense LDL

Hemodynamic

↑ SNS Activity
↑ Na Retention
Hypertension

Hemostatic

↑ PAI-1
↑ Fibrinogen

Coronary Heart Disease
### Abnormalities Associated with Insulin Resistance/Hyperinsulinemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Abnormalities</th>
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<tr>
<td>Some degree of glucose intolerance</td>
<td>Impaired fasting glucose, impaired glucose tolerance</td>
</tr>
<tr>
<td>Abnormal uric acid metabolism</td>
<td>↑ Plasma uric acid concentration, ↓ Renal uric acid clearance</td>
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<tr>
<td>Dyslipidemia</td>
<td>↑ Triglycerides, ↓ HDL-C, ↓ LDL-particle diameter, ↑ Postprandial lipemia</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td>↑ Sympathetic nervous system activity, ↑ Renal sodium retention, ↑ Blood pressure (50% of patients with hypertension are insulin resistant)</td>
</tr>
<tr>
<td>Hemostatic</td>
<td>↑ Plasminogen activator inhibitor-1, ↑ Fibrinogen</td>
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<tr>
<td>Endothelial dysfunction</td>
<td>↑ Mononuclear cell adhesion, ↑ Plasma concentration of cellular adhesion molecules, ↑ Plasma concentration of asymmetric dimethyl arginine, ↓ Endothelial-dependent vasodilatation</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Polycystic ovary syndrome</td>
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<tr>
<td>Inflammatory</td>
<td>↑ C-reactive protein, WBC</td>
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<tr>
<td>Sleep disordered breathing</td>
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</table>
Insulin resistance is not a disease; it is a physiological change that increases the risk of developing one or more of these abnormalities. The more insulin resistant an individual, and the greater the degree of compensatory hyperinsulinemia, the more likely to develop one or more of these abnormalities.
Parallel paths for development of Type 2 Diabetes Mellitus and Atherosclerosis

Hsueh W, Am J Cardiol 2003;92(suppl):3J–9J
Quartet of tissue abnormalities causing Type 2 Diabetes Mellitus

- **Adipokines** regulate insulin mediated glucose uptake in skeletal muscle.
- **Pancreas** secretes excess insulin to overcome the defect in insulin action.
- Exposure to free fatty acids impairs glucose-stimulated insulin release and can lead to apoptosis in susceptible subjects, and, ultimately, progressive loss of β-cell function.
- The **liver** is unable to suppress glucose production in response to insulin.
Adipose Tissue as an Endocrine Organ

Traditional view
Fat is an inert storage depot

Emerging View
Fat is a secretory/endocrine organ

Fatty acids
Glucose

Fatty acids
Glycerol

Leptin, fatty acids, adiponectin, TNF-α, PAI-1, cytokines

PAI-1=plasminogen activator inhibitor-1.
Multiple factors associated with adiposity promote insulin resistance, visceral inflammation, and atherosclerosis

- ↑FFA → Insulin Resistance
- ↑TNF-α → Vascular Inflammation
- ↑CRP → Predicts Diabetes and CVD
- ↑sd LDL-C → Promotes Foam Cell Formation
- ↑Leptin → Insulin-Mediated Glucose Uptake

AM J CARDIOL 2003 92 (4A):3J-9J.
Abdominal Adiposity Is Associated With Increased Risk of Diabetes

P value for trend < 0.001

Abdominal Adiposity Is Associated With Increased Risk of CHD

Relative Risk for CHD by Waist Circumference

$P$ for trend vs referent=0.007

Cardiometabolic Risk Factors Tend to Cluster
Metabolic Syndrome

Assessment of CHD risk is not limited to cholesterol

Identification of Metabolic Syndrome patients can lead to aggressive evaluation for other manifestations of insulin resistance, and these risk factors aggressively treated.
Clinical syndromes associated with insulin resistance

- Type 2 diabetes
- Cardiovascular disease
- Essential hypertension
- Polycystic ovary syndrome
- Nonalcoholic fatty liver disease
- Certain forms of cancer
  - Breast cancer
  - Prostate cancer
  - Colorectal cancer
  - Liver cancer
- Sleep apnea
ATP III criteria for diagnosing the metabolic syndrome

Abdominal obesity
   Men: waist circumference >40 inches
   Women: waist circumference >35 inches
Fasting glucose >110 <126 mg/dL
Blood pressure >130/80 mm Hg
Triglycerides >150 mg/dL
HDL-C
   Men <40 mg/dL
   Women <50 mg/dL

The metabolic syndrome is present when three or more of the five criteria are met.

Metabolic Syndrome Treatment

- Exercise and diet
  - ↑ coronary artery endothelial function
  - ↑ adiponectin
  - balanced low carbohydrate diet preferred
  - ? pharmacologic weight loss agents useful

- Statins
  - Reduce cardiovascular outcomes
  - ↑ eNOS
  - ↓ endothelin-1, ↓ AT₁ receptor expression
  - ↓ IL-1β, IL-6, PAI-1 expression
  - High risk patients goal LDL is 70 mg/dl
Metabolic Syndrome Treatment

- **Fibrates**
  - Activate PPAR-α to ↓ TG and ↑ HDL
  - ↓ vascular inflammation, ↓ cytokines

- **ACE inhibitors, ARBs**
  - Inhibit the Renin-Angiotensin System
  - Improve endothelial function / reduce microalbuminuria
  - Reduce incidence of progression to Type 2 DM

- **Aspirin**
  - Important in primary and secondary prevention
  - Acute treatment in an evolving MI
Our first duty is for the **PREVENTION** of cardiovascular disease

We need a high index of suspicion
Think increased cardiovascular risk if you see......

- ↑Triglycerides and ↓ HDL
- Gout
- Fasting glucose >110 mg/dl
  - “a touch of diabetes”
- Fatty liver on CT scan or Ultrasound
- Polycystic ovary disease
- Hypertension
- Increased visceral adiposity
Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes.

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group.

**DCCT** (Diabetes Control & Complication Trial)

**Methods**
- 1,441 type 1, mean follow-up = 6.5 yrs
- Intensive (insulin pump or 3+ injections) versus conventional (1-2 injections)
- Conducted between 1983 and 1993

**Results (intensive)**
- ↓ 76% risk retinopathy development (primary prevent.)
- ↓ 54% retinopathy progression (secondary prevent.)
- ↓ 39% microalbuminuria (I vs C)
- ↓ 54% albuminuria (I vs C)
- ↓ 60% clinical neuropathy (I vs C)
- ↑ 2-3x severe hypoglycemia
Diabetes Control and Complications Trial
DCCT/EDIC Metabolic Results

Risk of Progression of Diabetic Complications

Diabetes Control and Complications Trial (DCCT) in Type 1 Diabetes

Epidemiology of Diabetes Interventions and Complications (EDIC)

- Long-term observational follow-up of DCCT cohort initiated in 1994
- Conventional treatment group taught intensive therapy
- Care provided by subjects’ own health care providers
- Major goal: to study longer-term effects of previous glycemic separation, especially on renal failure and CVD

Diabetes Care 1998; 22: 99-111
A1C During DCCT and Follow-Up


Conventional group encouraged to switch to intensive treatment.
Schematic Course of DCCT/EDIC
Intensive & Conventional Groups

HbA$_1c$% vs. Time

Baseline → DCCT 6.5 years → EDIC 8 years

Conventional
Intensive

Retinopathy
Nephropathy
Neuropathy

DCCT/EDIC
Prevalence of Coronary Calcium in EDIC Years 8 - 9

![Bar chart showing the prevalence of coronary calcium scores in DCCT Conventional and DCCT Intensive groups.](chart.png)

- DCCT Conventional
- DCCT Intensive

- > 0: p = NS
- > 100: p = .044
- > 200: p = .01

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Cardiovascular Events

Cumulative Incidence of First of Any Event

Risk reduction 42%
95% CI: 19, 63
Log-rank P = 0.016

Number at Risk
Intensive: 705  683  629  113
Conventional: 714  688  618  92

Cardiovascular Events
Non-Fatal MI, Stroke or CVD Death

Risk reduction 57%
95% CI: 12, 79
Log-rank P = 0.018

DCCT/EDIC Cardiovascular Results

- A 10% reduction in HbA1c was associated with a 21% reduction in the risk of a CVD event
- Other covariates associated with the occurrence of CVD independent of treatment group
  - Age
  - Duration of diabetes
  - Presence of retinopathy
  - Current smoking
  - Increased BMI
  - Increased LDL cholesterol
  - Increased urine albumin excretion

UKPDS: Tight Glycaemic Control Reduces Complications

Epidemiological extrapolation showing benefit of a 1% reduction in mean HbA$_{1c}$

- Deaths related to diabetes *
  - 21%

- Microvascular complications e.g. kidney disease and blindness *
  - 37%

- Heart attack *
  - 14%

- Amputation or fatal peripheral blood vessel disease *
  - 43%

- Stroke **
  - 12%

* p<0.0001
** p=0.035

DCCT: Rates of Severe Hypoglycemia Increase as A1C Levels Decrease in Patients With Type 1 Diabetes

- Major barrier to intensive diabetes management

Squares correspond to >400 patient-years.
## Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
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<td><img src="arrow" alt="↔" /></td>
<td><img src="arrow" alt="down" /></td>
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<tr>
<td>DCCT / EDIC*</td>
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<td><img src="arrow" alt="↔" /></td>
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<tr>
<td>ACCORD</td>
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<tr>
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<td><img src="arrow" alt="↔" /></td>
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**Kendall DM, Bergenstal RM. © International Diabetes Center 2009**

# Glucose Lowering & Complications

<table>
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<tr>
<th></th>
<th>Macrovascular</th>
<th>Microvascular</th>
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</thead>
<tbody>
<tr>
<td><strong>Early DM</strong></td>
<td>Benefit</td>
<td>Benefit</td>
</tr>
<tr>
<td><strong>Advanced DM</strong></td>
<td>No Benefit; Possible Harm</td>
<td>Benefit</td>
</tr>
</tbody>
</table>

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**Legend:**
- **Benefit:** Positive outcome
- **No Benefit; Possible Harm:** Negative outcome
Hypoglycemia and CV Disease

<table>
<thead>
<tr>
<th></th>
<th>Hypoglycemia</th>
<th>HR For Mortality</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>STD</td>
<td>INT</td>
</tr>
<tr>
<td>ACCORD</td>
<td>1%</td>
<td>3.1%</td>
</tr>
<tr>
<td>VADT</td>
<td>1.5%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>


Glucose & CV Risk

- If other CV risk factor control is good, there is no additional CV benefit of lowering HbA1c from 8.4% to 6.9% in older people with advanced DM (VADT).

- If other CV risk factor control is good, there **may be CV harm in lowering HbA1c from 7.5% to 6.4% in older people with advanced DM**, perhaps due to hypoglycemia (ACCORD).  

- Reducing blood glucose early in the course of the disease may not be harmful (ADVANCE) and may even confer CV benefit (UKPDS Follow-Up).
Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Diabetes Care 2015;38:140–149
Diabetologia 2015;10.1077/s00125-014-3460-0
3. ANTI-HYPERGLYCEMIC THERAPY

• Glycemic targets

- **HbA1c < 7.0%** (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
- Pre-prandial PG <130 mg/dl (7.2 mmol/l)
- Post-prandial PG <180 mg/dl (10.0 mmol/l)
- **Individualization** is key:
  - Tighter targets (6.0 - 6.5%) - younger, healthier
  - Looser targets (7.5 - 8.0%+) - older, comorbidities, hypoglycemia prone, etc.
- Avoidance of hypoglycemia

PG = plasma glucose
**Goals for Glycemic Control**

- **A1c ≤ 6.5%**
  - For healthy patients without concurrent illness and at low hypoglycemic risk

- **A1c > 6.5%**
  - Individualize goals for patients with concurrent illness and at risk for hypoglycemia
Hypoglycemia, a major risk factor in diabetes management
Physiologic Responses to Hypoglycemia

- Decreased glucose
- Increased glucagon
- Increased epinephrine
- Increased sympathoadrenal outflow
- Increased NE (palpitations, tremor, arousal)
- Increased ACh (sweating, hunger)
- Increased neurogenic symptoms

Liver:
- Increased glycogenolysis
- Increased gluconeogenesis
- Increased glucose production
- Increased lactate, amino acids, glycerol

ACh—acetylcholine; CNS—central nervous system; NE—norepinephrine; PNS—parasympathetic nervous system; SNS—sympathetic nervous system.

Hierarchical response to hypoglycemia in nondiabetic individuals.
Clinical Manifestations of Hypoglycemia

- **Neuroglycopenic**
  - Symptoms related to low glucose utilization in the brain

- **Adrenergic**
  - Symptoms related to response of increased sympathetic nervous system due to increased catecholamine levels

- **Cholinergic**
  - Symptoms related to response of increased parasympathetic nervous system
Clinical Manifestations of Hypoglycemia

- Neuroglycopenic
  - Weakness
  - Feeling tired
  - Drowsiness
  - Difficulty thinking
  - Difficulty speaking
  - Confusion
  - Clumsiness
  - Incoordination
  - Odd behavior – Irritability
  - Vivid dreams
  - Feeling warm
  - Seizures
  - Coma

- Adrenergic
  - Tremulousness
  - Palpitations
  - Tachycardia
  - Anxiety/Nervousness
  - Hunger

- Cholinergic
  - Cold Sweating
  - Tingling
  - Hunger
  - Parathesias
Attenuated Counterregulatory Responses Lead to Hypoglycemia Unawareness and Recurrent Hypoglycemia

Advanced Type 2 Diabetes
Relative insulin deficiency and insulin resistance

Type 2 diabetes

Pharmacotherapy with relative insulin excess

Antecedent hypoglycemia
Reduced sympathoadrenal responses to hypoglycemia
Reduced sympathetic neural responses
Hypoglycemia unawareness

Sleep

Antecedent exercise
Reduced epinephrine response
Defective glucose counterregulation

Recurrent hypoglycemia

Hyperinsulinemic hypoglycemic clamps on 2 consecutive mornings, with interval afternoon clamped hypoglycemia in adults without diabetes.
Thresholds for Hypoglycemia Awareness and Onset of Cognitive Dysfunction

Glycemic thresholds for awareness of hypoglycemia symptoms and for the onset of cognitive dysfunction in young and elderly healthy men

In a Hypoglycemic Clamp Study of Healthy Men, Symptom Recognition of Hypoglycemia Was Lower Among Older People

Change in Plasma Glucose in a Hypoglycemic Clamp Study of Healthy Men

- Young Without Diabetes (n=7)
- Elderly Without Diabetes (n=7)

Plasma Glucose, mg/dL ± SE

Time, min

Glucose infusion maintained at 90 mg/dL (5 mmol/L)
Glucose infusion reduced stepwise from 90 mg/dL to 43 mg/dL (5 mmol/L to 2.4 mmol/L)
Glucose infusion restored to 90 mg/dL (5 mmol/L)

Change in Total Symptom Score, ± SE

In a Hypoglycemic Clamp Study of Healthy Men, Hypoglycemia-Associated Decline in Psychomotor Function Was More Marked Among Older People

Change in Plasma Glucose in a Hypoglycemic Clamp Study of Healthy Men

- Young Without Diabetes (n=7)
- Elderly Without Diabetes (n=7)

**Mean Change in Reaction Time ± SE, ms**

- Glucose infusion maintained at 90 mg/dL (5 mmol/L)
- Glucose infusion reduced stepwise from 90 mg/dL to 43 mg/dL (5 mmol/L to 2.4 mmol/L)
- Glucose infusion restored to 90 mg/dL (5 mmol/L)

P<0.05.

Glucose lowering agents account for 25% of emergency admissions for adverse drug events

- 1. warfarin
- 2. insulins
- 3. oral antiplatelet drugs
- 4. oral hypoglycemic
- 5. opioid analgesics

Hypoglycemia admissions surpass hyperglycemic admissions

Hypoglycemia is a dominant complication of diabetes in older adults with long duration of disease
General risk factors for hypoglycemia in elderly patients with type 2 diabetes mellitus

- Advanced age
- Long duration of diabetes
- Polypharmacy
- Recent hospitalization
- Use of sulfonylurea and/or insulin
- Poor nutrition or fasting/missed meals
- Intercurrent illness
- Chronic liver, renal or cardiovascular disease
- Prolonged physical exercise
- Alcohol consumption
- Endocrine deficiency (thyroid, adrenal, pituitary)
- Loss of normal counter-regulation
- Hypoglycemic unawareness
Risk factors for insulin-induced hypoglycaemia in elderly patients with diabetes mellitus

- **Insulin administration errors**
  - Excessive insulin dose
  - Improper timing of insulin relative to timing of food intake
  - Injection of wrong insulin type (e.g. rapid-acting in place of long-acting insulin)

- **Decreased glucose influx**
  - Missed meals
  - Fasting
  - Gastroparesis with delayed carbohydrate absorption

- **Increased insulin sensitivity**
  - Weight loss
  - Intensive insulin therapy
  - Increased exercise

- **Delayed insulin clearance, erratic insulin absorption**
  - Renal failure
  - Insulin injection in hypertrophic sites

- **Decreased endogenous glucose production**
  - Severe liver disease
  - Defective glucagon or epinephrine counter-regulation
  - Alcohol (ethanol) ingestion
Strategies to Prevent Hypoglycemia in Elderly Patients with Diabetes

• Patient education
  • Teach patient how drugs act and how to recognize hypoglycemia
• Inquire about the occurrence of hypoglycemia
  • Inappropriate insulin
  • Inappropriate med combination
  • Possible drug interaction
  • Eating habits/Erratic intake
  • Comorbid disease
    • Renal or hepatic
  • HbA1c Assessment – If too low suspect unappreciated hypoglycemia
• Reinforce prevention of hypoglycemia
• Avoid exercise induced hypoglycemia – abdominal injections
• Caution excess alcohol
• Pick diabetes medications that have low risk of hypoglycemia
Figure 1

Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]
3. ANTI-HYPERGLYCEMIC THERAPY

• Therapeutic options:

*Oral agents & non-insulin injectables*

- Metformin
- Sulfonylureas
- Thiazolidinediones
- DPP-4 inhibitors
- GLP-1 receptor agonists
- Meglitinides
- α-glucosidase inhibitors
- Bile acid sequestrants
- Dopamine-2 agonists
- Amylin mimetics
# Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>DPP-4i</th>
<th>GLP-1 RA</th>
<th>TZD</th>
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<td>Loss</td>
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<td>RENAL/ GU</td>
<td>Contra-indicated Stage 3B,4,5</td>
<td>Dose Adjustment May be Necessary (Except Linagliptin)</td>
<td>Exenatide Contra-indicated CrCl &lt; 30</td>
<td>May Worsen Fluid Retention</td>
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<td>Neutral</td>
<td>Safe</td>
<td>?</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>BONE</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Bone Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>? Bone Loss</td>
<td>Neutral</td>
<td></td>
</tr>
</tbody>
</table>

- **Few adverse events or possible benefits**: Green
- **Use with caution**: Yellow
- **Likelihood of adverse effects**: Red

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Patients with metabolic syndrome manifestations require aggressive risk factor modification. Aggressive glycemic control early is essential for limiting diabetic complications. In advanced age aggressive glycemic control is more often associated with hypoglycemia mediated adverse complications and less aggressive glucose management is appropriate. Choose medications that do not cause severe hypoglycemia.