Oral Anti-diabetic Drugs in Older Adults with Diabetes

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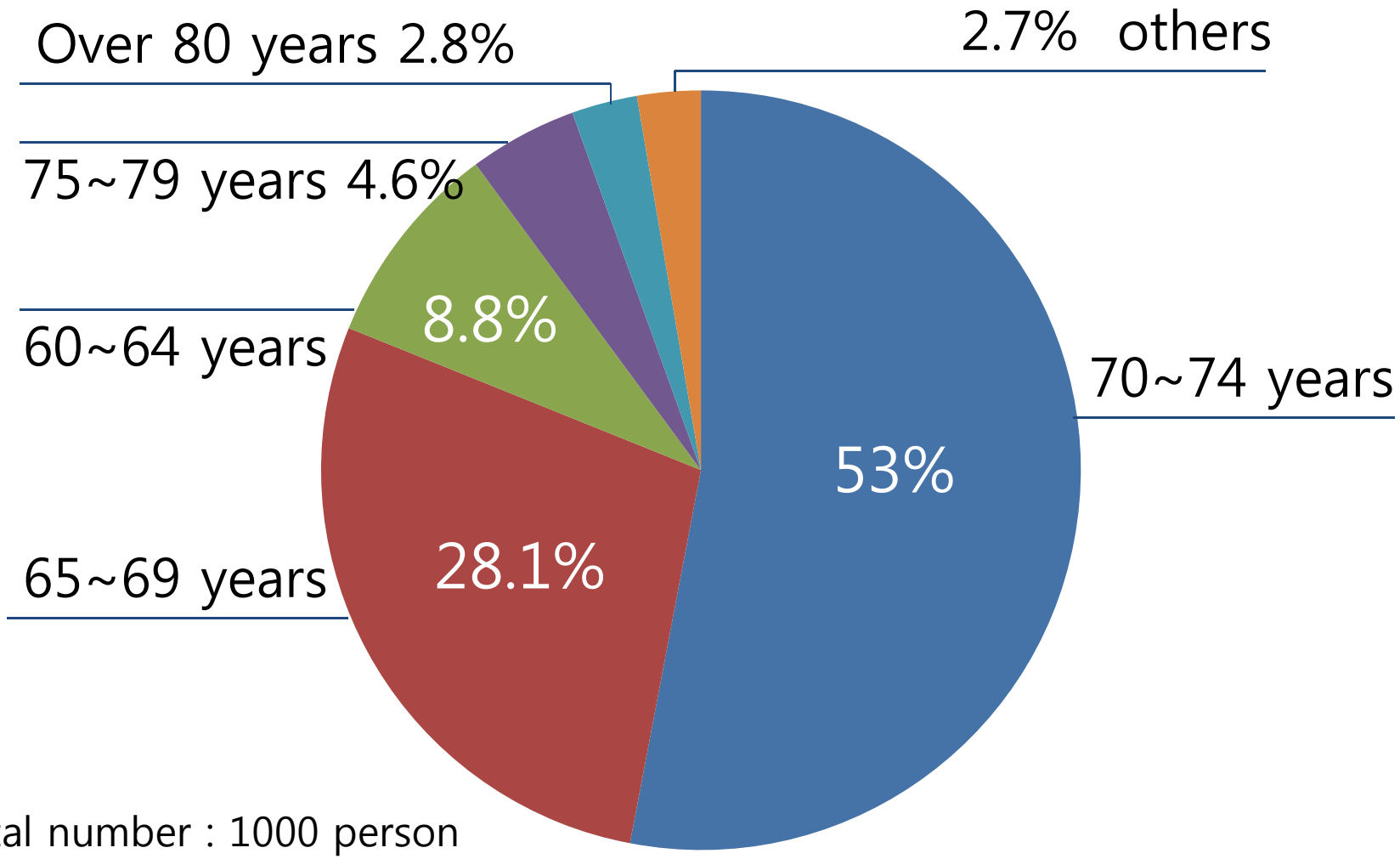
How old is The Old Man?



Total number : 1000 person

Sourced by KIHASA

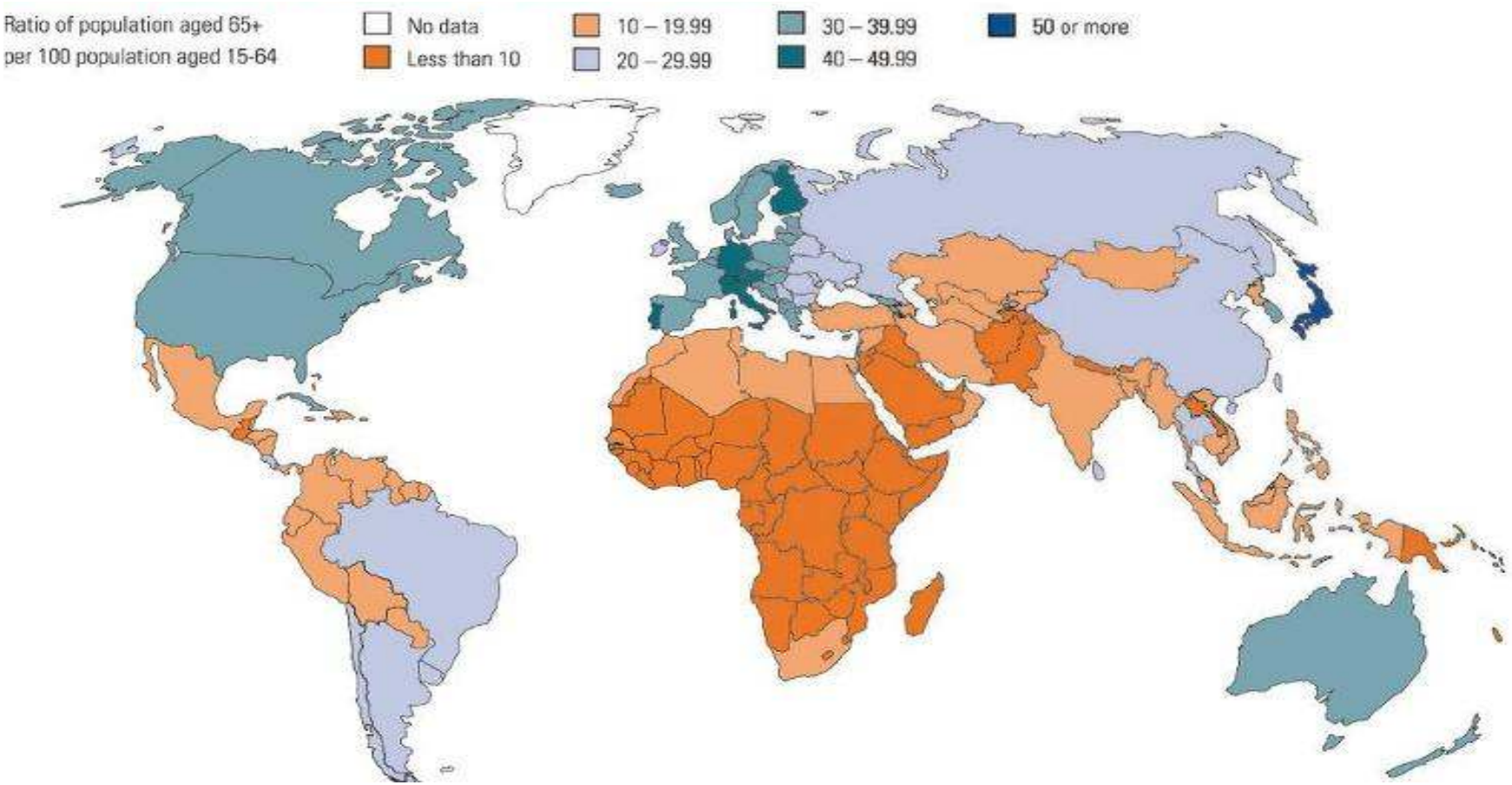
Agenda

1. *Why we are interested in the elderly diabetes?*
2. *What are the characteristics of the elderly diabetes?*
3. *What are the considerations of the elderly diabetes?*
4. *What are the oral hypoglycemic agents and the cautions of the elderly diabetes?*

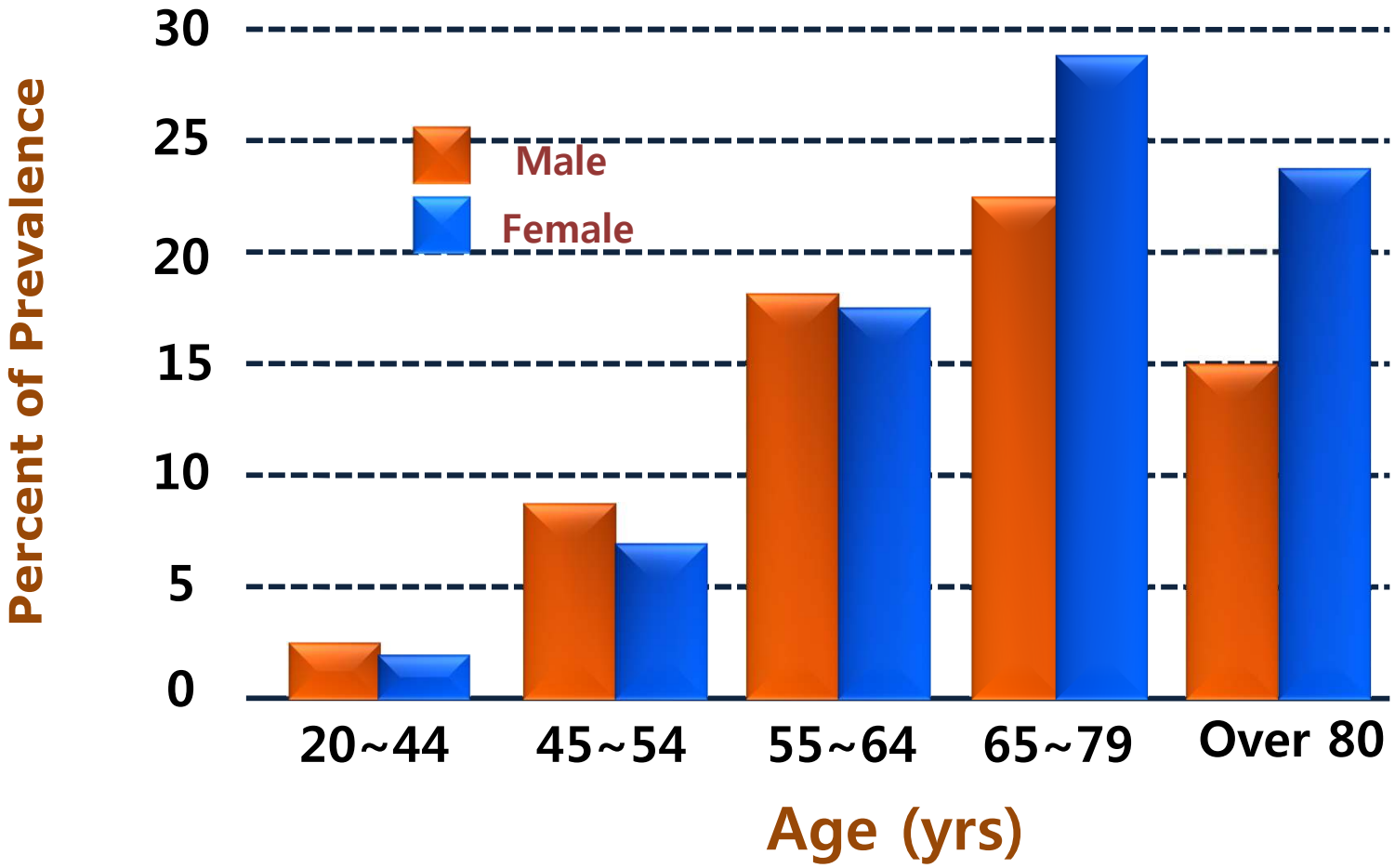
Why we are interested in the elderly diabetes?

Proportion of elderly people in the World

Old-age dependency ratio in 2030



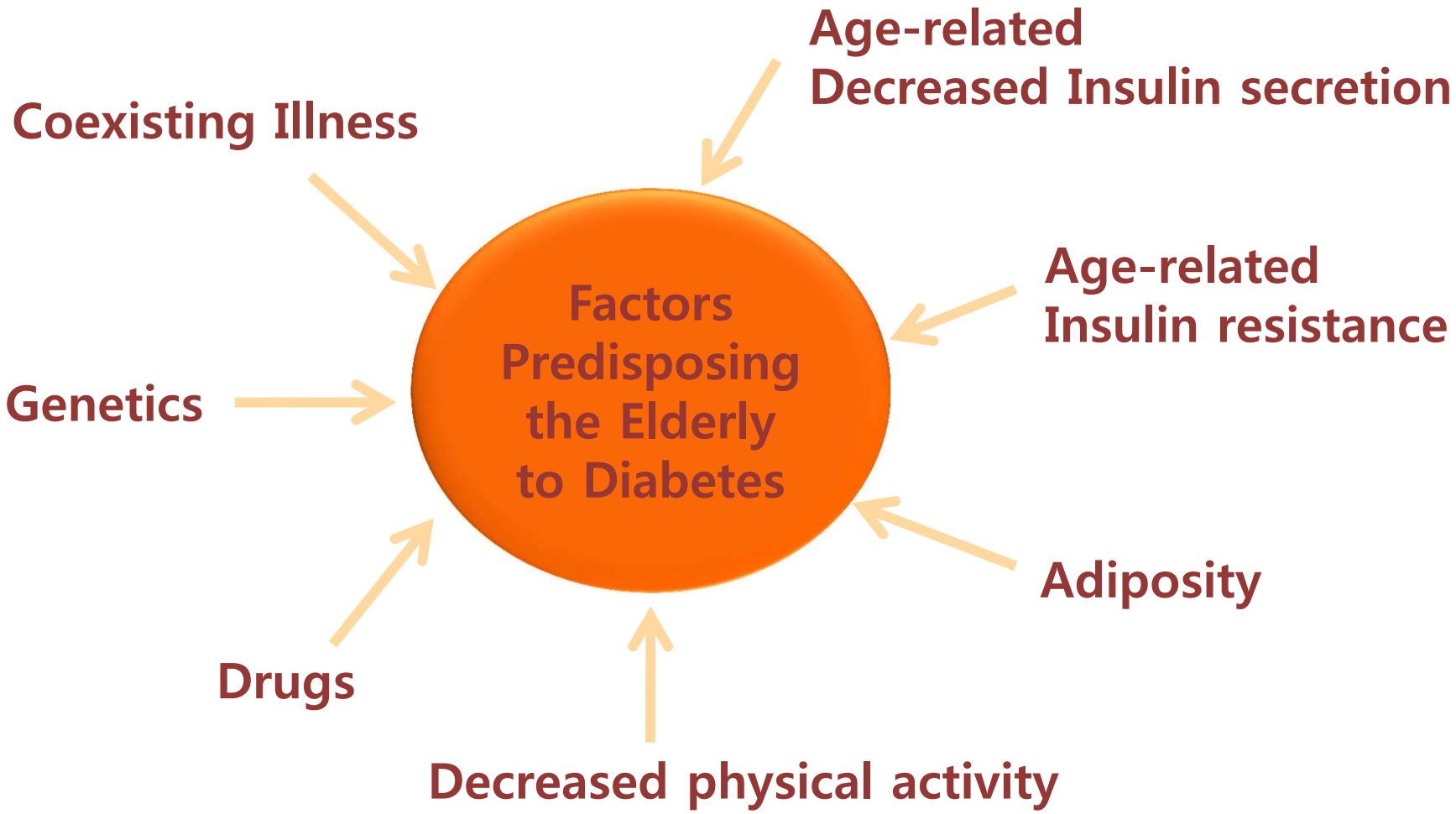
Prevalence of Korean diabetic patients according to the gender and age



Diabetes 2007

What are the characteristics of the elderly diabetes?

Pathogenesis of hyperglycemia in elderly patients



Comprehensive Physiology

Characteristics of elderly diabetes

- Rare typical Sx
- Frequent Atypical Sx

  : urinary incontinence, falling, infection etc
- Hypoglycemia increase
- Cognitive function decrease
- Heterogeneity
- Concomitant disease

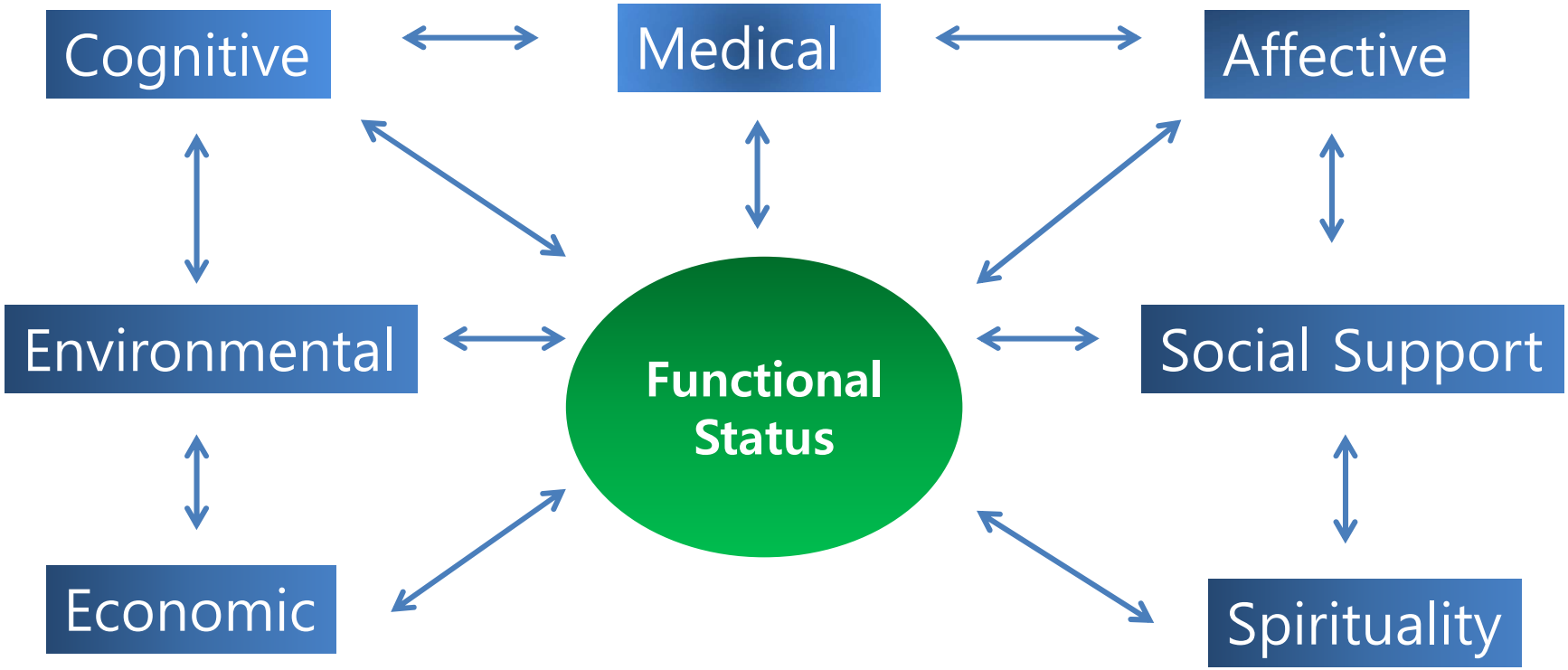
gerontology 2008;12:61-7

Treatment goal for elderly diabetes

- Control of Hyperglycemia and its symptoms
- Prevention, evaluation and treatment of macrovascular and microvascular complications of DM
- DM self-management through education
- Maintenance or improvement of general health status

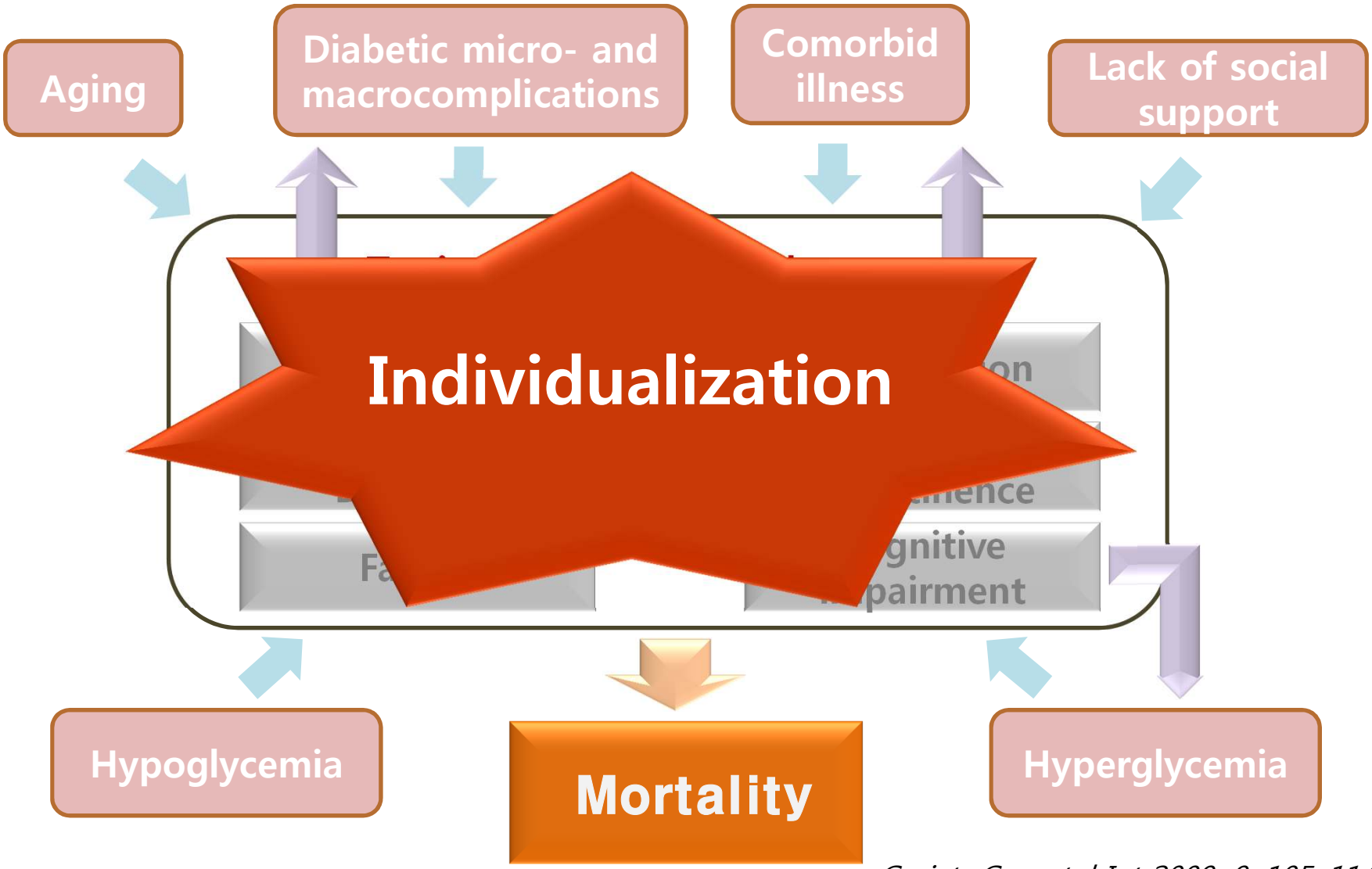
J Am Geriatr Soc 2003; 51: S265–S280

Essential factors of assessment of elderly



Principles of Geriatric Medicine & Gerontology p.100

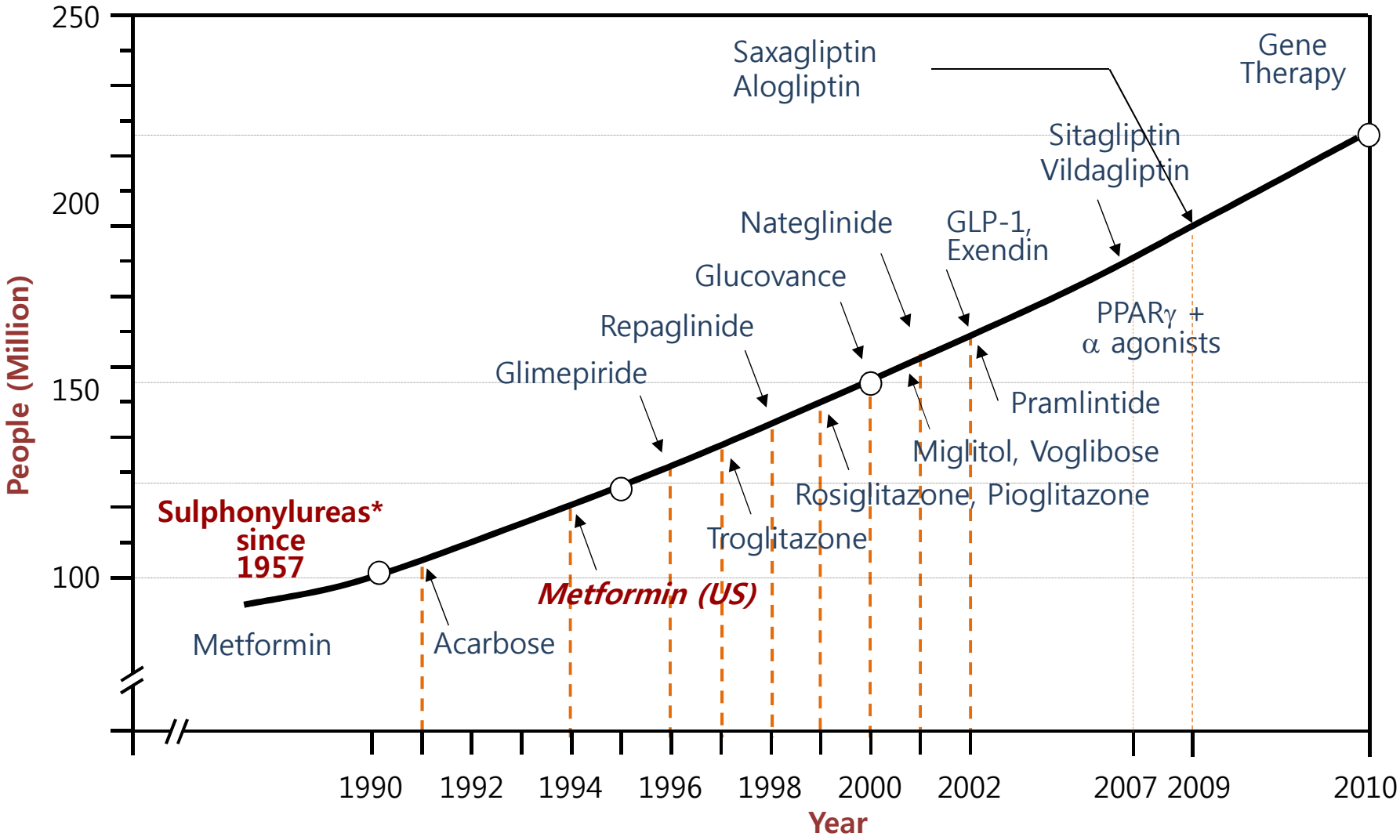
Geriatric syndrome and elderly diabetes



Geriatr Gerontol Int 2009; 9: 105–114

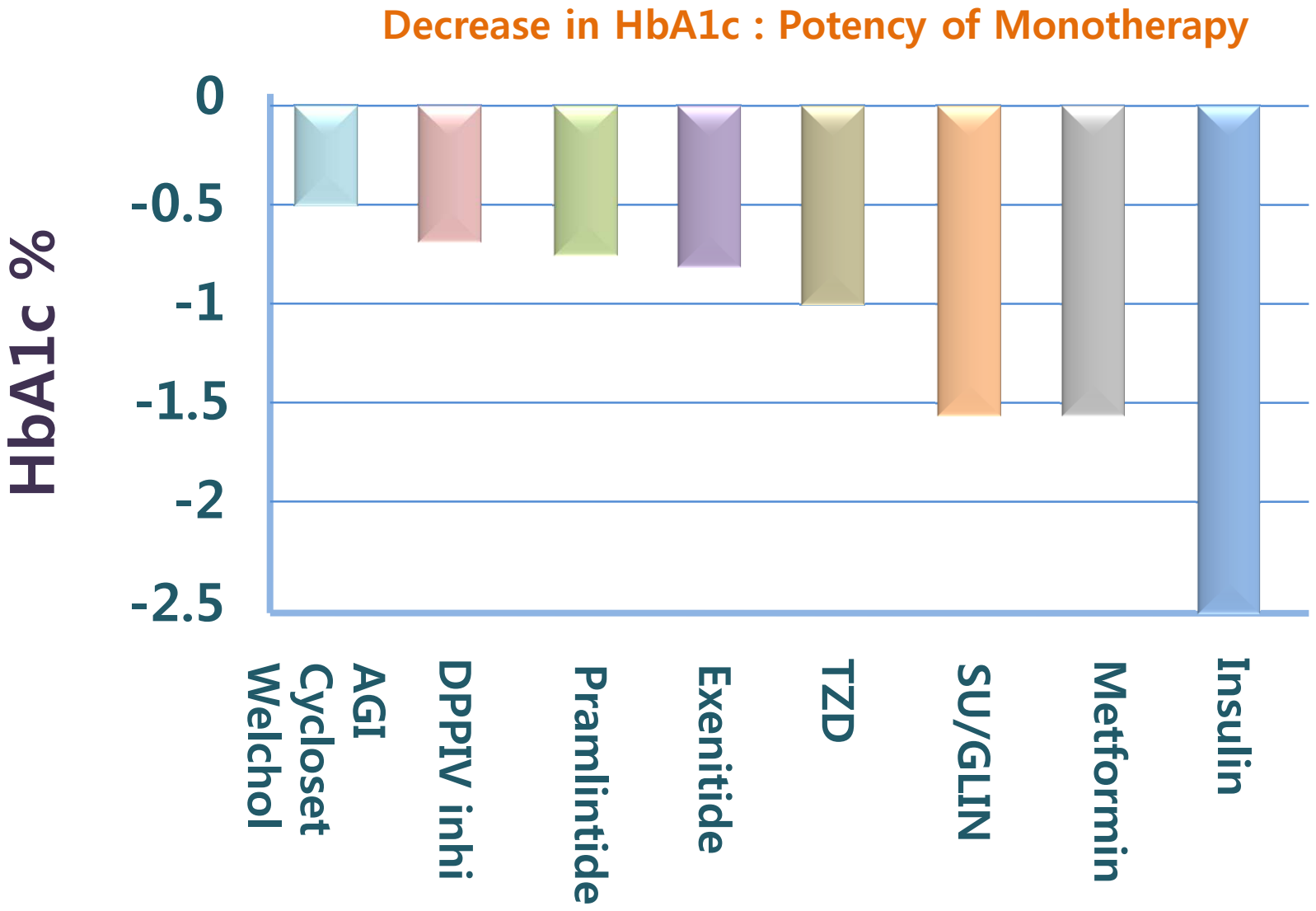
What are the considerations of the elderly diabetes?

Treatment Options for T2DM



* Tolbutamide, chlorpropamide, glibenclamide, gliclazide, glipizide

Relative Merits of Hypoglycemic Agents



2011 71th ADA Current Issue

Treatment with T2DM

Pharmacologic Options

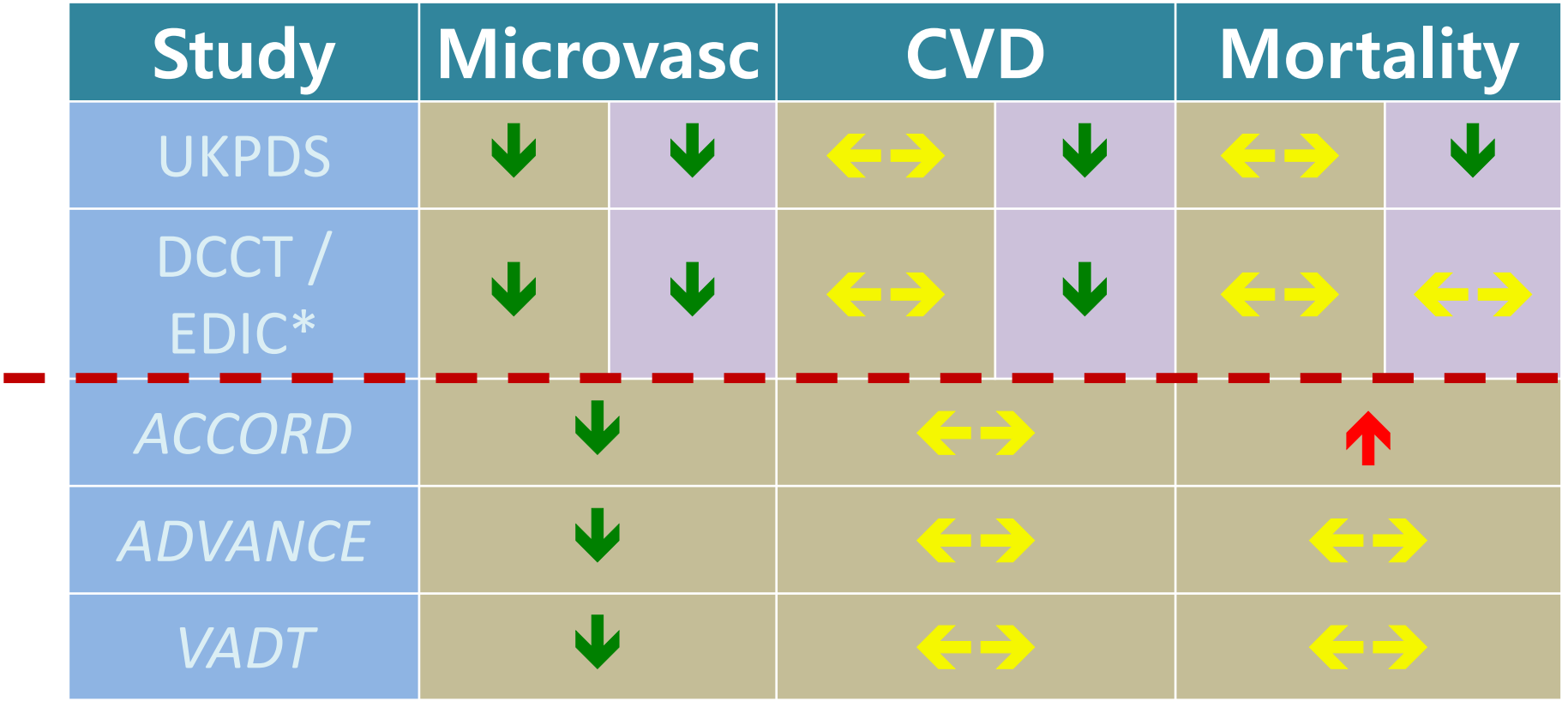
Elderly patients = Younger adults

Treatment Considerations

Elderly patients ≠ Younger adults

Am J Geriatr Pharmacother. 2009;7:324–342

Glycemic control



Initial Trial

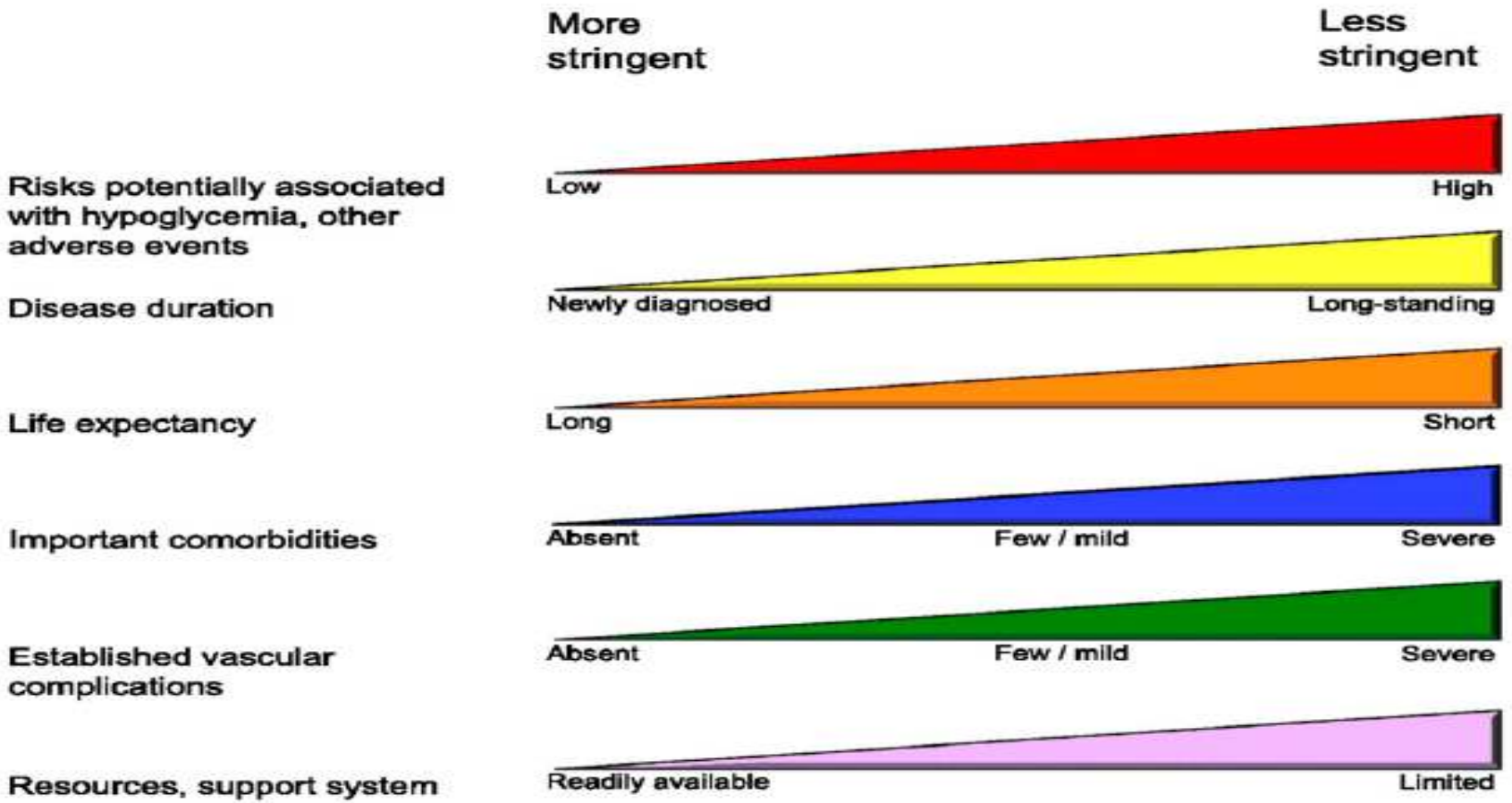
Long Term Follow-up

* in T1DM

Kendall DM, Bergenstal RM. © International Diabetes Center 2009

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)

Management of hyperglycemia



ADA Standards of Medical Care in Diabetes-2014

Target of HbAlc in elderly diabetes

- CATEGORY 1: *FUNCTIONALLY INDEPENDENT*
  : HbA1c target : 7.0~7.5%

- CATEGORY 2: *FUNCTIONALLY DEPENDENT*
  Sub-category A: Frail
  - HbA1c target : ~8.5%

  Sub-category B: Dementia
  - HbA1c target : ~8.5%

- CATEGORY 3: *END OF LIFE CARE*
  - glycemic target : avoid hypoglycemia, individualized therapy

IDF Global Guideline for Managing Older People with Type 2 Diabetes 2013

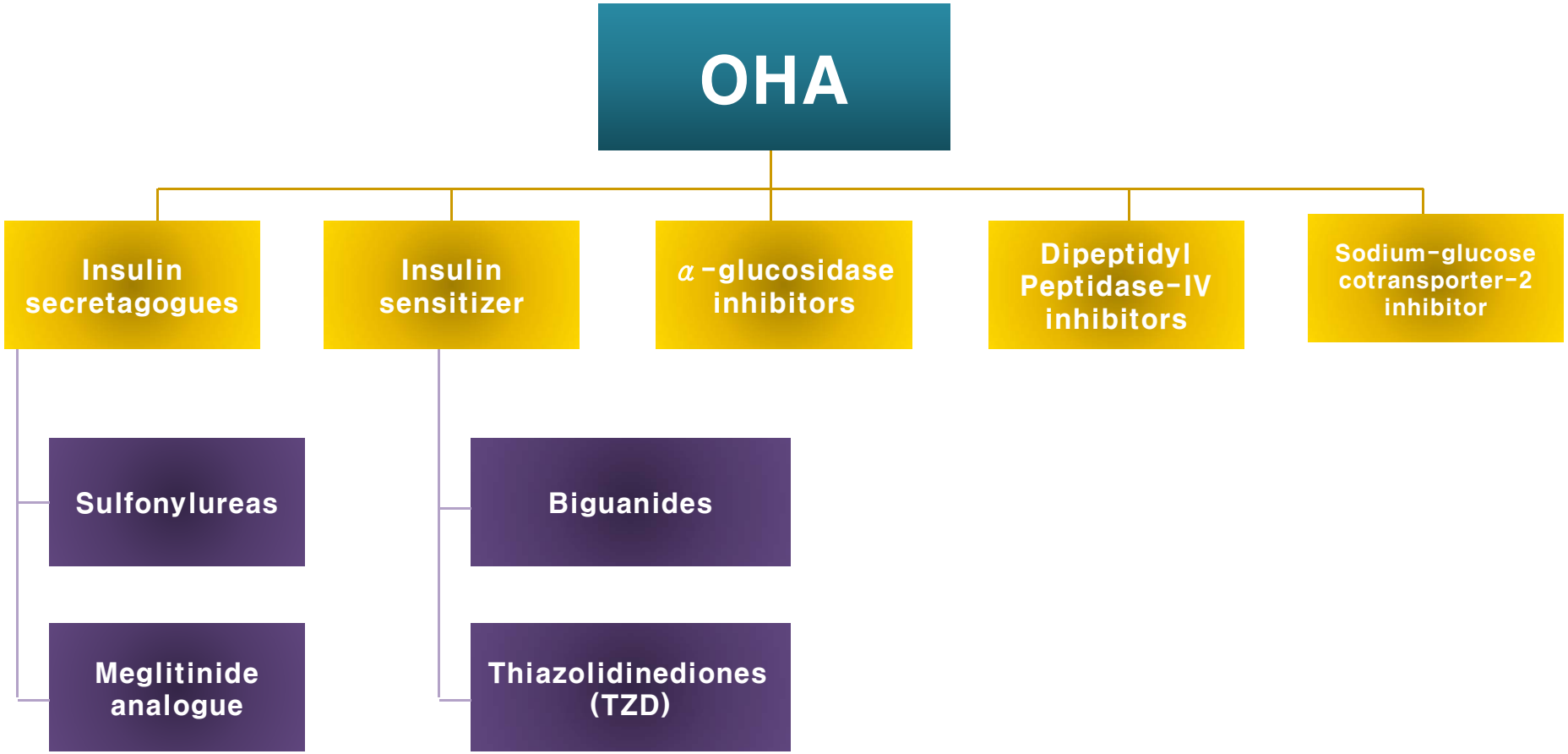
Target in elderly diabetes

Patient characteristics/ health status	Rationale	Reasonable A1C goal (A lower goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden)	Fasting or preprandial glucose (mg/dL)	Bedtime glucose (mg/dL)	Blood pressure (mmHg)	Lipids
Healthy (Few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5%	90–130	90–150	<140/80	Statin unless contraindicated or not tolerated
Complex/intermediate (Multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild to moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0%	90–150	100–180	<140/80	Statin unless contraindicated or not tolerated
Very complex/poor health (Long-term care or end-stage chronic illnesses** or moderate to severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%†	100–180	110–200	<150/90	Consider likelihood of benefit with statin (secondary prevention moreso than primary)

Med Care 2010; 48:327–334

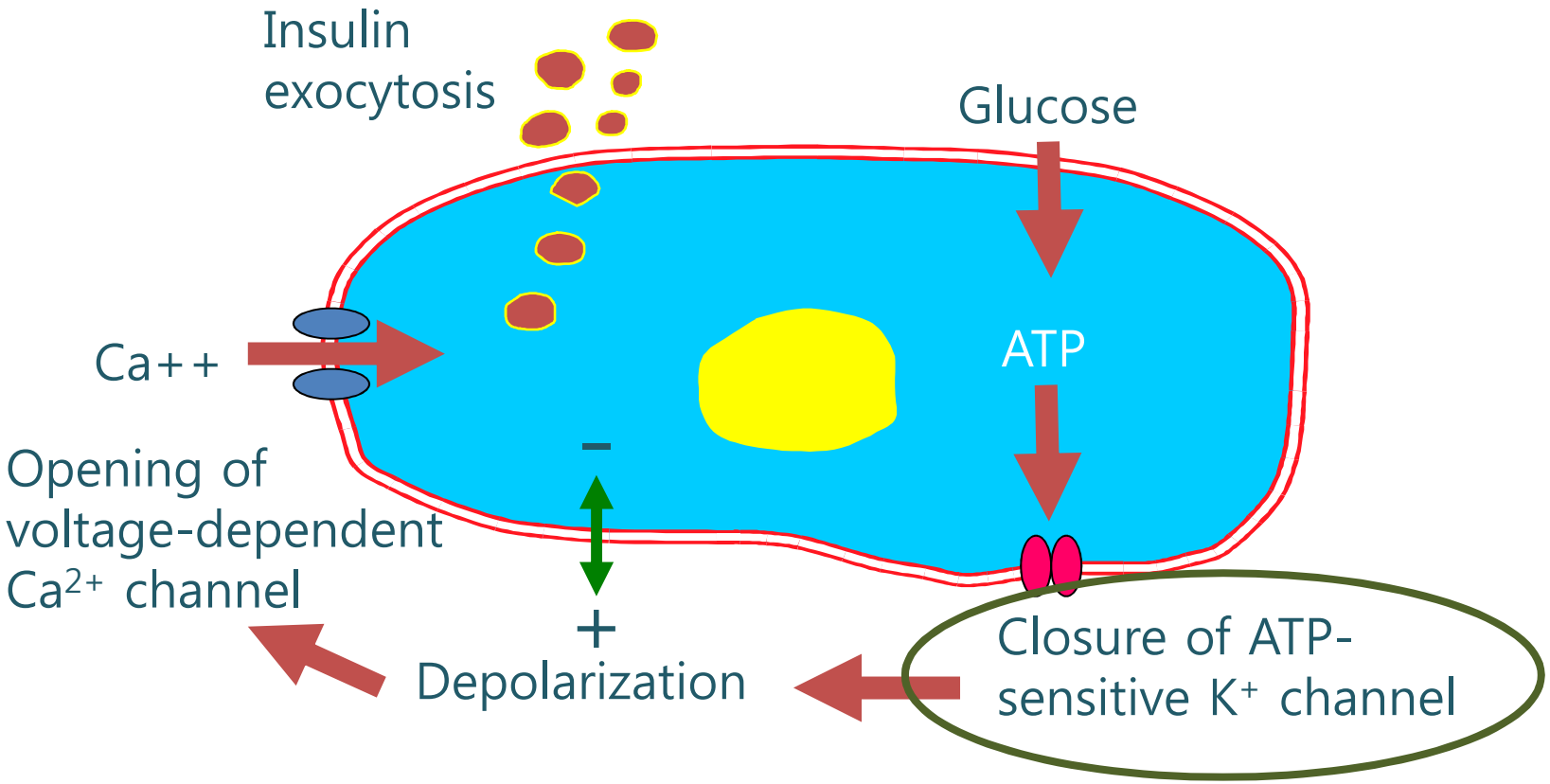
What are the oral hypoglycemic agents and the cautions of the elderly diabetes?

Drug Groups


OHA
Insulin secretagogues
Insulin sensitizer
α-glucosidase inhibitors
Dipeptidyl Peptidase-IV inhibitors
Sodium-glucose cotransporter-2 inhibitor
Sulfonylureas
Meglitinide analogue
Biguanides
Thiazolidinediones (TZD)

Insulin Secretagogues :
SU & Meglitinide

Insulin Secretagogues



Sulfonylurea

- Mainstay of Treatment for T2DM
- Main Side Effects : Hypoglycemia and Weight gain

Risk factors of Hypoglycemia on older adults

Adrenergic-blocking agents
Alcohol consumption
Cognitive impairment
Endocrine deficiency (thyroid, adrenal, pituitary)
Hepatic dysfunction
Intercurrent illness
Poor nutrition
Renal Insufficiency
Sedative agents
Advanced age
Autonomic neuropathy
Complex drug regimens
Hypoglycemia unawareness
Polypharmacies
Recent hospitalization
Secretagogues/insulin
Tight glycemic control

Drugs Aging. 2004;21:511–530, Cleve Clin J Med. 2008;75:70–78

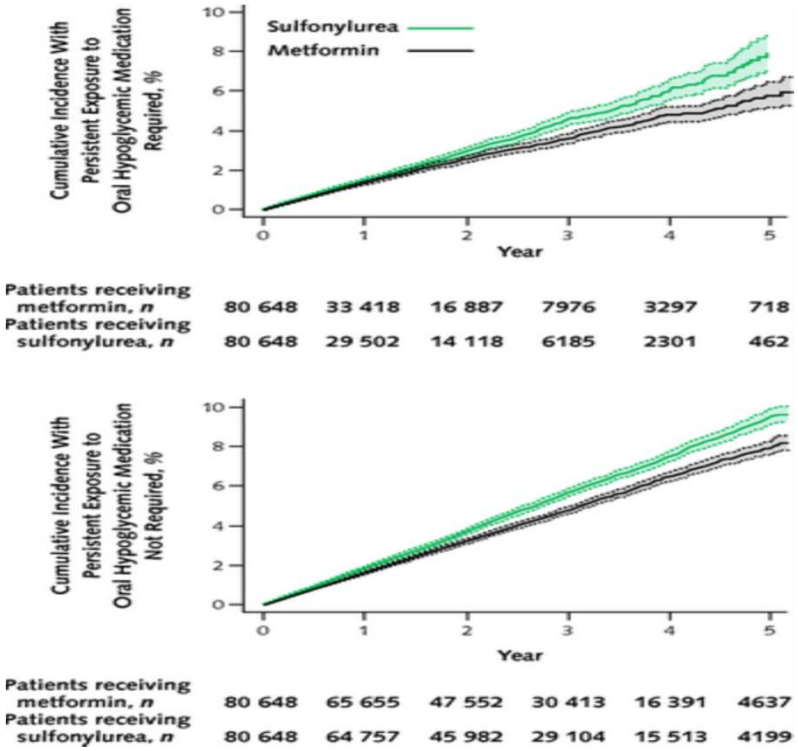
Pharmacological characteristics of SU

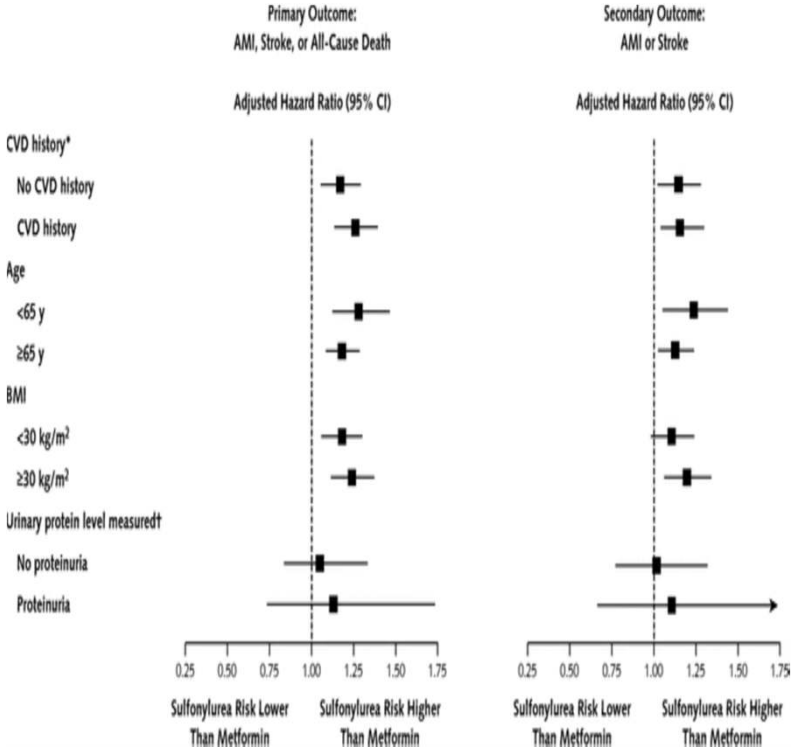
Drugs	Dose range (mg)	Duration (hr)	Dosage/day (T)	Metabolism/Excretion
First generation				
Tolbutamide	500-3,000	6-12	2-3	Hepatic with renal excretion
Chlorpropamide	100-500	24-72	1	Renal excretion(30%), some hepatic metabolism
Second generation				
Glipizide	2.5-40	16-24	1-2	Hepatic, renal excretion of inactive metabolites
Glibenclamide	1.25-20	12-24	1-2	Hepatic, renal excretion of inactive metabolites
Glimepiride	1-8	12-24	1	Hepatic with renal excretion of active metabolites
Gliquidone	15-60	8-10	1-2	Hepatic with renal excretion of inactive metabolites
Gliclazide	40-320	10-15	1-2	Hepatic with renal excretion of inactive metabolites

J Nephrol 2010;23(Suppl15):S72-S79

CV outcome of Sulfonylurea

Comparative Effectiveness of Sulfonylurea and Metformin Monotherapy on Cardiovascular Events in Type 2 Diabetes Mellitus: A Cohort Study





Ann Intern Med. 2012;157(9):601-610

Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Sulphonylureas are widely used for patients with type 2 diabetes mellitus. Sulphonylureas lower blood glucose by stimulating insulin secretion from the pancreas thereby increasing the insulin levels in the blood. Seventy-two trials were included in the systematic review assessing the effects of sulphonylurea as sole therapy versus other comparators in patients with type 2 diabetes mellitus. A total of 22,589 participants were included. The number of participants randomised to a sulphonylurea was 9707 and the number of participants randomised to a comparator was 12,805. The duration of the interventions varied from24 weeks to 10.7 years. All trials had deficiencies (risk of bias) and for the individual comparisons the number of participants were small, resulting in a high risk of random errors (play of chance). Data on mor Data on mortality and diabetic complications were sparse and inconclusive the antidiabetic drug due to adverse events were more common with alpha-glucosidase inhibitors (for example acarbose) compared with second-generation sulphonylureas (for example glibenclamide, glipizide, glibornuride and gliclazide), but the data were sparse. Severe hypoglycaemia was more common with second-generation sulphonylureas compared with metformin and thiazolidinediones (for example pioglitazone), but again the data were sparse. Due to lack of data we could not adequately evaluate health-related quality of life and costs.
There is insufficient evidence regarding patient-important outcomes from high-quality randomised controlled trials (RCTs) to support the decision as to whether to initiate sulphonylurea as sole therapy. Large-scale and long-lasting randomised clinical trials with low risk of bias, which focus on mortality, diabetic complications, adverse events and health-related quality of life, are needed.

THE COCHRANE COLLABORATION®

- second-generation sulfonylureas
  - ✓ selective for the pancreatic sulfonylurea receptors

: toxicity of older sulfonylureas on ATP-dependent potassium channels on cardiac cells and coronary vessels

The Cochrane Library 2013, Issue 4

Diabetes, Metabolic Syndrome and Obesity 2014:7 391–400

Meglitinide

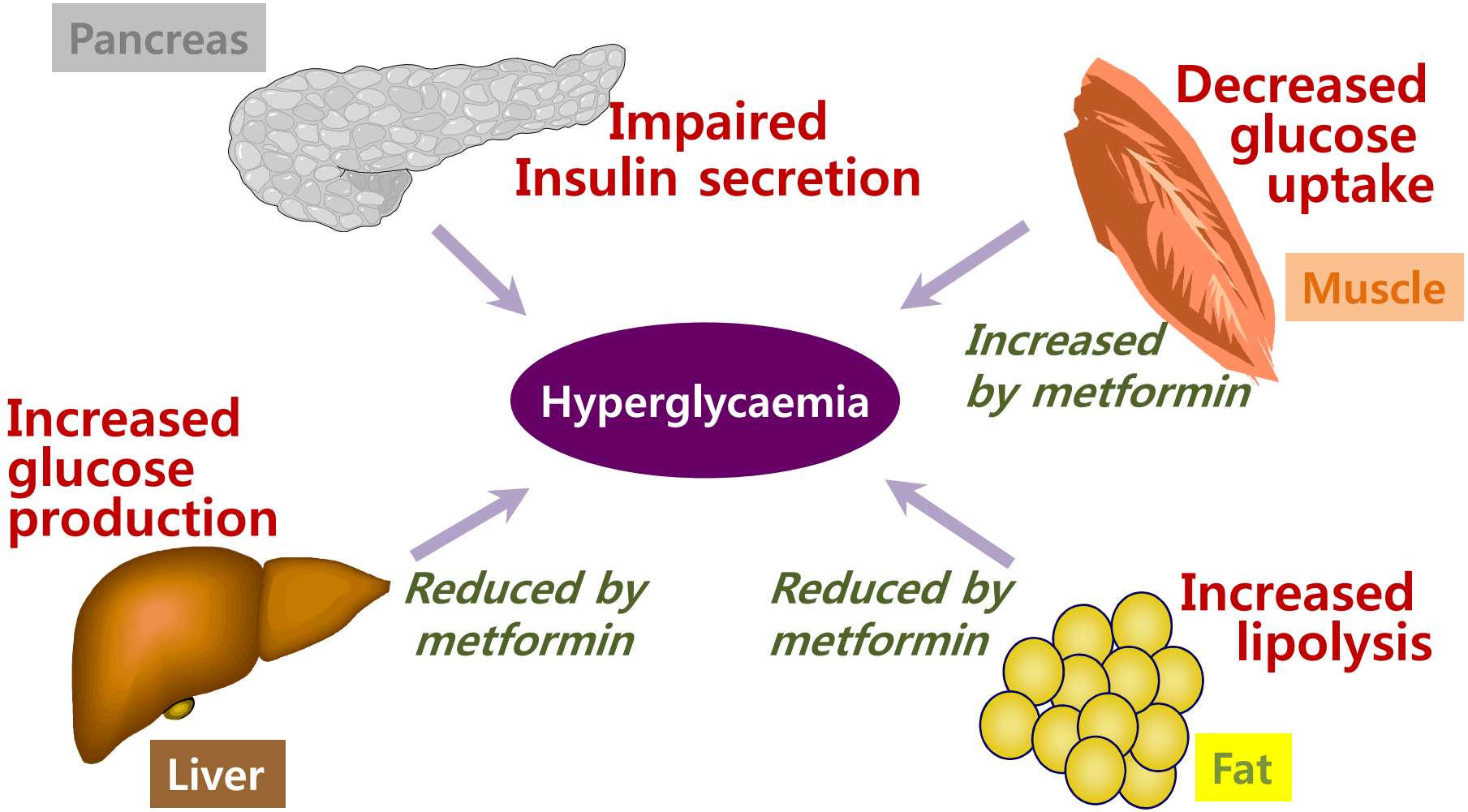
- Rapid-acting insulin secretagogues
- Avoid under 30 ml/min of CCR

Drug	Repaglinide, Nateglinide, Mitiglinide
Action Mechanism	Release of insulin from pancreatic β-cell
Dosing in Elderly	
Repaglinide	0.5-4 mg 30 min before each meal
Nateglinide	60-120 mg 30 min before each meal
Mitiglinide	10 mg 30 min before each meal
Geriatric Considerations	May be helpful in those with **irregular eating habits**

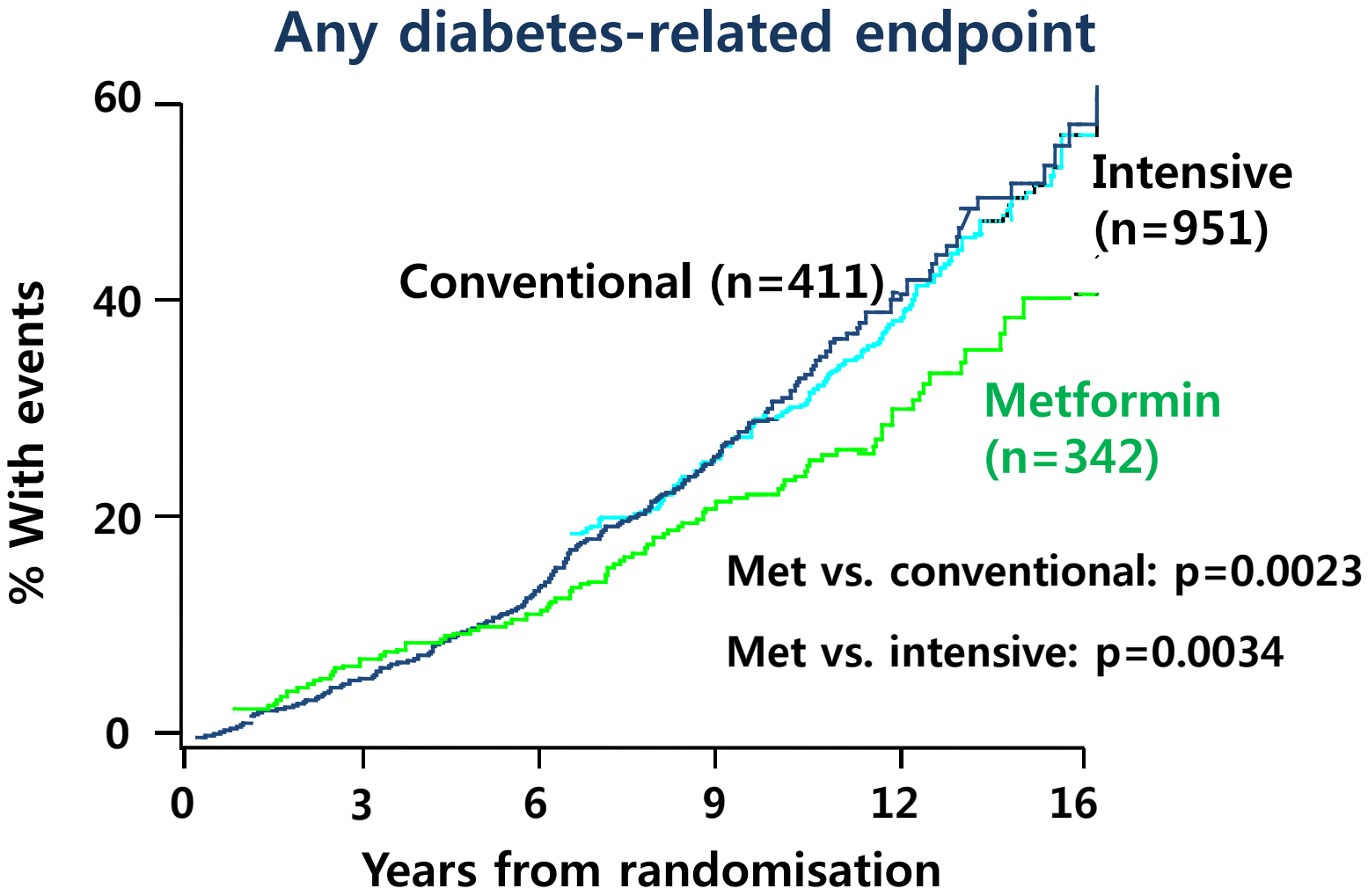
Am J Geriatr Pharmacother. 2009;7:324–342

Insulin Sensitizers :
Biguanides & Thiazolidinediones

Metformin addresses key endocrine defects in the pathophysiology of type 2 diabetes



Clinical outcomes in overweight Pts in the UKPDS



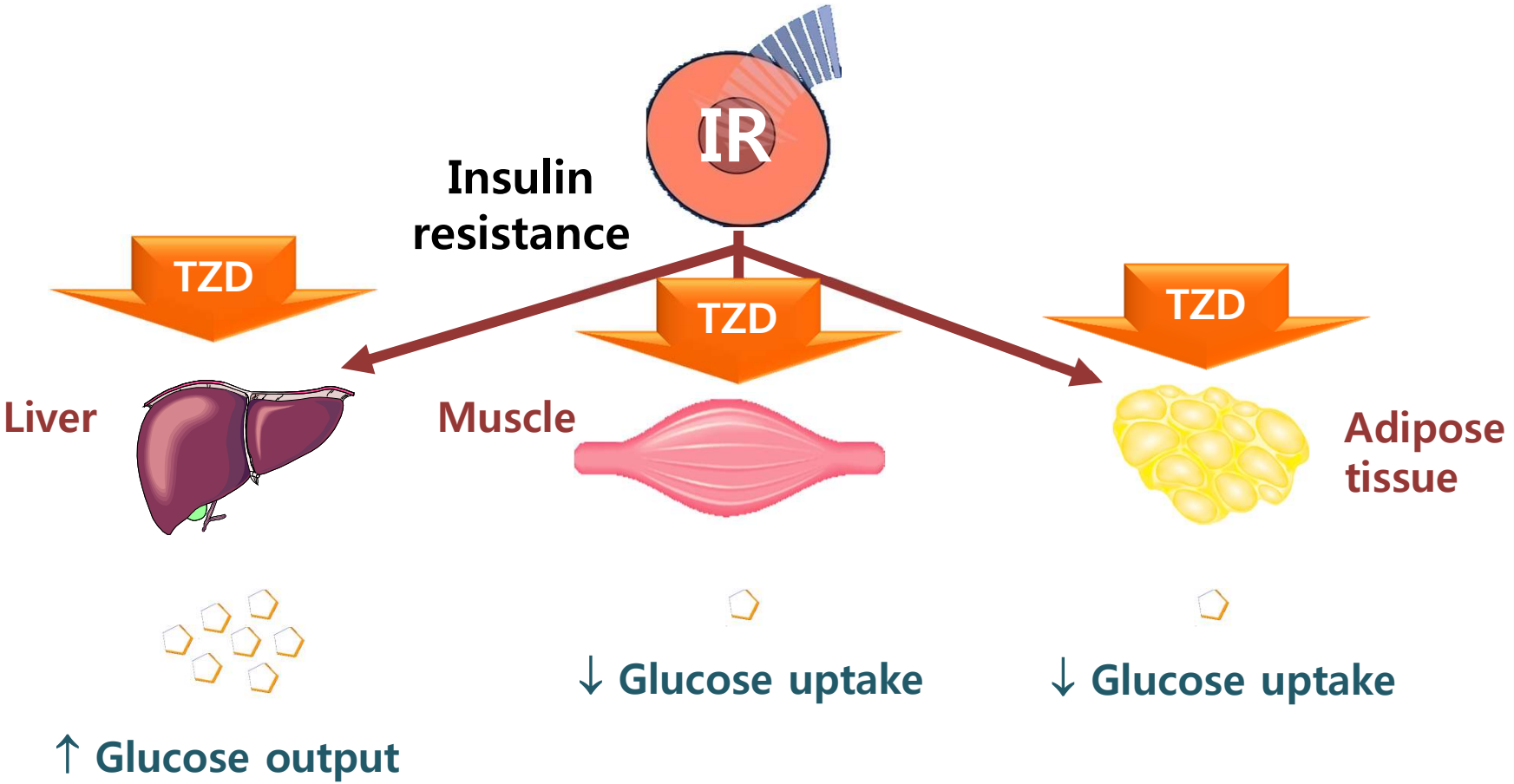
UKPDS 34. *Lancet* 1998;352:854-65

Consideration of Metformin

- Common side effects
  - GI upset, diarrhea, anorexia, weight loss
  - Vitamin B_{12} deficiency
  - Lactic acidosis
- No candidates
  - frail, anorexic, underweight, CHF, renal or hepatic insufficiency or dehydration
- Contraindication
  - S-Cr ≥1.5 mg/dl(men), ≥1.4 mg/dl(women)
  - CrCl < 60 mL/min

Am J Geriatr Pharmacother. 2009;7:324–342

Effects of TZD on Insulin Sensitivity



N Engl J Med. 2004; 351:1106–1118

TZD and Heart failure

Absolutely contraindication in patients with class III or IV heart failure

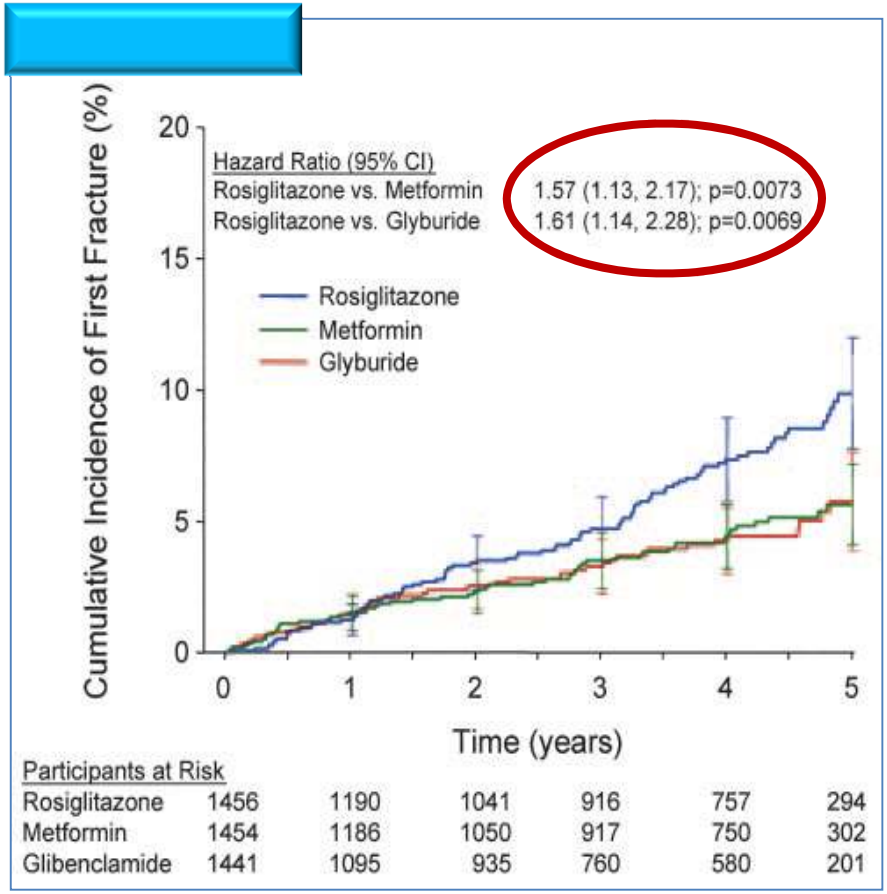
Risk factors for TZD-associated *Heart Failure*

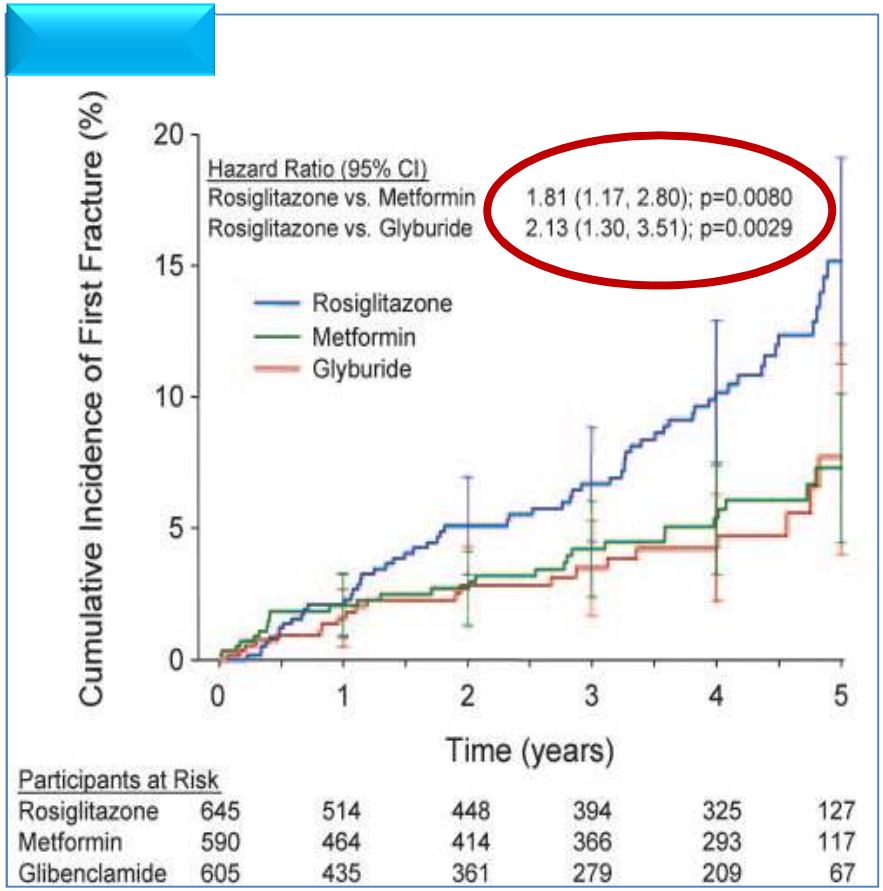
Age > 70 years
S-Cr > 2.0 mg/dL
Weight gain or development of edema while taking a TZD
Treatment with loop diuretics
Use of insulin
Left ventricular hypertrophy
Presence of aortic or mitral valve heart disease

Diabetes Care. 2004;27:256–263

TZD and Fracture risk

A Diabetes Outcome Progression Trial (ADOPT)





Diabetes Care. 2008;31:845–851

Geriatric Considerations of TZD

- CHF exacerbation
- Potential CV risk
- Risk of edema
- Weight gain
- Increased fracture risk
- CHF increased at higher doses and with insulin

Am J Geriatr Pharmacother. 2009;7:324–342

α-glucosidase inhibitors

α-glucosidase inhibitor

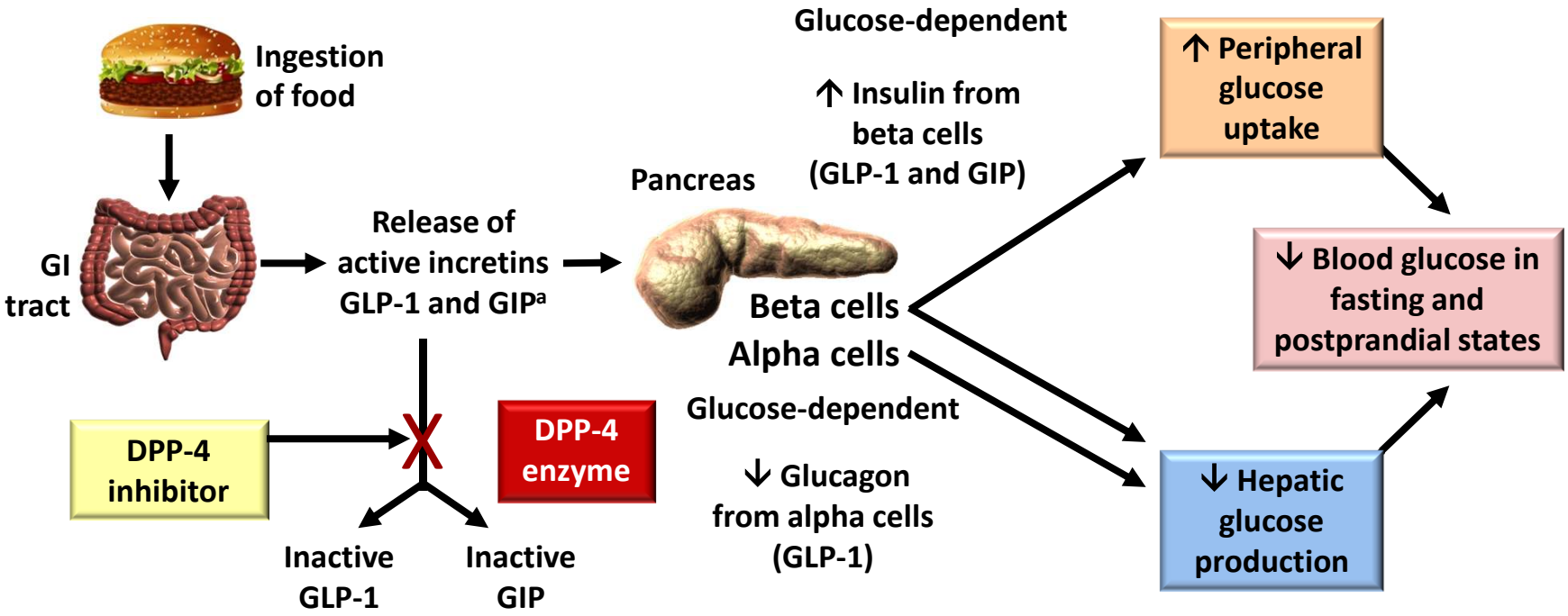
Drug	Acarbose. Voglibose
Action Mechanism	Competitive and reversal inhibition of intestinal α-glucosidase hydrolase and pancreatic amylase
Dosing in the Elderly Acarbose	Initiate at 25 mg, titrated in 25-mg , increments q 4-8wk to max. of 50-100mg Weight ≤60 kg: maximum 50 mg/meal Weight >60 kg: maximum 100 mg/meal
Use in Renal Impairment	CrCl ≤ 24 mL/min : not recommended
Use in Hepatic Impairment	Contraindicated in cirrhosis
Common AEs	Flatulence, diarrheas, GI upset, increased LFT
Geriatric consideration	Minimal risk of hypoglycemia

CAUTION !!!
: concurrent prandial insulin or insulin secretagogues

Am J Geriatr Pharmacother. 2009;7:324–342

Dipeptidyl Peptidase-IV inhibitors

DPP-IV inhibitor

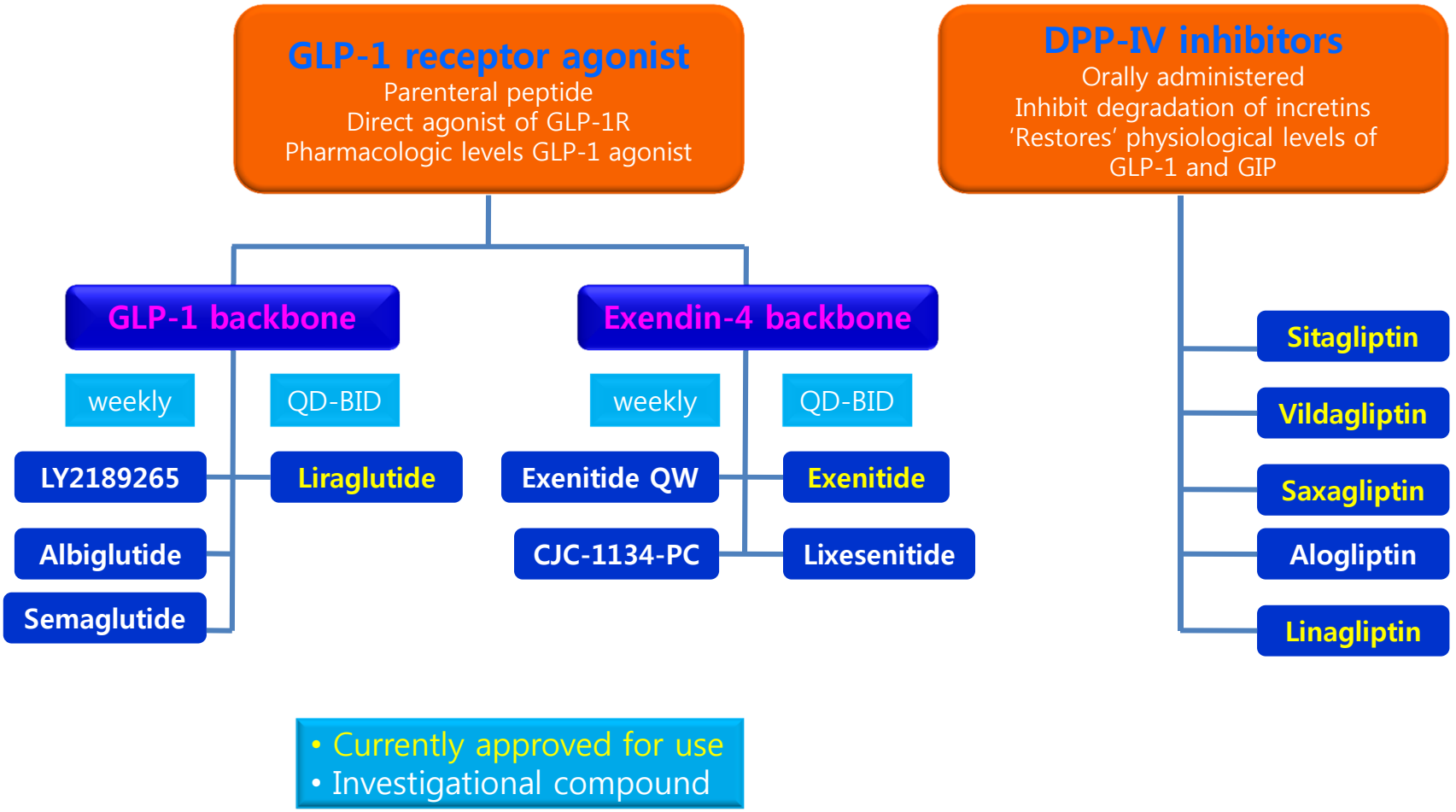


The glucose-dependent mechanism of DPP-4 inhibitors targets 2 key defects

: insulin release and unsuppressed hepatic glucose production.

Adapted from Brubaker PL, Drucker DJ *Endocrinology* 2004;145:2653–2659; Zander M et al *Lancet* 2002;359:824–830; Ahrén B *Curr Diab Rep* 2003;3:365–372; Buse JB et al. In *Williams Textbook of Endocrinology*. 10th ed. Philadelphia, Saunders, 2003:1427–1483.

Incretin :
GLP-1 Agonists and DPP IV inhibitors



2011 71th ADA Current Issue

Considerations of DPP-IV inhibitors

Drug	Sitaglipitin, Vildagliptin
Dosing in the Elderly	
Sitagliptin	100 mg/d
Vildagliptin	100 mg/d
Use in Renal Impairment	
Sitagliptin	CrCl 30-50 mL/min : 50mg/d CrCl ≤ 30 mL/min : 25 mg/d
Use in Hepatic Impairment	No adjustment required
Common AEs	Headache, Nausea, vomiting, diarrhea
Geriatric consideration	Minimal reisk of hypoglycemia, weight neutral

Am J Geriatr Pharmacother. 2009;7:324–342

Clinical Guideline about DPP-IV Inhibitor

2009 Clinical Guidance from UK National Institute for Health and Clinical Excellence

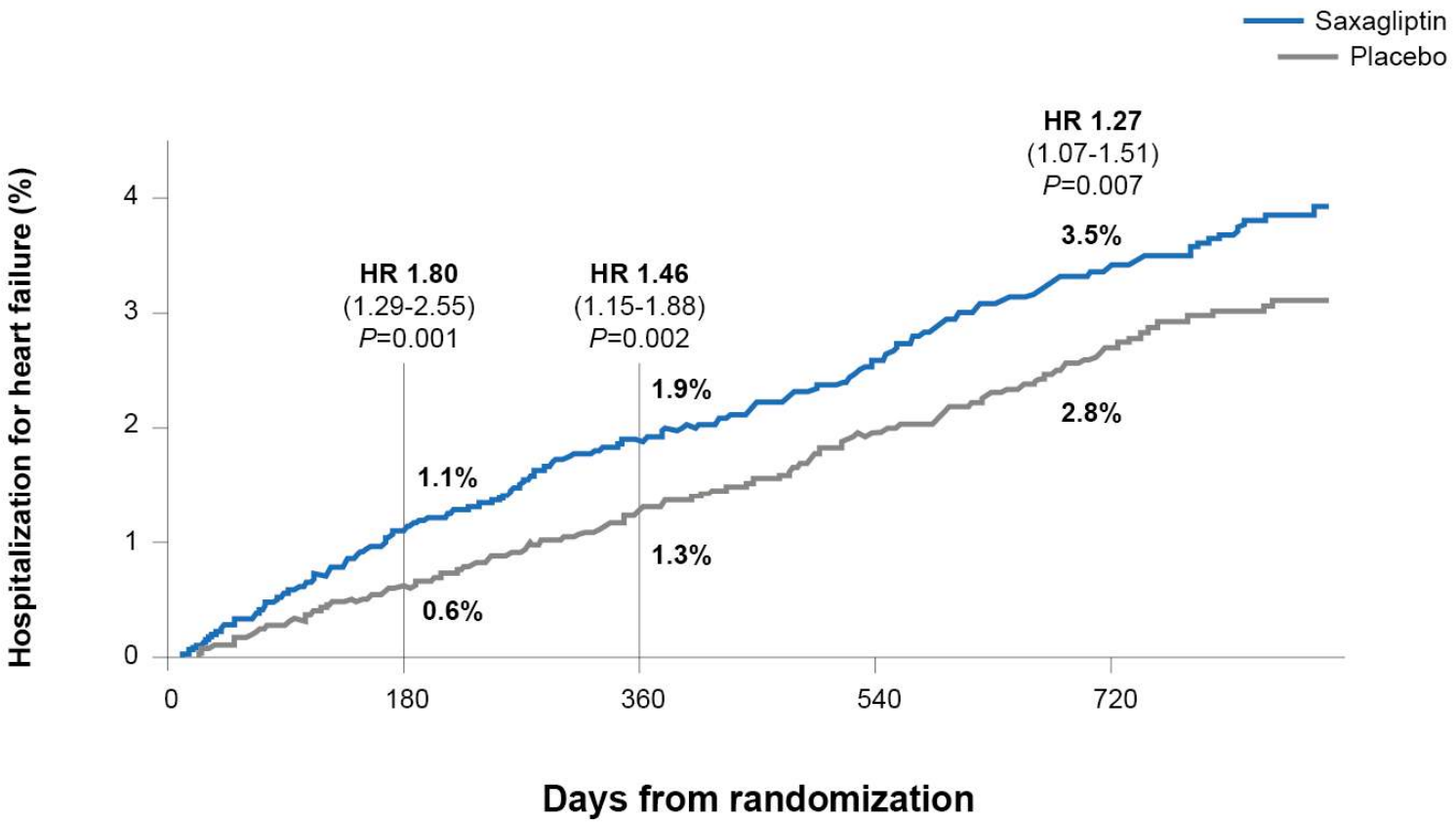
Considering **DPP-4 inhibitors** rather than SUs as second-line therapy after first-line metformin in patients who are at **high risk for hypoglycemia** or **its consequences** for example older adults with hazardous jobs (eg, working at heights, working with heavy machinery) and those who **live alone**

European Diabetes Working Party for Older People 2011 Clinical Guidelines for Type 2 Diabetes Mellitus

Consider a **DPP-4 inhibitor** as an add-on to metformin when use of a sulphonylurea may pose an unacceptable **hypoglycemia risk** in an older patient with diabetes

http://www.nice.org.uk/CG87shortguideline. Accessed July 3, 2009 ,
Diabetes & Metabolism ,2011:37;S27-S38

SAVOR-TIMI: more patients receiving saxagliptin were hospitalized for heart failure compared to placebo

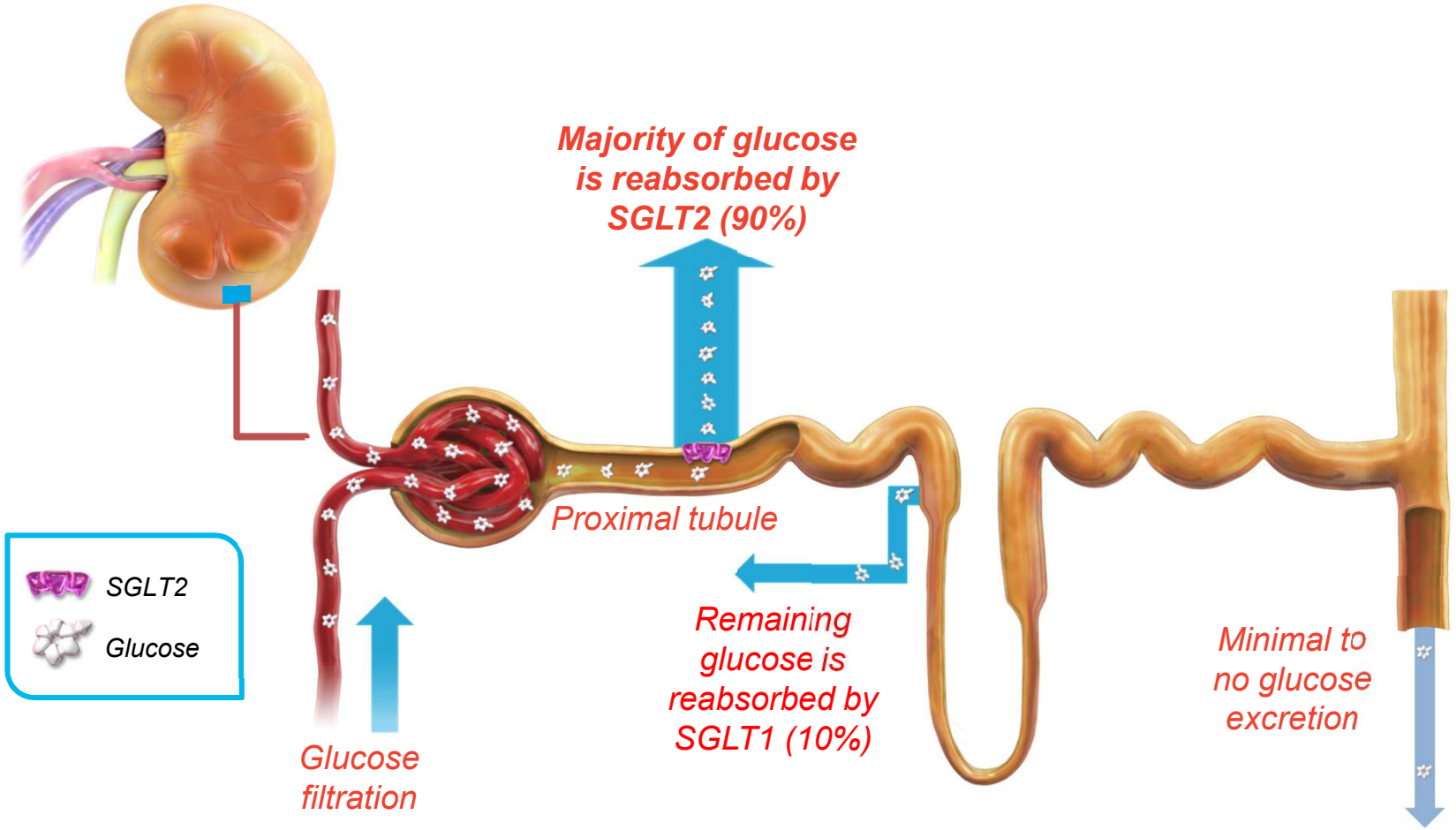


Placebo	8212	8036	7856	7389	4959
Saxagliptin	8280	8064	7867	7375	4978

Scirica BM, et al. *Circulation* 2014, Sept [ePub ahead of print]; doi: 10.1161/CIRCULATIONAHA. 114. 010389

Sodium-glucose cotransporter 2 Inhibitor

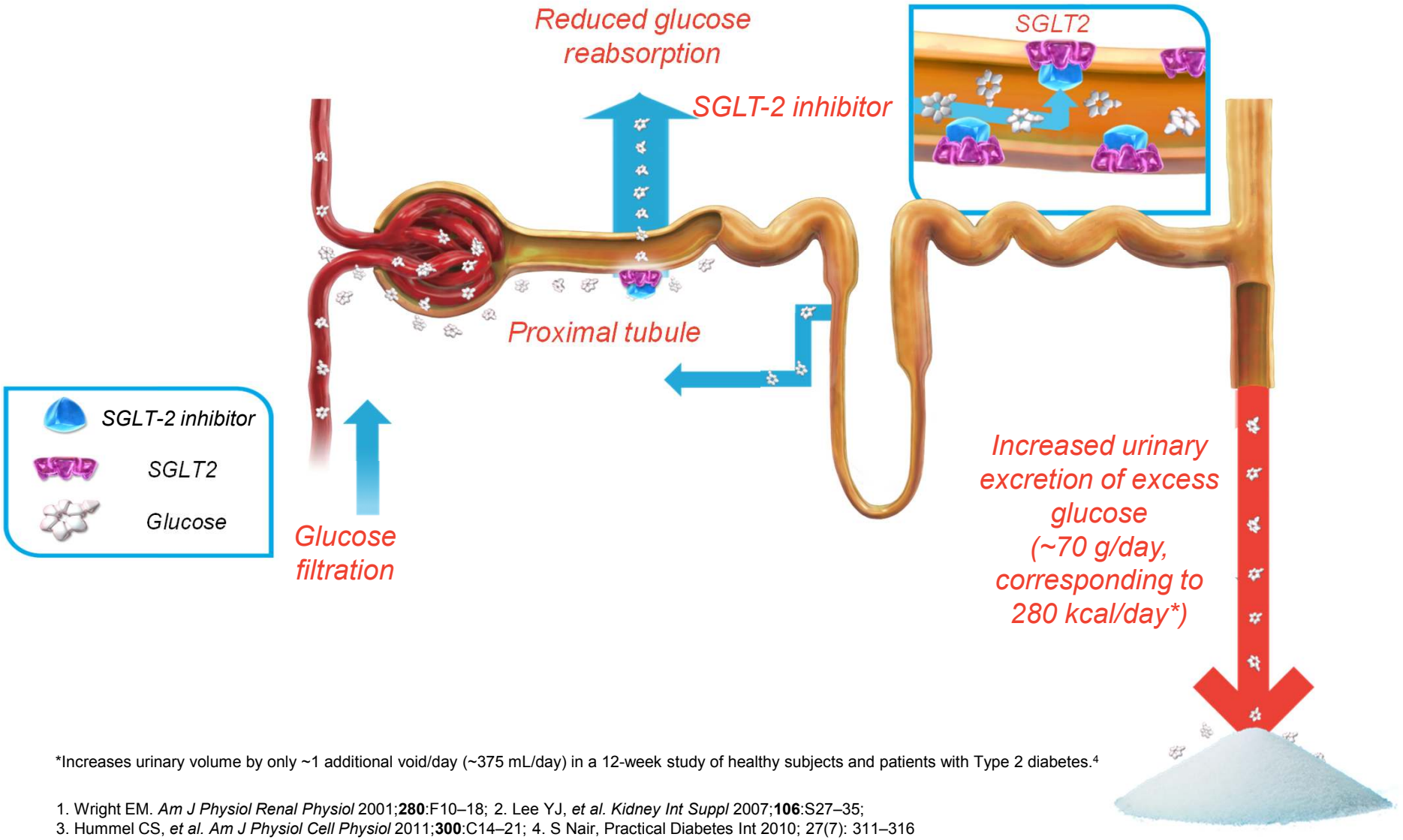
Normal renal glucose handling



SGLT, sodium-glucose co-transporter.

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35;
3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21.

Action mechanism of SGLT-2 Inhibitor



*Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy subjects and patients with Type 2 diabetes.[4]

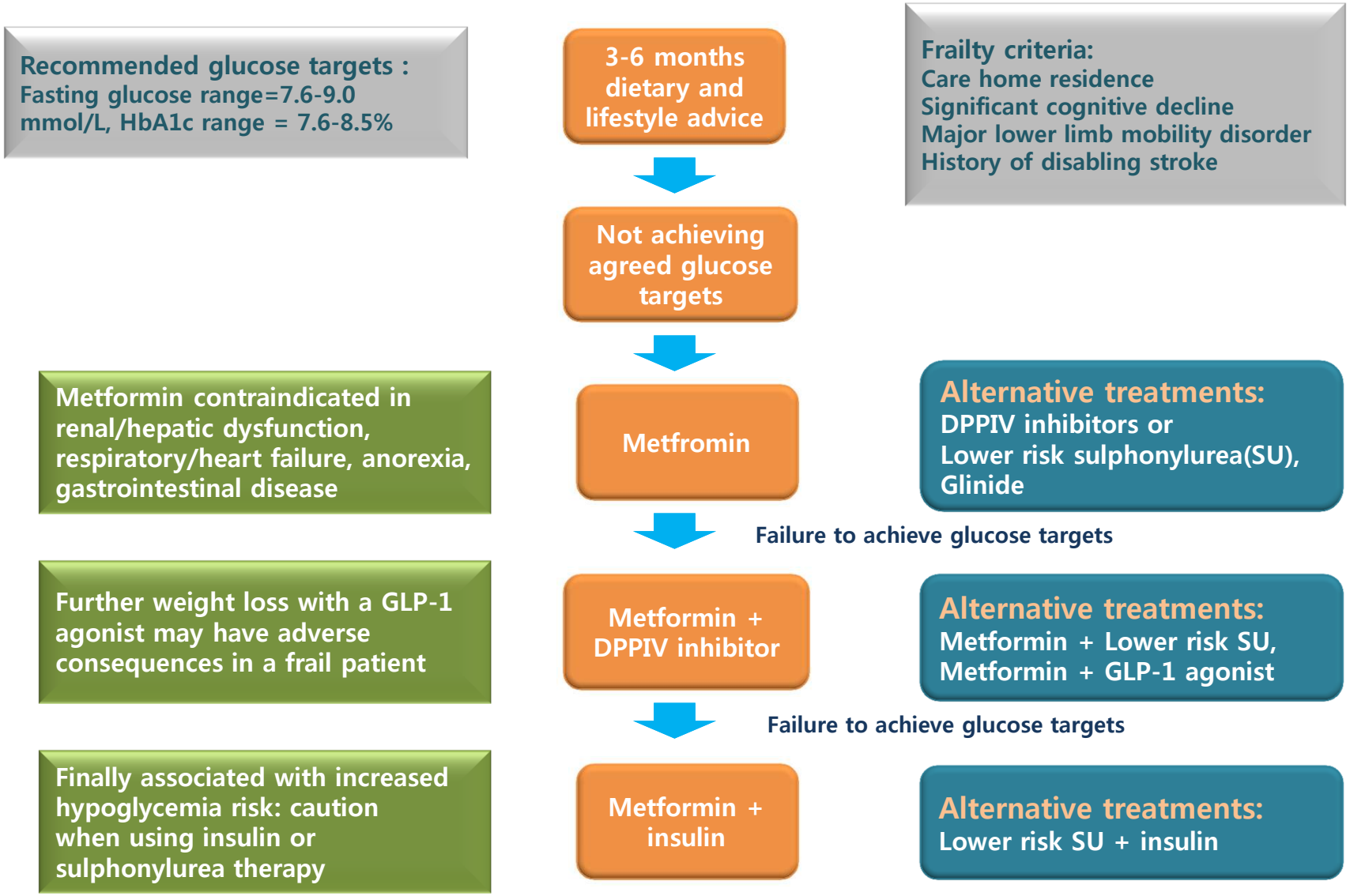
1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35;
3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21; 4. S Nair, Practical Diabetes Int 2010; 27(7): 311–316

SGLT-2 inhibitor

- Benefit
  - ✓ Low incidence of hypoglycemia
  - ✓ Decreasing weight & blood pressure
- Main side effect
  - ✓ Increase incidence of genitourinary tract infection
- Geriatric consideration
  - ✓ Caution
    - ➢ Renal impairment patient (GFR < 60 ml/min/1.73 m^2)
    - ➢ Loop diuretic user
    - ➢ Low body weight

Curr Med Res Opin. 2012;28(7):1173–1178
Ann Med. 2012;44(4):375–393

glucose-lowering algorithm for frail patients with T2DM



European Diabetes Working Party for Older People / Diabetes & Metabolism 37 (2011) S27-S38

CONCLUSIONS

- Individualization
- Start low and Go slow

Thank you for your attention!!