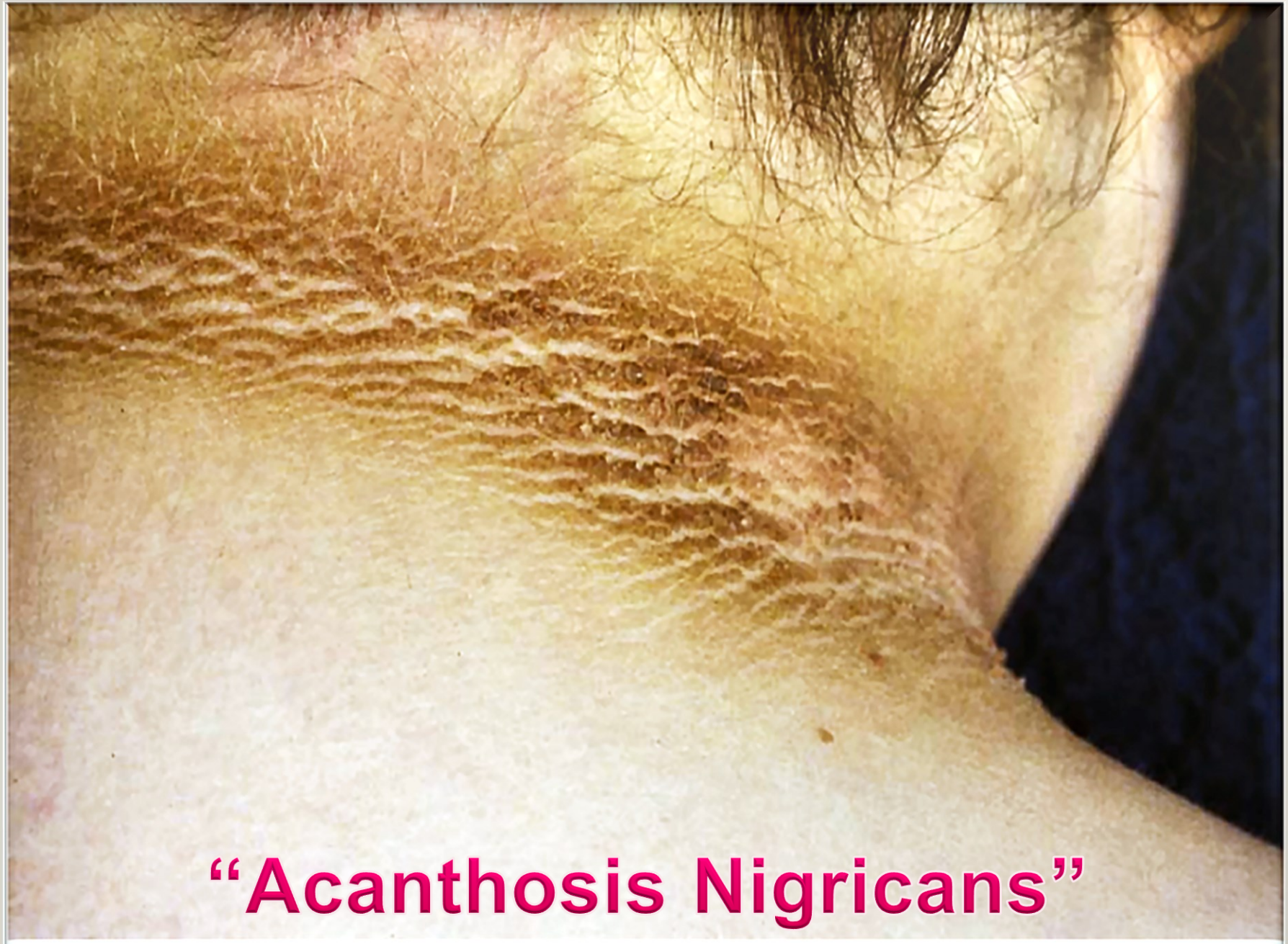
In the Name of God

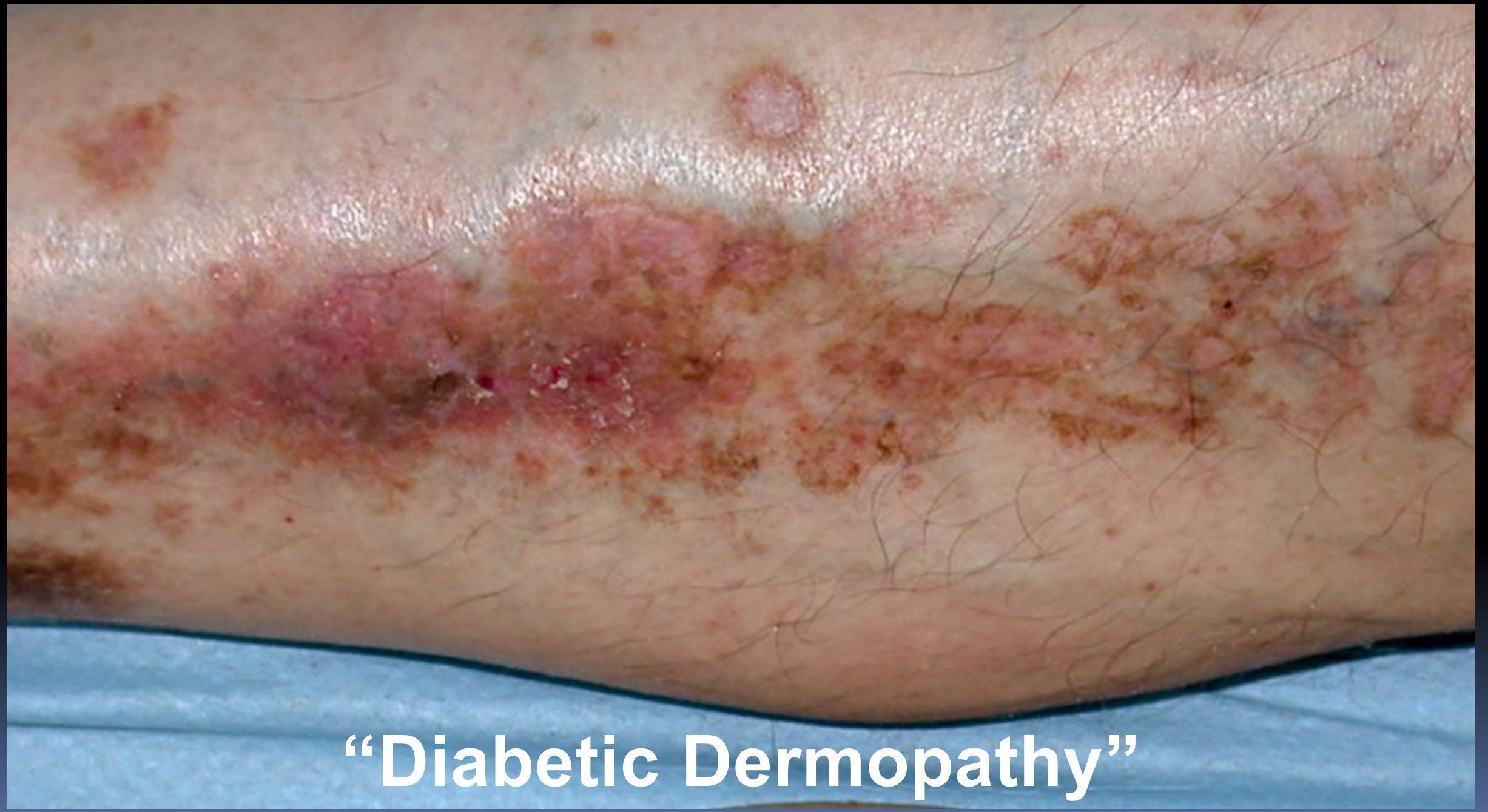
Oral Antidiabetic Agents
(Sulfonylureas,Glinides and TZDs)

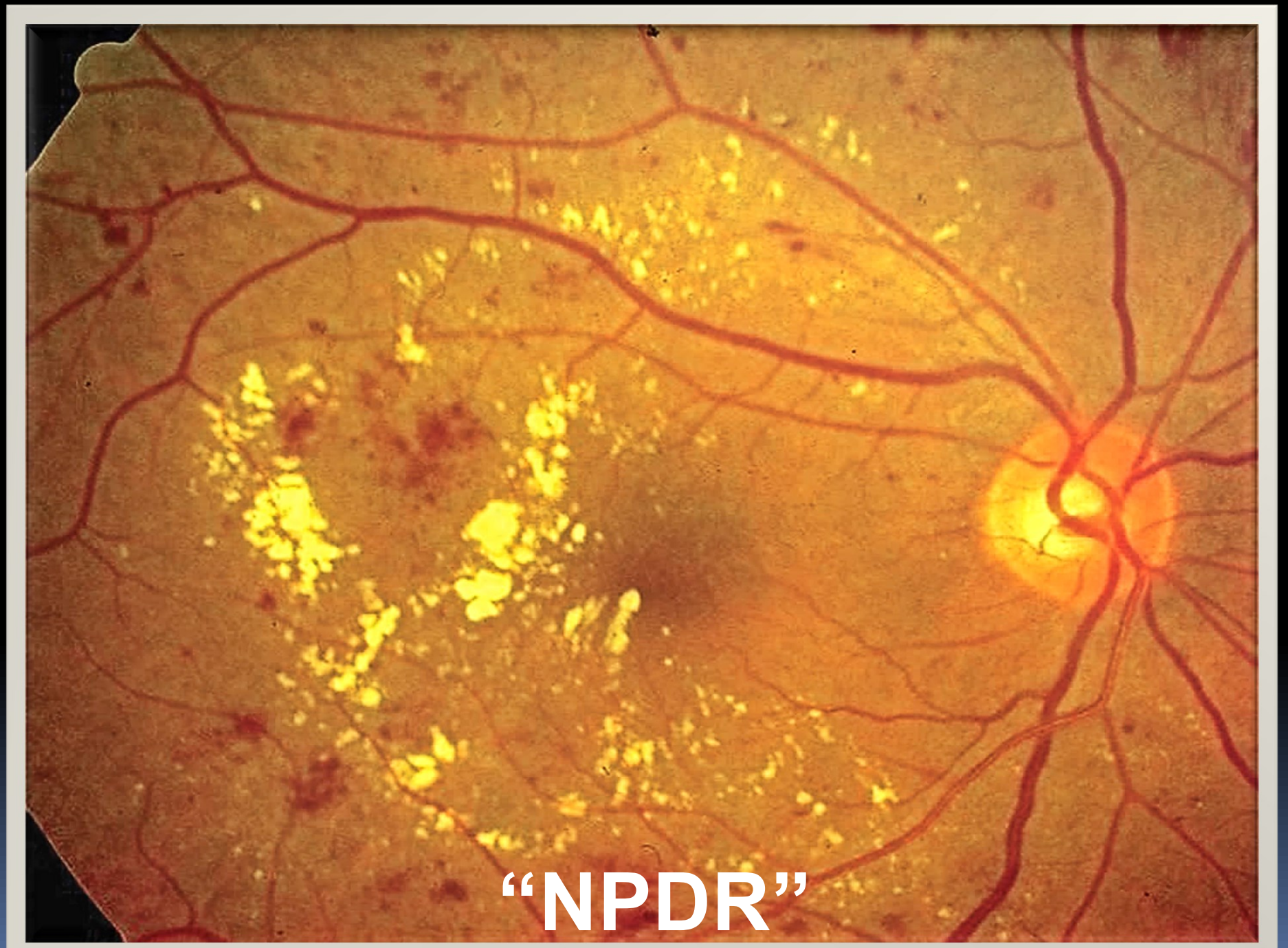
Navid Saadat, MD
Associate Professor of Endocrinology
Shahid Beheshti University of Medical Sciences

Case Study

آقای ۶۲ ساله ای با سابقه ۷ ساله دیابت بعلت کنترل نامناسب قند و فشار خون از طرف پزشک خانوادگی خود به درمانگاه داخلی ارجاع می گردد. سابقه دیابت در مادر وی وجود داشته است و در طی ۵ سال اخیر ۸ کیلوگرم کاهش وزن را ذکر می کند. وی روزانه ۱۰ نخ سیگار و گاهی الکل مصرف می نماید. در سابقه خود تنگی نفس کوششی از دو سال پیش داشته و در سال گذشته بعلت آنژین صدری سه روز در CCU بستری بوده است. داروهای فعلی وی شامل گلیکلازید (۸۰ mg دو بار در روز)، متفورمین (۵۰۰ mg سه بار در روز)، متوپرولول (۵۰ mg دو بار در روز)، آتورواستاتین (۲۰ mg روزانه) و آسپرین (۸۰ mg روزانه) می باشد. در معاینه فیزیکی رالهای پراکنده در قاعده هر دو ریه و در سمع قلب S3دارد. بعلاوه "Acanthosis Nigricans" در پشت گردن و زیر بغل، ادم 1+ اندام تحتانی همراه با خشکی پوست و ریزش مو و درموپاتی درقدام ساق هر دو پا و کاهش نبض در "Tibialis Anterior" و "Dorsal Pedis" و کاهش حس سرما و گرما و مختل بودن آزمون مونوفیلامان بعلاوه باریک شدن عروق ته چشم و وجود اگزودا و نقاط پراکنده خونریزی Dot & Blot جلب توجه می کند.


“Acanthosis Nigricans”


“Diabetic Dermopathy”


“NPDR”

BP = 170/100 mmHg
PR = 68 bpm
Weight = 97 kg
Height = 172 cm
WC = 105 cm

FBS = 240 mg/dl
BS-2hpp = 380 mg/dl
HbA_{1c} = 9.3%
Na^+ = 142 mEq/l
K^+ = 4.2 mEq/l
Creatinine = 1.4 mg/dl

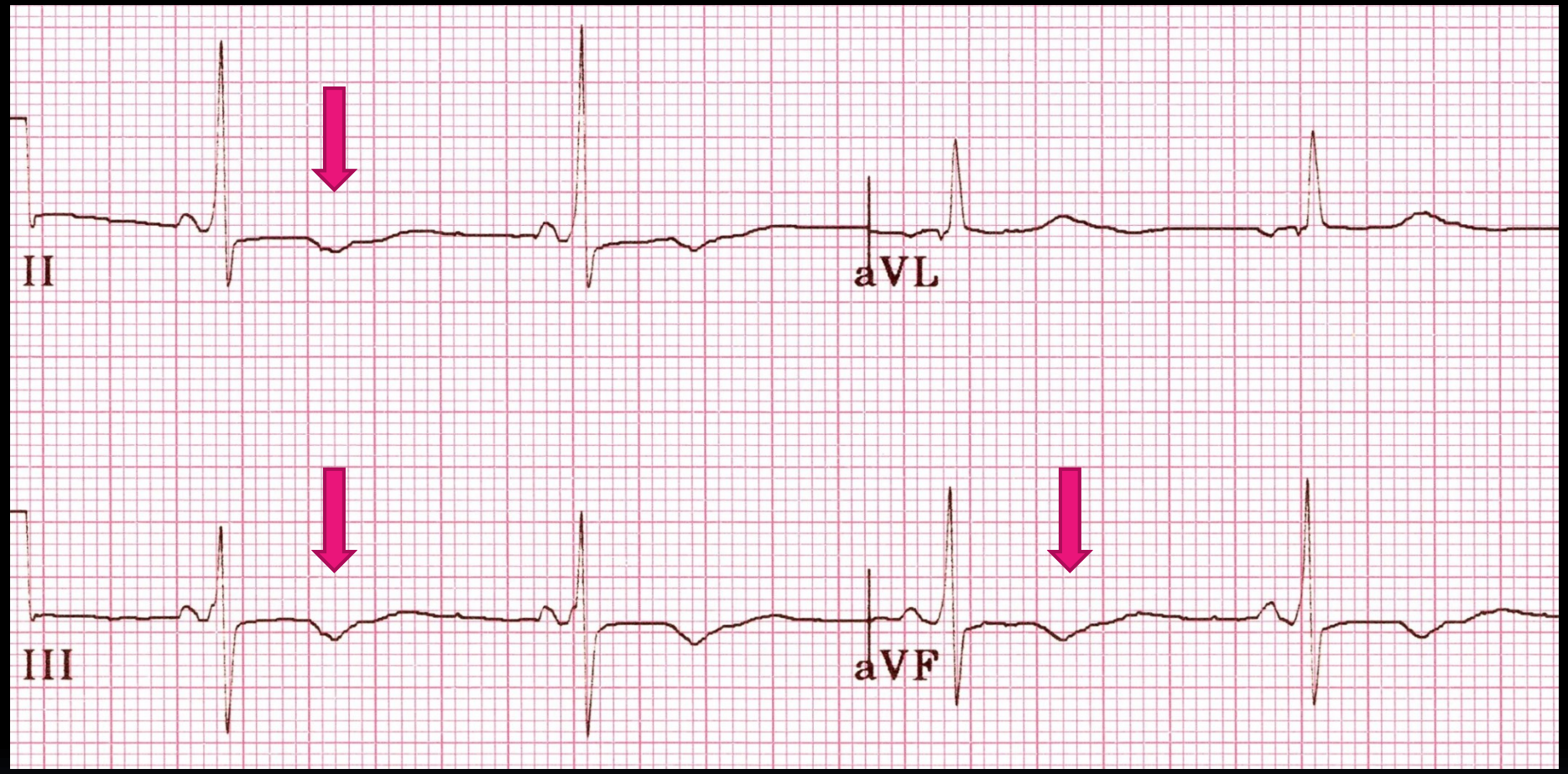
Cholesterol = 230 mg/dl
Triglyceride = 330 mg/dl
HDL-C = 32 mg/dl
LDL-C = 132 mg/dl
Non-HDL = 198 mg/dl

ALT = 98 IU/L (up to 35)
AST = 66 IU/L (up to 35)
GGT = 97 IU/L (up to 85)
ALP = 310 IU/L (up to 290)
Albumin = 4.2 g/dl (3.5–5.5)
INR = 1.0 (0.9-1.1)
PT = 12 sec (11-13)
Bilirubin (total) = 0.7 mg/dl (0.3-1.0)

ANA and ASMA = Negative
HBV-Ab and HCV-Ab = Negative

Ferritin = 112 (40-200 ng/ml)
SI = 93 μg/dl (60-150) & TIBC = 340 μg/dl (300-360)
Saturation = 27%

24 hr U_{vol} = 3200 ml
24 hr U_{Pro} = 260 mg
24 hr U_{creat} = 1850 mg



Echocardiography

EF = 35%

LVH + Diastolic dysfunction

BMI Definition (kg/m^2)

- < 18.5 Underweight
- 18.5-24.9 Normal
- 25.0-29.9 Overweight
- 30.0-34.9 Obesity (Class I)
- 35.0-39.9 Obesity (Class II)
- 40.0-49.9 Obesity (Class III)
- ≥ 50.0 Obesity (Class IV)

- BMI = $97 / 1.72^2 \simeq 33\ kg/m^2$ (class I)
- eGFR :
  - EPI-CKD ≃ 57 ml/min
  - MDRD ≃ 52 ml/min

شیوه انتخابی برای کنترل هیپرگلیسمی بیمار چیست؟

چه ملاحظاتی در انتخاب و تجویز منطقی دارو بایستی مد نظر باشد؟

Individualized Approach

ABCDEF of diabetes treatment

- **A** = **A**ge
- **B** = **B**ody weight
- **C** = **C**omplications (micro - & macrovascular)
- **D** = **D**uration of diabetes
- **E** = **E**xpense
- **F** = Li**F**e expectancy

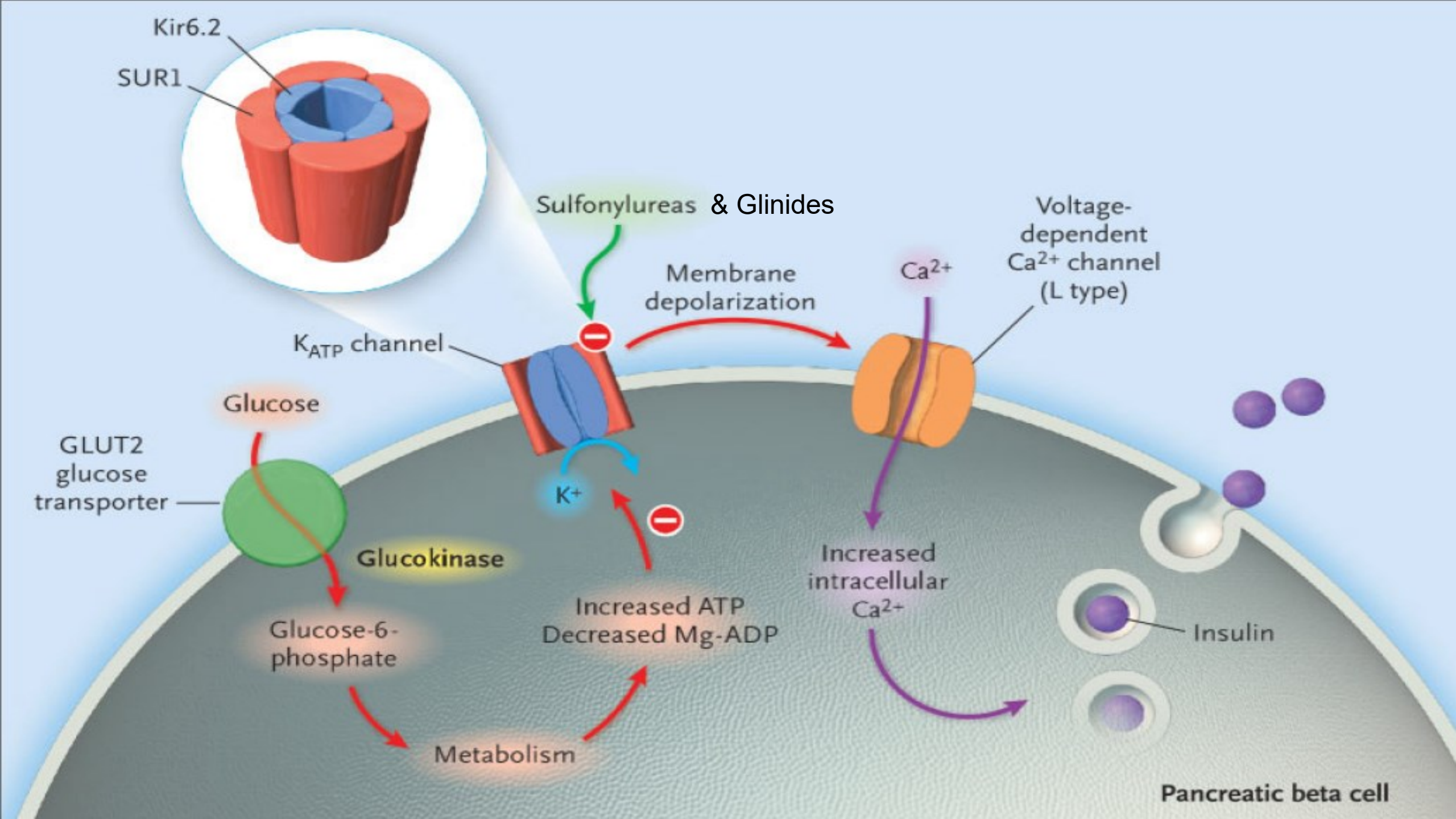
- **Fasting hyperglycemia**
  - Gliclazide
- **Postprandial hyperglycemia**
  - Repaglinide
- **Insulin sensitizer**
  - Pioglitazone

Efficacy

Intervention	Expected ↓ in HbA_{1c} (%)
Sulfonylureas	1.0 to 2.0%
Glinides	0.5 to 1.5%
TZDs	0.5 to 1.4%

Sulfonylureas

- Hypoglycemic effects of sulfonamide antibiotics were first recognized during a typhoid epidemic in France in 1942
  - Further work led to the development of sulfonylureas
  - The first agent being Carbutamide in 1955
- Binding to the SulfonylUrea Receptor (SUR1)
  - ATP-sensitive potassium (K_{ATP}) channel
    - Potassium Inward Rectifier (KIR6.2) closes
      - Intracellular calcium ↑
        - Insulin release


Kir6.2
SUR1
Sulfonylureas & Glinides
Membrane depolarization
Ca2+
Voltage-dependent Ca2+ channel (L type)
KATP channel
Glucose
GLUT2 glucose transporter
K+
Glucokinase
Increased intracellular Ca2+
Increased ATP Decreased Mg-ADP
Glucose-6-phosphate
Insulin
Metabolism
Pancreatic beta cell

SulfonylUreas Receptors (SUR) Isoforms

- SUR1
  - Pancreatic
- SUR2A
  - Cardiac
- SUR2B
  - Vascular

Sulfonylureas

- First generation
  - Tolbutamide
  - Acetohexamide
  - Tolazamide
  - Chlorporpamide
- Second generation
  - Glibenclamide
  - Gliclazide
  - Glipizide
- Third generation
  - Gliclazide MR
  - Glimepiride

Sulfonylurea Responsive Patients

- Absence of T1DM
- FBS < 250 mg/dl
- BS < 300 mg/dl
- Normal weight
- Onset of DM after age of 30-40 years
- Duration of DM < 5-10 years
- Residual β-cell function

Sulfonylureas : Adverse Effects

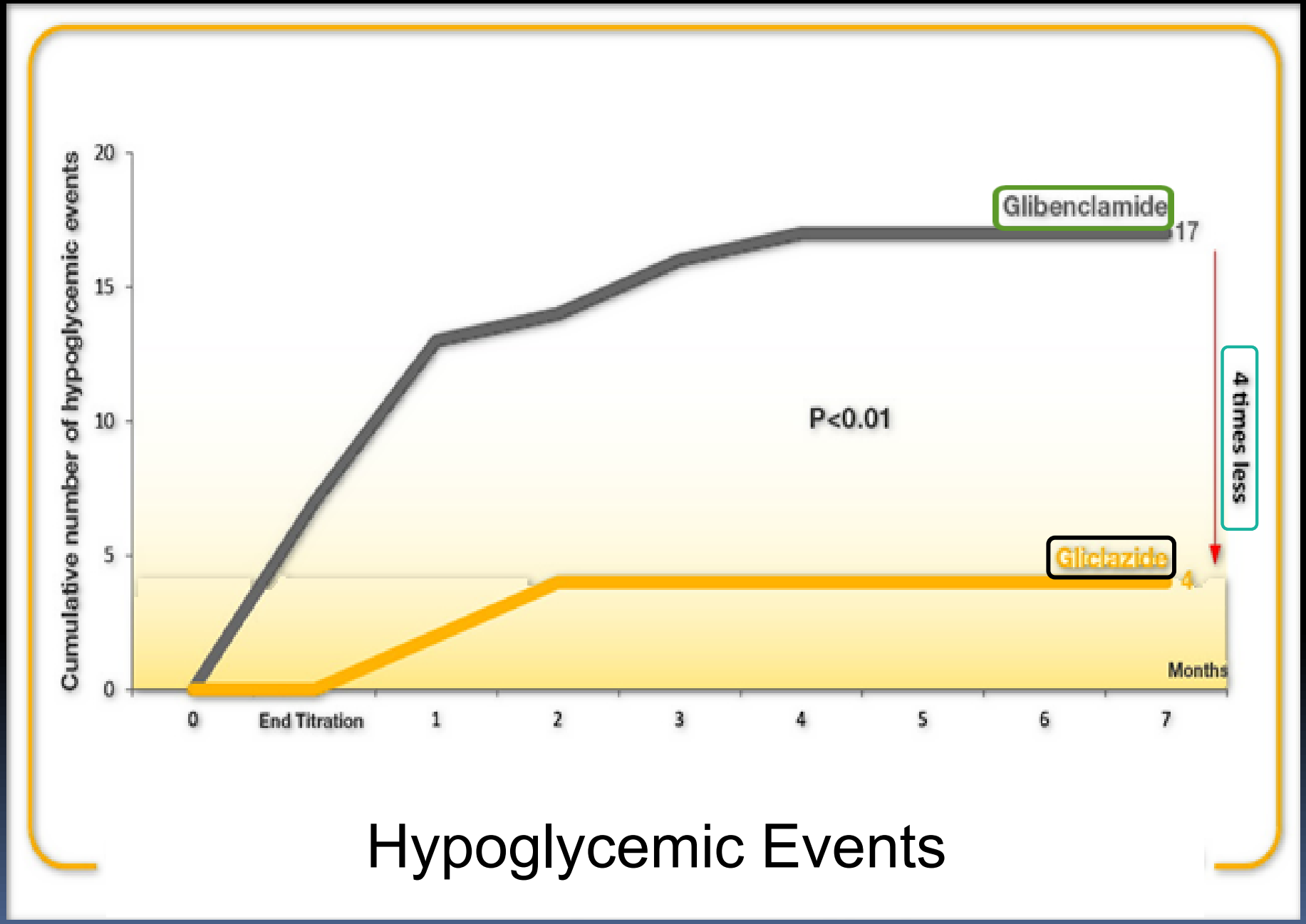
- Weight gain (1-4 kg)
- Hypoglycemia
  - Longer-acting agents
  - The use of other anti-diabetes agents
  - Tight glycemic targets
  - Excessive alcohol intake
  - Old age
  - Intercurrent infection
  - Renal impairment
- Cardiovascular events ?

Gliclazide

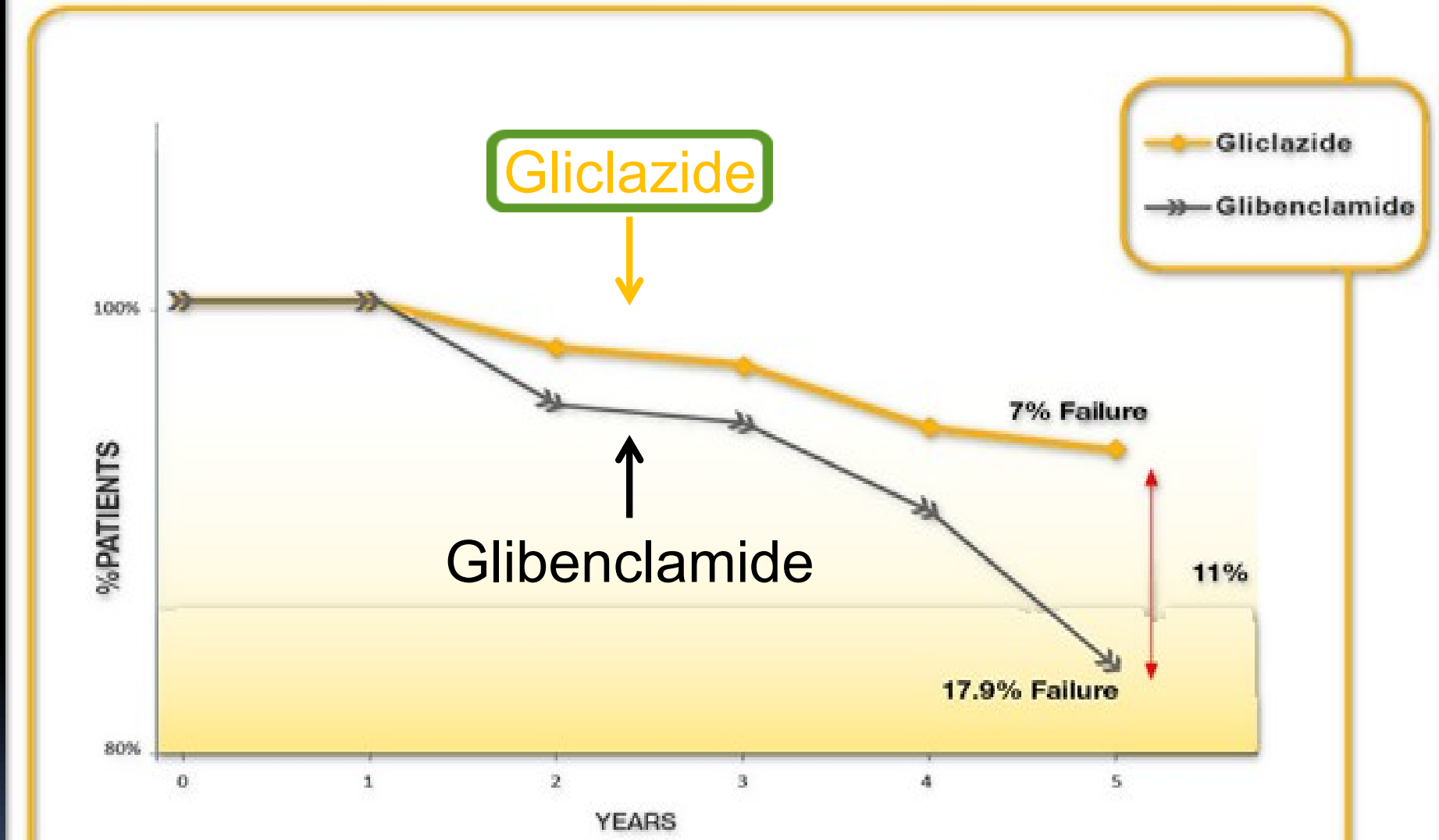
- Pharmacodynamic and kinetics
  - Pancreatic β-cells specific (SUR1)
  - Well absorption
  - Extensively bound to plasma proteins
  - Peak plasma concentration = 4-6 hrs.
  - Half-life = 10-12 hrs.
  - Metabolized in the liver to inactive metabolites
  - Metabolites are primarily eliminated via the kidneys

Gliclazide

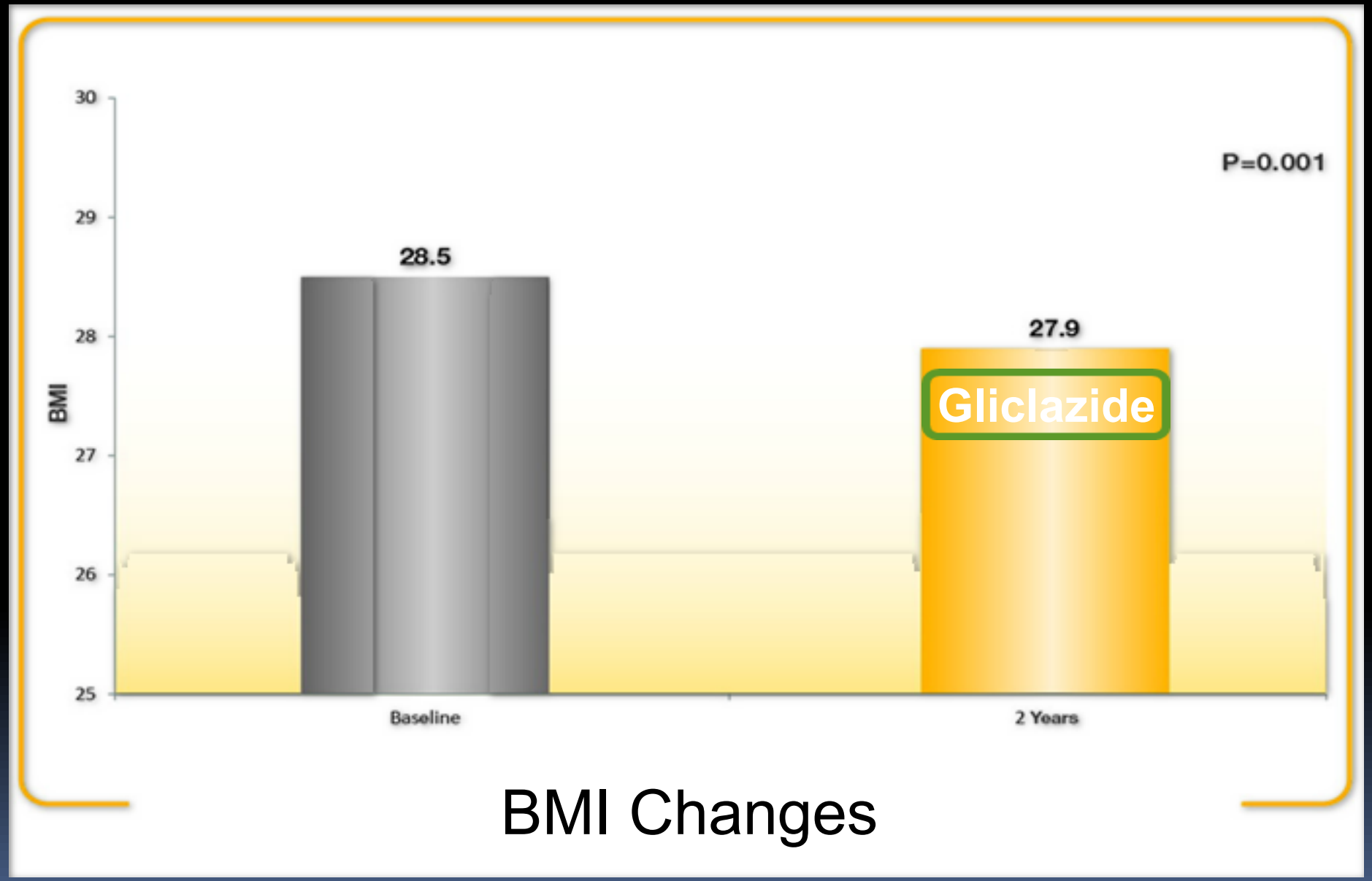
- Less likely to cause (vs. glibenclamide)
  - Hypoglycemia
  - Weight gain
  - Secondary failure
- Initial dose : 40-80 mg qd/bid (MR 30-60 mg qd)
- Adjustment : 80 mg (MR 30-60 mg) weekly
- Maintenance dose : 80-320 mg qd/bid (MR 30-120 mg qd)
- Maximum dose : 320 mg (MR 120 mg) daily
- Pregnancy : Category C
- Lactation : Contraindicated



Hypoglycemic Events



Secondary Failure


30
29
28
27
26
25
BMI
28.5
27.9
P=0.001
Gliclazide
Baseline
2 Years

BMI Changes

Contraindications

- T1DM
- LADA (Latent Autoimmune Diabetes in Adults)
- Diabetes secondary to destruction or removal of pancreas
- Advanced renal insufficiency
  - eGFR < 30 ml/min
- Advanced liver insufficiency
- General anesthesia / Major surgery
- Severe infection, stress, trauma

DIABEZID® 80

Gliclazide 80 mg

Oral Anti-Diabetic Drug


DIABEZID 60
Gliclazide Modified Release
DIABEZID 30
Gliclazide Modified Release
abidi

Glinides / Meglitinides

- Repaglinide / Nateglinide
  - Binding to the SUR1 at different, but closely related, site from the sulfonylurea site closing the K_{ATP} channel
- Rapidly metabolized
  - Short duration of action (< 3hr)
- Restore early-phase post-prandial insulin release
  - Without prolonged stimulation during subsequent periods of fasting

Glinides : Clinical Use

- Best suited for post-prandial hyperglycemia with normal FBS levels
- The pharmacokinetics means that they need to be taken 15-30 min before meals
- Useful where avoidance of hypoglycemia is important
  - Frail older people

Glinides : Adverse Effects

- Less severe hypoglycemia
  - Shorter duration of action
- Less weight gain
  - Reduced need to snack between meals

Repaglinide

- Initial : 0.5-2.0 mg tid
- Adjustment : 0.5 mg/week
- Maintenance : 2 mg bid, tid and qid
- Maximum : 16 mg daily
- Renal failure : eGFR = 20-40 ml/min 0.5 mg tid
- eGFR < 20 ml/min (Contraindicated)
- Hepatic failure : Longer intervals / lower doses
- Pregnancy : Category C
- Lactation : Not recommended


100 Tablets
Newbet® 0.5
Repaglinide
Each tablet contains:
Repaglinide 0.5 mg
Manufactured by:
Aburaihan Pharma. Co.


100 Tablets
Newbet® 1
Repaglinide
Each tablet contains:
Repaglinide 1mg
Manufactured by:
Aburaihan Pharma. Co.


100 Tablets
Newbet® 2
Repaglinide
Each tablet contains:
Repaglinide 2 mg

Formulations

- Gliclazide 80 mg
- Diabezid 80 mg
- Repaglinide (Newbet) 0.5 & 1 & 2 mg

کوتاه اثر :

- Diabezid MR 30 & 60 mg

آهسته رهش :

Insulin Secretagogues

Most Rapid →

Repaglinide
Gliclazide

Thiazolidinediones (TZDs) / Glitazones

- Thiazolidinediones (TZDs) decrease insulin resistance directly through activation of PPAR γ which
  - Facilitate differentiation of mesenchymal stem cells into adipocytes
  - Promote lipogenesis in peripheral adipocytes
  - Decrease hepatic and peripheral triglycerides
  - Decrease activity of visceral adipocytes
  - Increase adiponectin

Thiazolidinediones (TZDs) : Uses

- Pioglitazone is more often prescribed as second-line or more commonly as third-line therapy
- May take up to 3-6 months to reach their maximal effect
- Reduces hepatic fat
  - May improve liver fibrosis in patients with NASH
- The most significant advantages
  - They do not cause hypoglycemia as monotherapy
  - Are not contraindicated in patients with renal disease
    - Risk of fluid retention

Pioglitazone

- Monotherapy:
  - 15-30 mg qd
  - 15 mg qd increments every 4-12 weeks
  - Maximum : 45 mg qd daily
- Renal failure
  - No adjustment
  - May increase fluid retention
- Pregnancy
  - Not recommended
- Lactation
  - Not recommended

Adverse Reactions

- Weight gain
- Fluid Retention / Edema
- Heart failure
- Fractures
- Bladder cancer ?
- Hepatotoxicity

Heart Failure (HF) / Edema

- Increased risk of HF / worsening of HF
- Dose-dependent edema / weight gain (≃5 kg)
- Risk factors
  - Advanced CVD / History of CHF / LVH
  - HTN
  - Concurrent administration of drugs associated with fluid retention
    - Insulin
    - NSAIDs
    - Amlodipine
  - Older adults (>70 years)
  - Diabetes for >10 years
  - CKD (creatinine >2 mg/dL)

Fractures

- Activation of PPAR γ
  - Suppression of osteoblast differentiation
  - Induction of marrow adipocyte proliferation
  - Enhances the formation and activity of osteoclasts
  - Osteocyte apoptosis
- Risk associated with pioglitazone is conflicting
- Fractures are dose and time related
- Fractures may occur in any skeletal region
- Risk factors
  - Duration of drug therapy (>2 years)
  - Older adults
  - Prior stroke
  - Retinopathy

Bladder Cancer

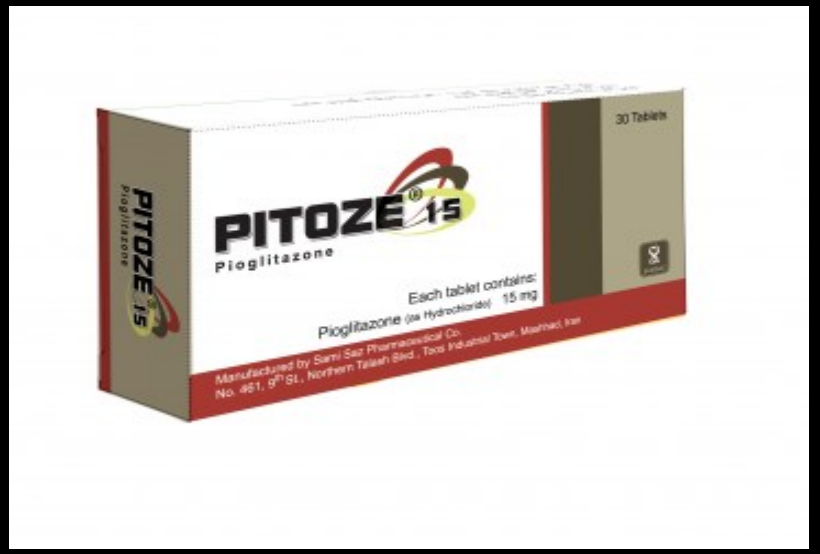
- Pioglitazone may increase the risk of bladder carcinoma
  - Risk factors
    - Cumulative doses (>28,000 mg)
    - Duration of therapy (>24 months)
    - European ethnicity
    - Caucasian race
    - Prior history of bladder cancer

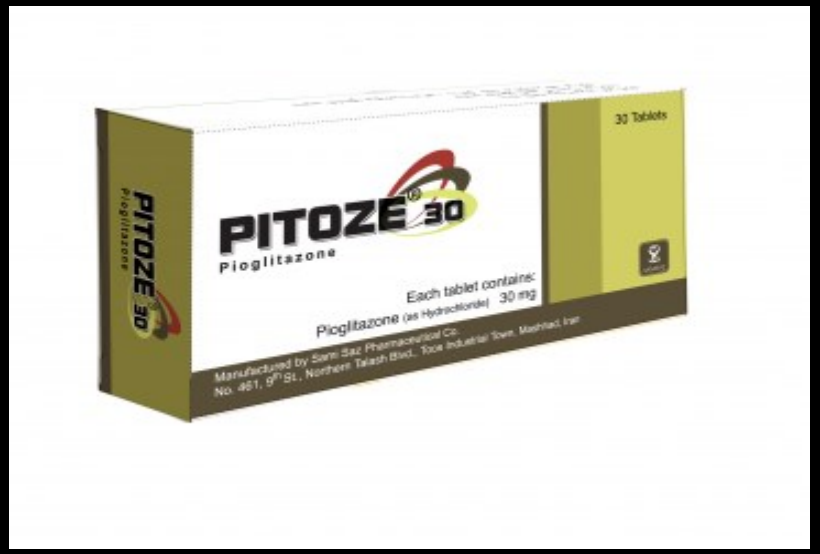
Hepatotoxicity

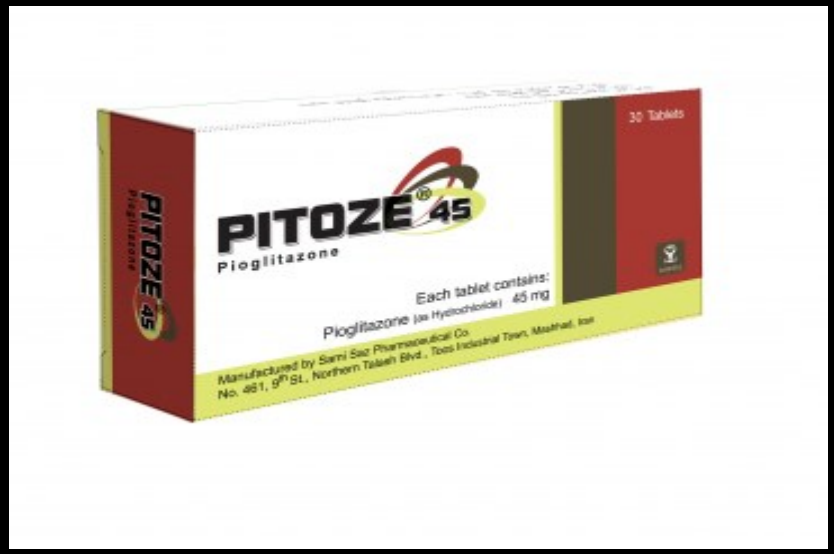
- Older TZDs (troglitazone) have stronger evidence of liver injury
- Acute hepatic failure has been reported with pioglitazone
  - It is rare for the outcome to be fatal
- All patterns of serum enzyme elevations have been described
  - Hepatocellular
  - Cholestatic
  - Mixed
- Pioglitazone has been shown to
  - Improve hepatic fat in patients with diabetes and liver steatosis
  - Resolution of NAFLD in patients without diabetes

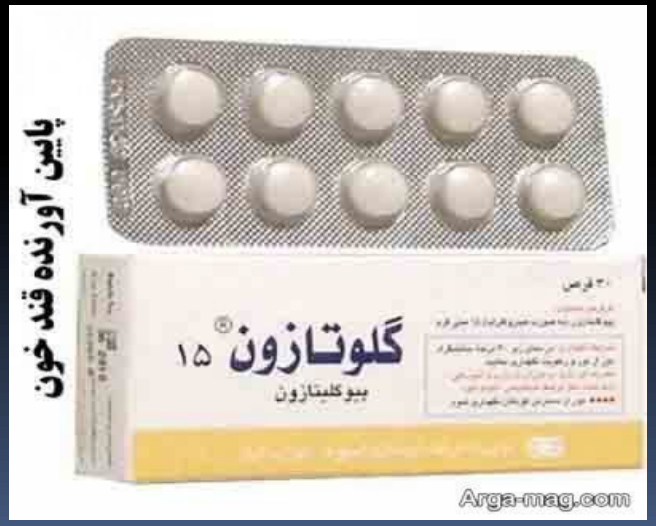
Contraindications

- CHF / Fluid overload
- History of fracture or at high risk for fracture
- Active liver disease (liver transaminases ≥2.5)
  - NASH is exception!
- Active or history of bladder cancer
- T1DM
- Pregnancy
- Macular edema


PITOZE 15
Pioglitazone
30 Tablets
Each tablet contains:
Pioglitazone (as Hydrochloride) 15 mg


PITOZE 30
Pioglitazone
30 Tablets
Each tablet contains:
Pioglitazone (as Hydrochloride) 30 mg


PITOZE 45
Pioglitazone
30 Tablets
Each tablet contains:
Pioglitazone (as Hydrochloride) 45 mg


پایین آورنده قند خون
گلوتازون ۱۵
پیوگلیتازون
Arga-mag.com


گلوتازون ۳۰
پیوگلیتازون
داروسازی اسوه تهران - ایران


گلوتازون ۴۵
پیوگلیتازون
داروسازی اسوه تهران - ایران