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# Brief Overview of Type 2 Diabetes Mellitus Treatment Options

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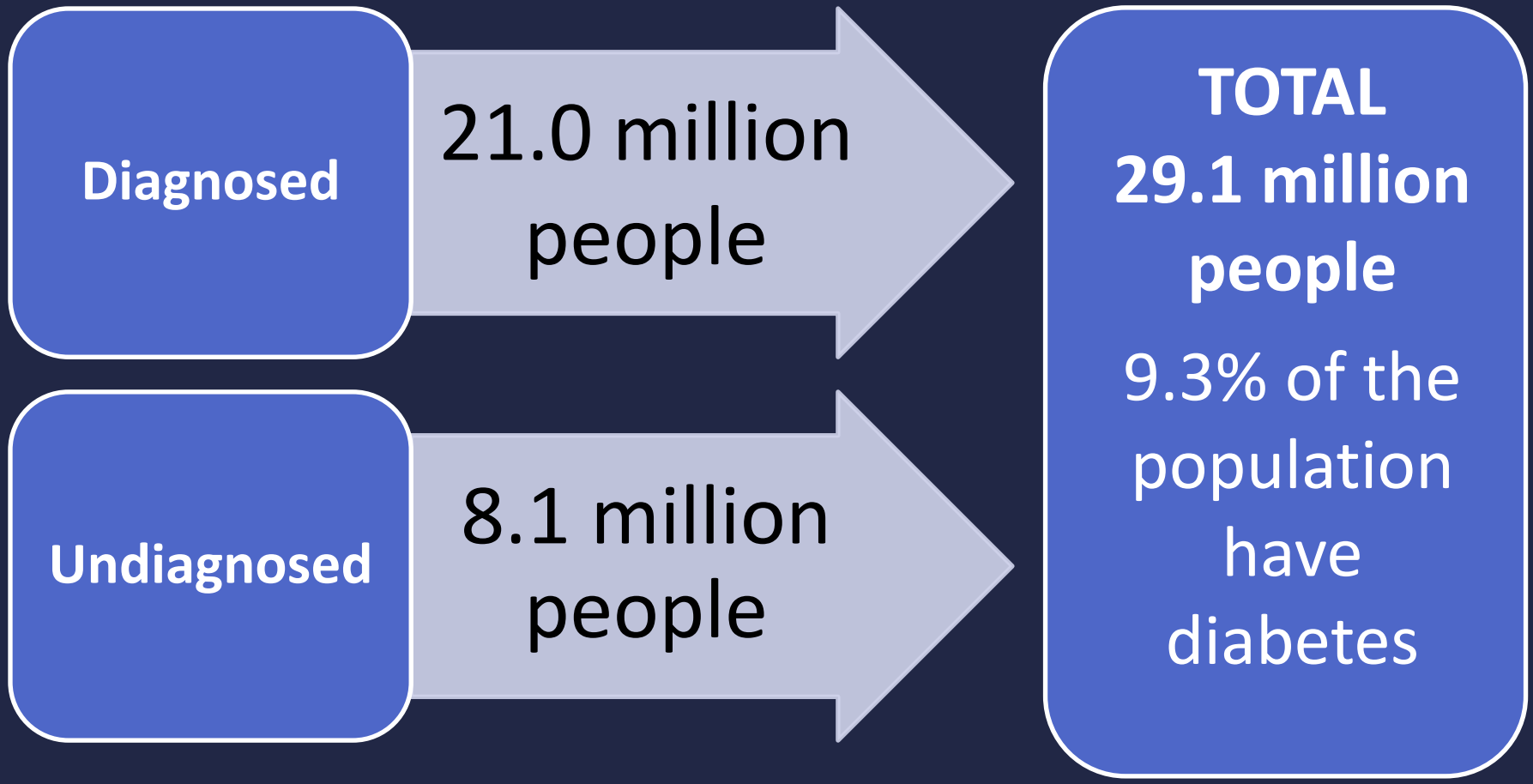
# What are we covering today?

- DM statistics
- Screening
- Pharmacotherapy


# What percent of the US population has Diabetes Mellitus?

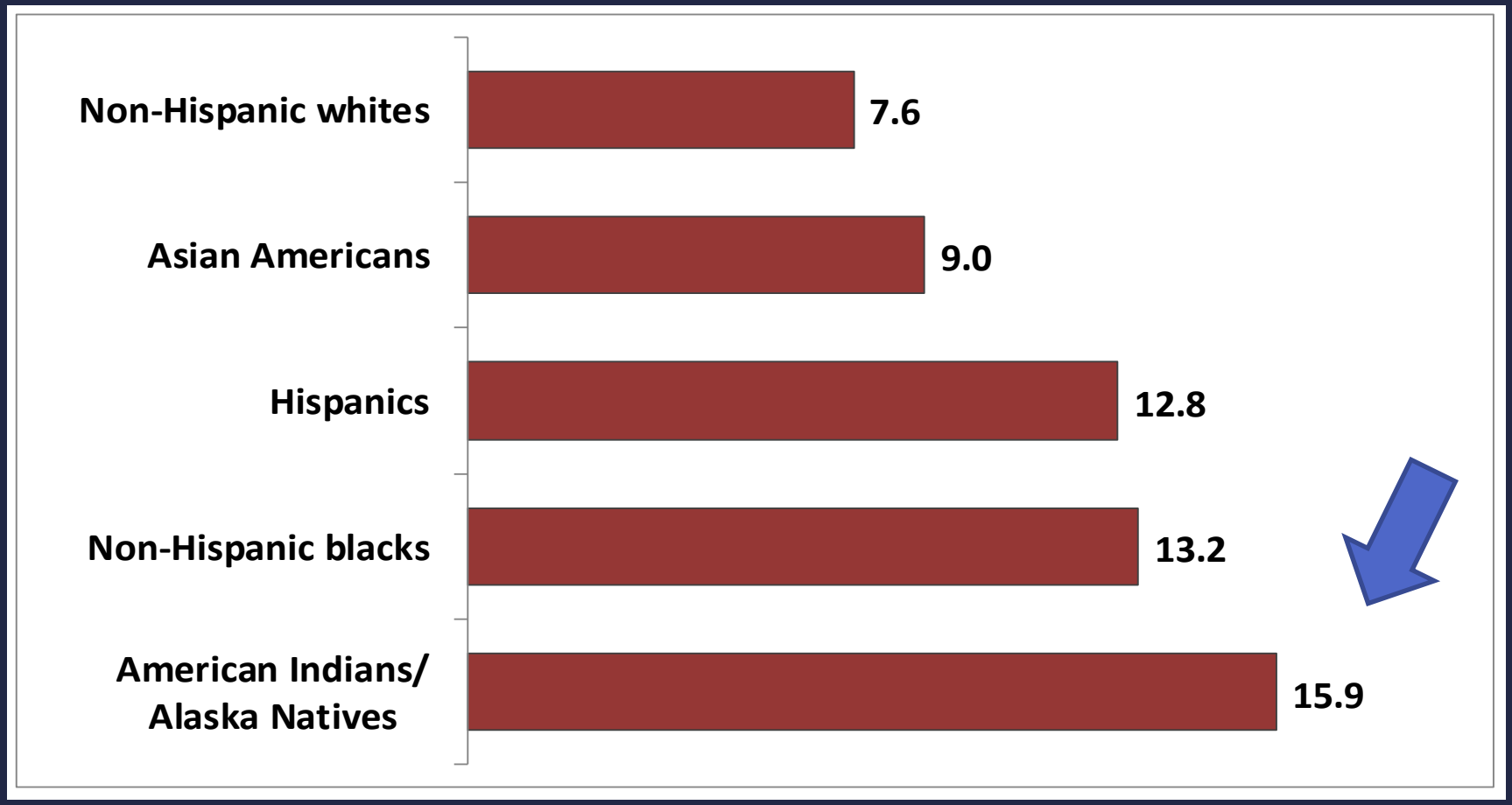
A. 9%
B. 18%
C. 27%
D. 36%
E. 45%

# Background



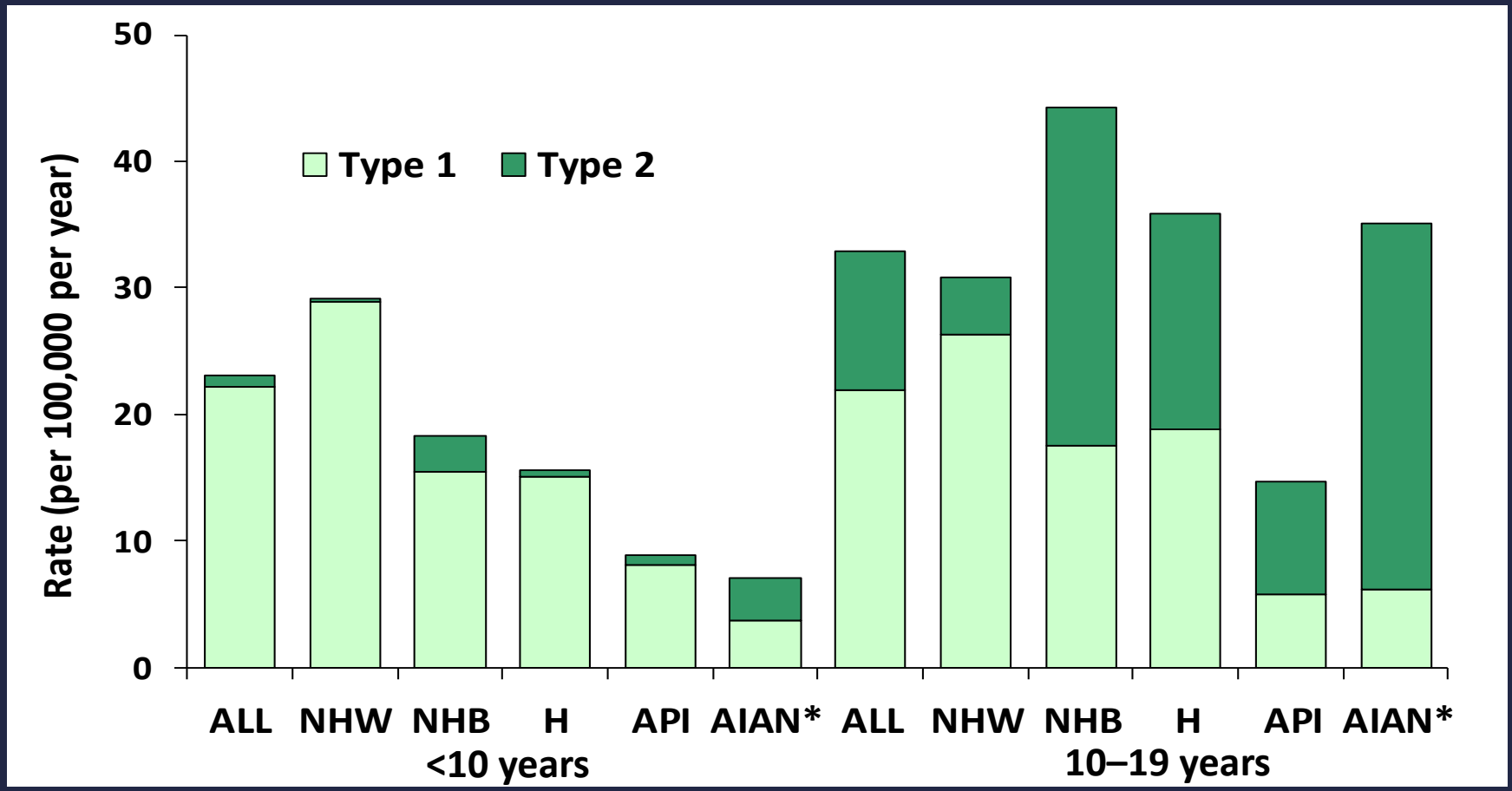

http://www.cdc.gov/diabetes/pubs/statsreport14.htm
*CDC* National Diabetes Statistics Report, 2014

# Age-adjusted* percentage of people aged 20 years or older with diagnosed diabetes, by race/ethnicity, United States, 2010–2012




*Based on the 2000 U.S. standard population. Source: 2010–2012 National Health Interview Survey and 2012 Indian Health Service's National Patient Information Reporting System. *CDC* National Diabetes Statistics Report, 2014

# Rate of new cases of type 1 and type 2 diabetes among people younger than 20 years, by age and race/ethnicity, 2008–2009




Source: SEARCH for Diabetes in Youth Study. NHW=non-Hispanic whites; NHB=non-Hispanic blacks; H=Hispanics; API=Asians/Pacific Islanders; AIAN=American Indians/Alaska Natives.

*The American Indian/Alaska Native (AI/AN) youth who participated in the SEARCH study are not representative of all AI/AN youth in the United States. Thus, these rates cannot be generalized to all AI/AN youth nationwide.

*CDC* National Diabetes Statistics Report, 2014

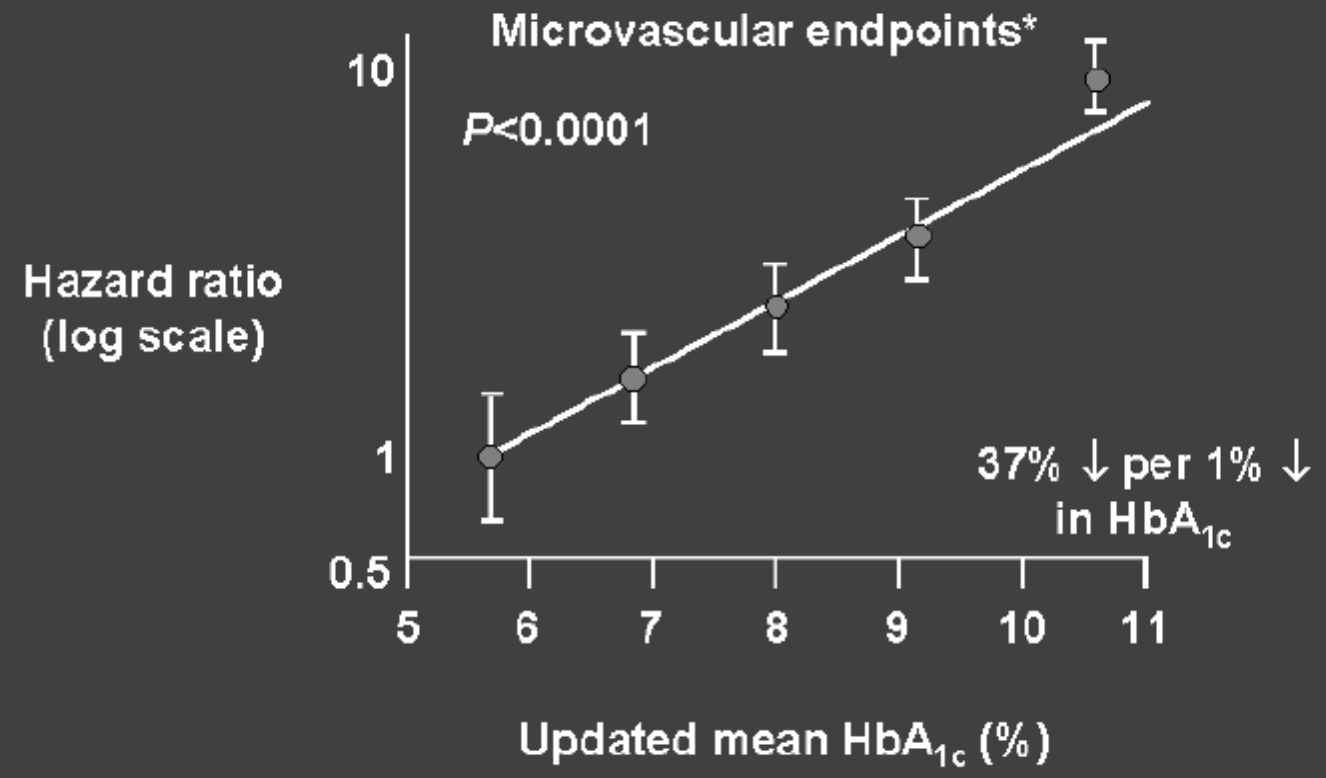
# Self Assessment

- For every 1 % decrease in A1c, risk of microvascular complications decreases by ____?

A. 20%
B. 40%
C. 60%
D. 80%

*Diabetes Care* 2007;30(suppl 1):S4-S41

# UKPDS: Glycemic Control-Effects on Microvascular Endpoints

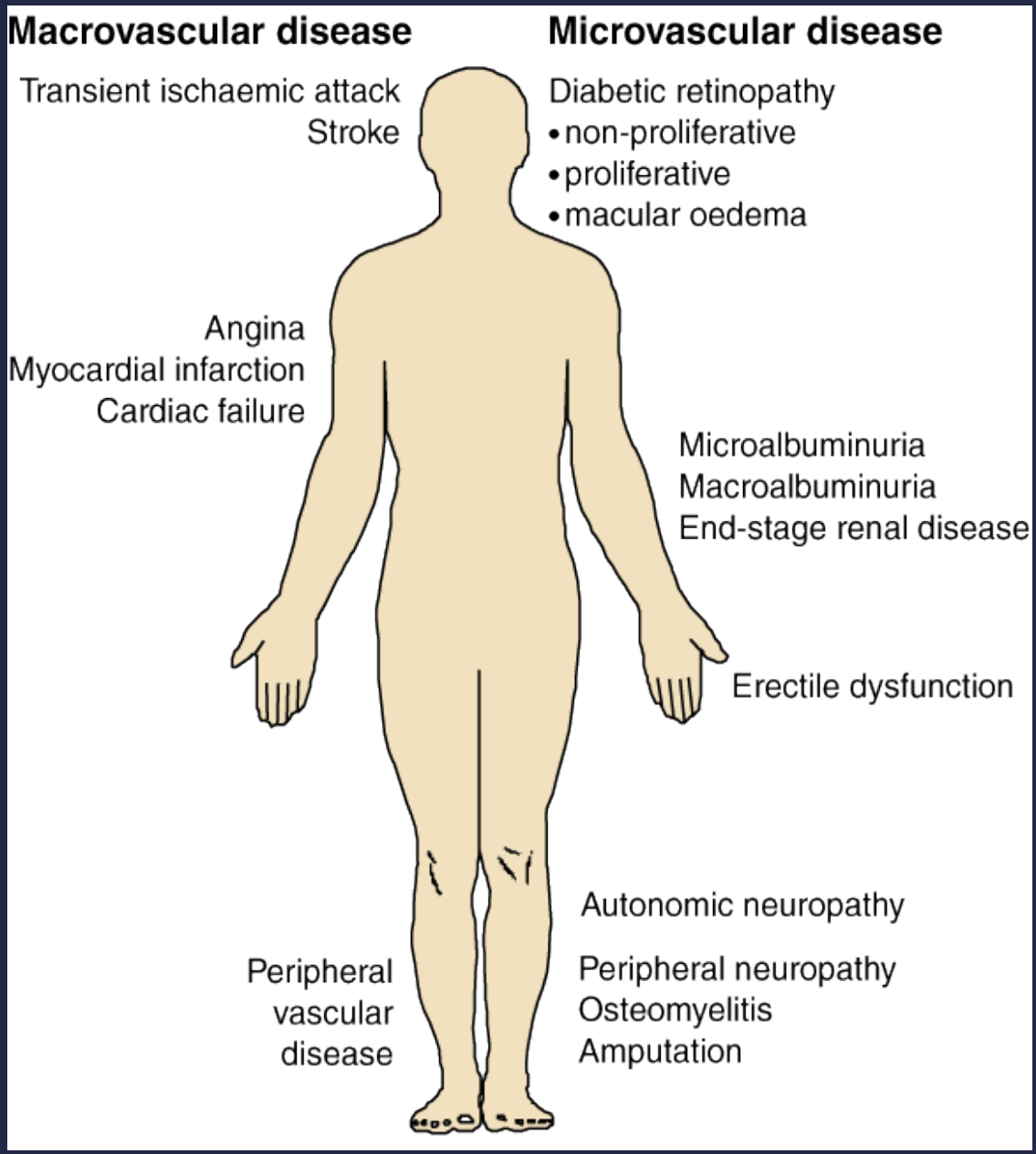



* Estimated hazard ratios (95% CI) between updated mean $HbA_{1c}$ and microvascular endpoints. Data are adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic BP, HDL-C, LDL-C, and TG.

Stratton IM, et al. BMJ. 2000; 321:405-412

# Chronic Complications

- Heart disease
- Stroke
- Hypertension
- Blindness/ Retinopathy
- Nephropathy
- Neuropathy
- Amputations
- Dental disease




*CDC* National Diabetes Statistics Sheet, 2014

Image: https://www.mja.com.au/journal/2003/179/9/3-preventing-complications-diabetes

# Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

| Study | Microvasc Initial/Long-term | | CVD Initial/Long-term | | Mortality Initial/Long-term | |
|---|---|---|---|---|---|---|
| UKPDS | ↓ | ↓ | ↔ | ↓ | ↔ | ↓ |
| DCCT / EDIC* | ↓ | ↓ | ↔ | ↓ | ↔ | ↔ |
| *ACCORD* | ↓ | | ↔ | | ↑ | |
| *ADVANCE* | ↓ | | ↔ | | ↔ | |
| *VADT* | ↓ | | ↔ | | ↔ | |

**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.
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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)

# At what age should we start screening for DM in ALL patients?

A. 25 years old
B. 45 years old
C. 65 years old
D. There is no set age, screen only if risk factors present

# Who Should be Tested? Asymptomatic Adults

- All adults ≥ 45 years
- Of any age if overweight (BMI ≥ 25) and one or more risk factors
  - Inactive
  - First degree relative with DM
  - High risk ethnic population
  - GDM or delivered baby >9 pounds
  - HTN
  - Low HDL (<35) or high triglycerides (>250)
  - PCOS
  - Previous A1c >5.7%, IGT, or IFG
  - Acanthosis nigricans
  - History of cardiovascular disease
- Repeat every year for pre-DM otherwise every 3 years

ADA. Testing for Diabetes in Asymptomatic Patients. Diabetes Care 2014;37(suppl 1):S17; Table 4

# When Should Children be Tested?

Overweight

(Weight > 120% ideal for height or BMI >85th percentile)

Plus any TWO

| | | | |
|---|---|---|---|
| Family history of DM in 1st or 2nd degree relative | High risk ethnic group | Signs of insulin resistance (acanthosis nigricans, HTN, dyslipidemia, PCOS) | Maternal h/o DM during child's gestation |

**Start at 10 years old and test every 3 years**

ADA. Testing for Diabetes in Asymptomatic Patients. Diabetes Care 2014;37(suppl 1):S17; Table 4

# Watch for Drug-Induced Hyperglycemia

- Pentamidine
- Glucocorticoids
- Nicotinic acid
- Interferon alfa
- Hydrochlorothiazide
- Atypical antipsychotics
- Protease inhibitors


Image: http://diabeteshealth.com/cartoons/general/506.html

# Which is the target for the newest class of oral medications in glucose control?

A. Sodium glucose co-transporters
B. Sodium potassium ATPase
C. Glucose transport by GLUT-4
D. Octreotide-like peptides

# Treatment Options-Oral

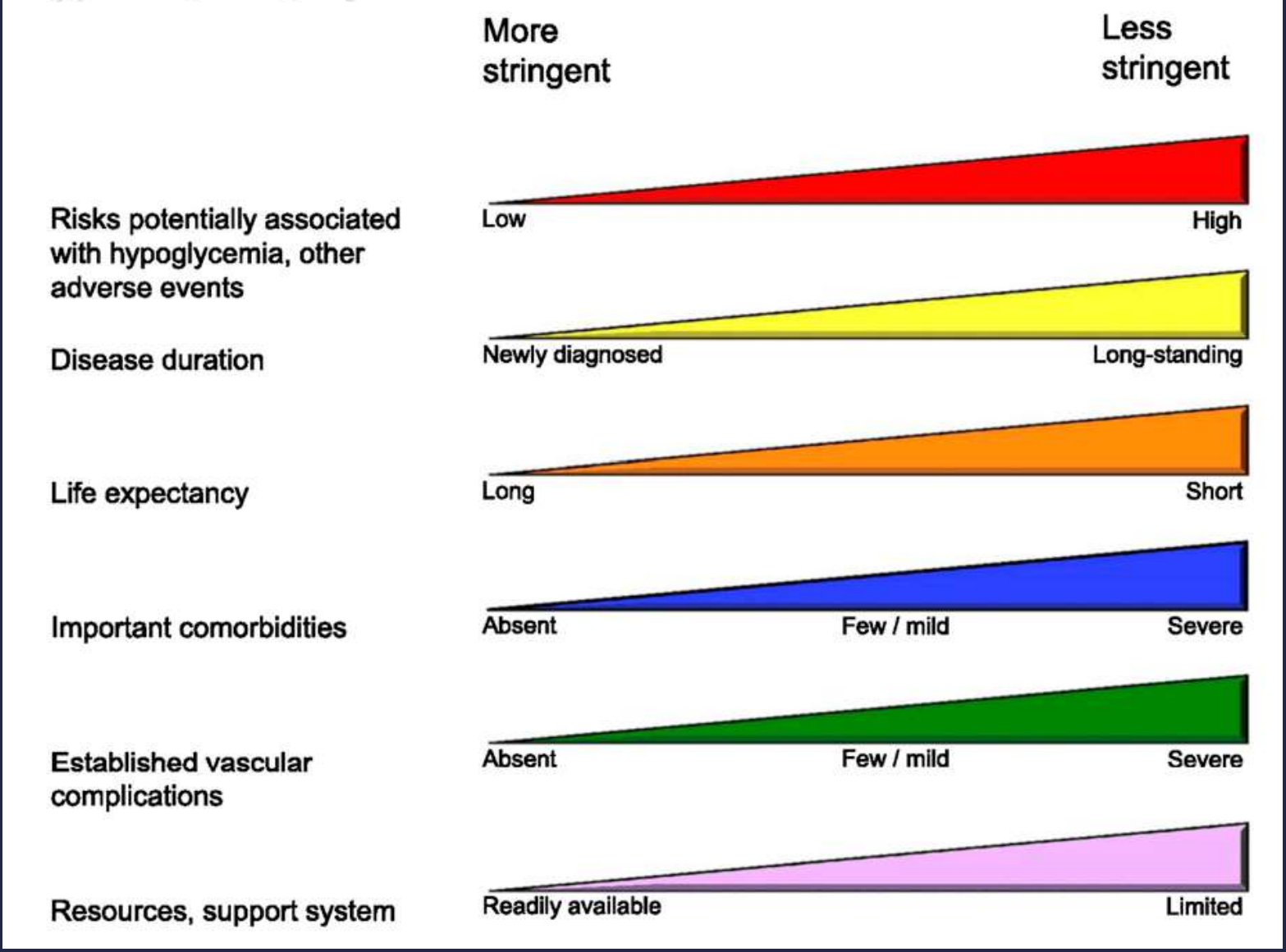
- Biguanide
- Sulfonylureas
- Meglitinides
- Thiazolidindiones
- Alpha-glucosidase inhibitors
- **Dipeptidyl peptidase-IV (DPP-4) inhibitors**
- **Selective sodium-glucose transporter-2 (SGLT-2)**
- *Bile acid sequestrants and dopamine agonists*

Garber AJ. Et al. Endocrine Practice. 2013; 19: 327-336 (NE

# FDA approved options- Injectable agents

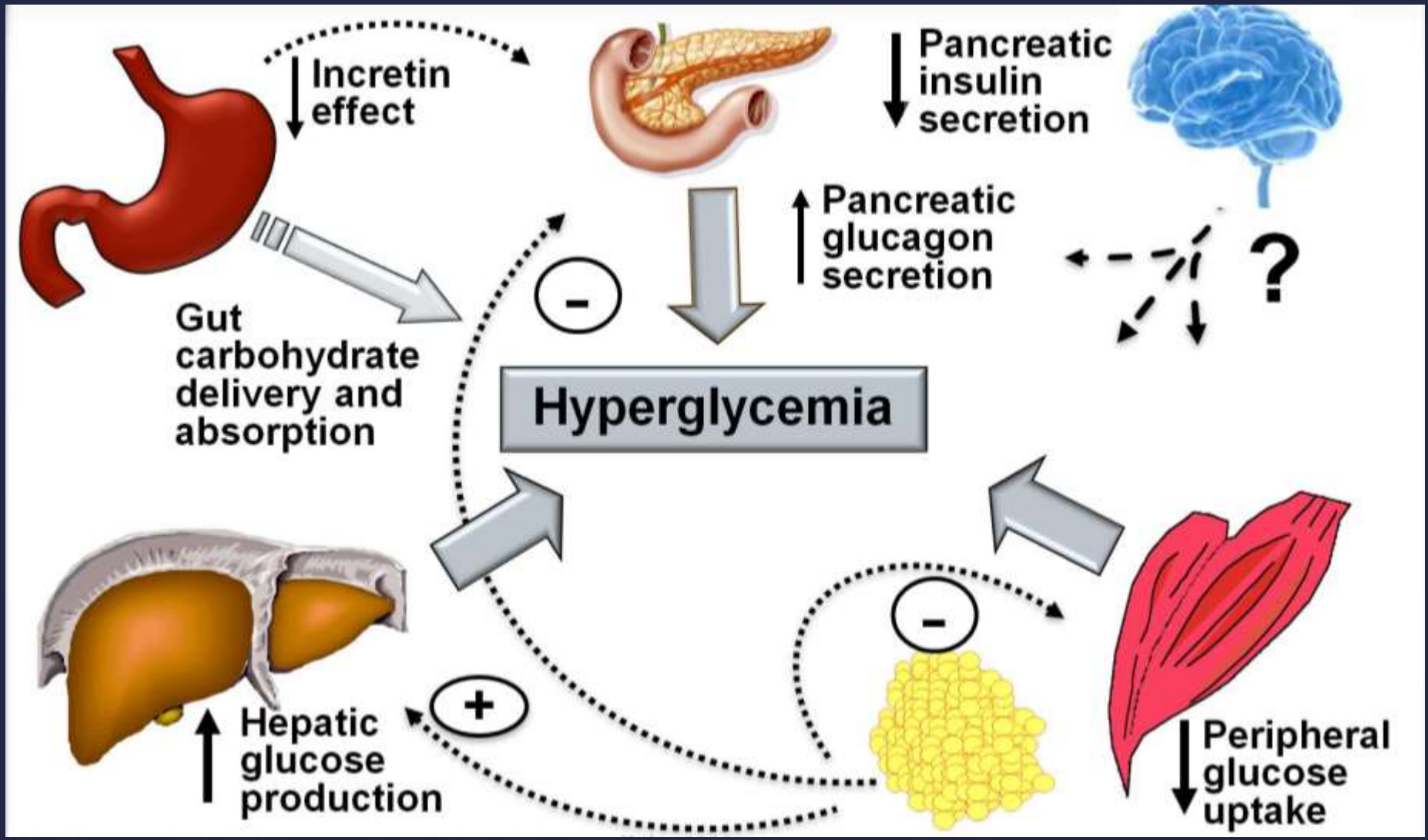
- Insulin
- **Glucagon like peptide-1 (GLP-1) agonists**
- Amylin analog

# Approach to Management of Hyperglycemia



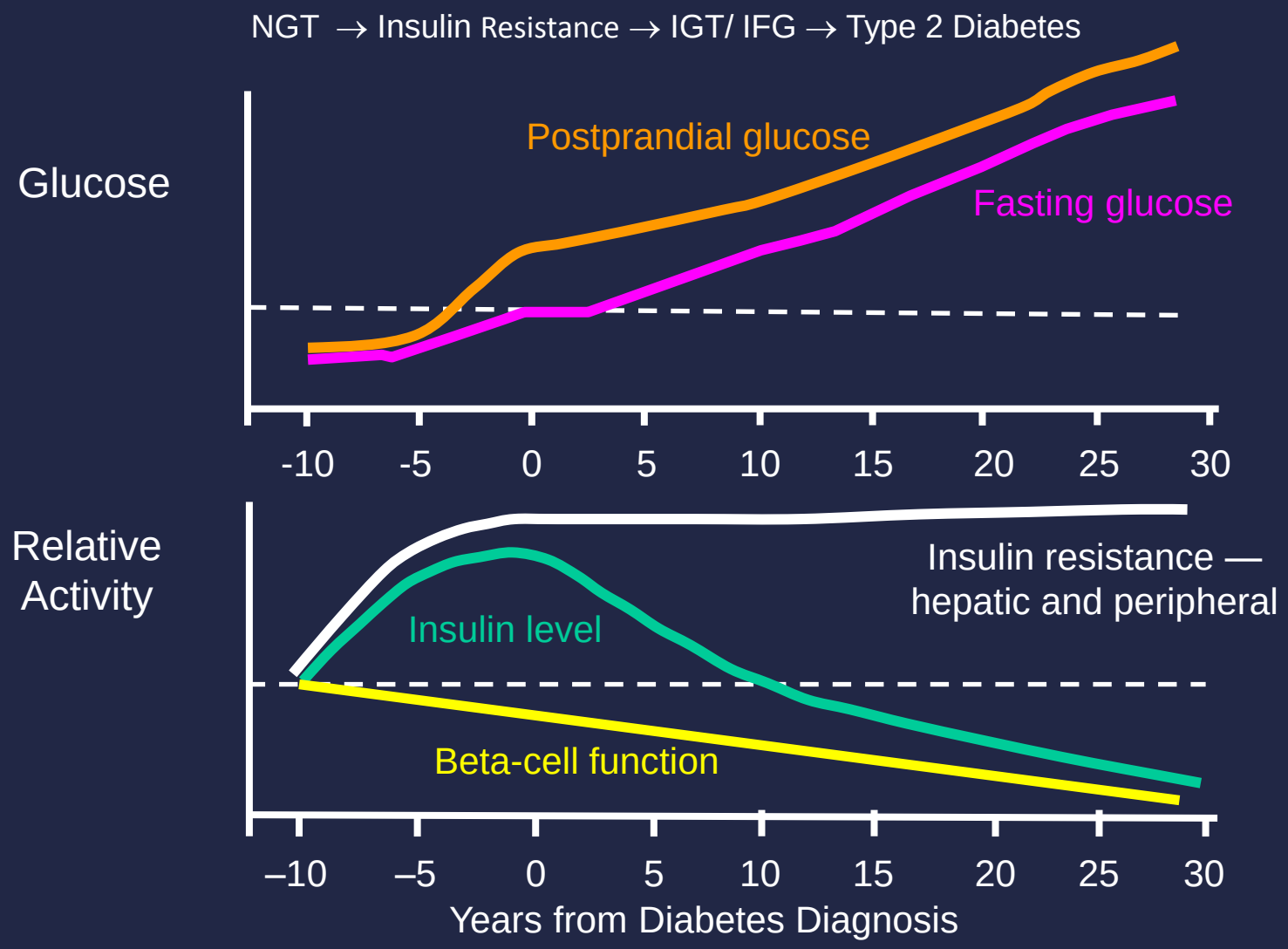

ADA. Diabetes Care. Diabetes Care 2014;37(suppl 1):S25. Figure 1; adapted with permission from Ismail-Beigi F, et al. Ann Intern Med 2011;154:554-559

# Pathophysiology of Diabetes




DeFronzo RA. Diabetes. 2009; 58: 773-95

# Progression of Type 2 Diabetes



# Biguanide (metformin)

- First line therapy
- Lowers HbA1c 1-2 %
- MoA-hepatic glucose production, increase insulin sensitivity
- ADR
  - Common: nausea, vomiting, diarrhea (especially early)
  - Uncommon-B12 deficiency, lactic acidosis
- Weight loss or negligible
- Contraindications/Precautions-renal insufficiency, HF, contrast CT scan

# Sulfonylureas (glipizide, glimepiride, glyburide)

- MoA-increase insulin secretion from pancreas
- Lowers HbA1c 1-2%
- ADR-weight gain, hypoglycemia
- Inexpensive
- Formulary
- Efficacy/Evidence-Decreases microvascular
- Monitoring
  - Renal function
  - Glyburide – active metabolite

# Meglitinides

- Repaglinide (Prandin), nateglinide (Starlix)
- MoA-similar to SU
- Decreases A1c  0.5-1.5%
- Monitoring
  - Renal function
- Concerns/Differences
  - Wt gain
  - Expense

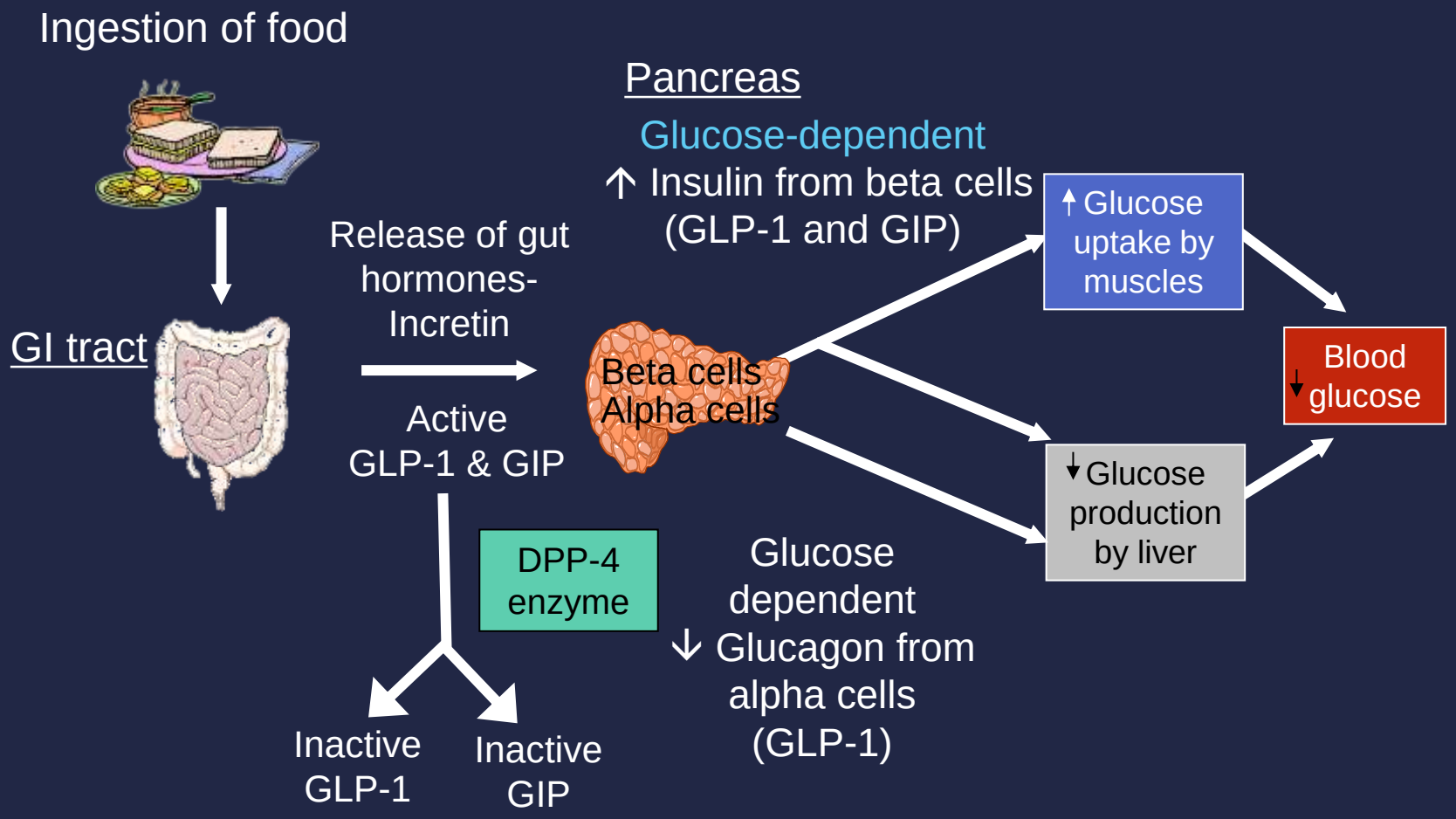
# Thiazolidindiones

- Pioglitazone (Actos), rosiglitazone (Avandia)
- Rosiglitazone-market status?
- MoA-increased glucose utilization
- Decreases A1c 0.5-1.5%
- Diabetes Prevention
- Monitoring
  - LFTs
- Concerns/Differences
  - CV risk – rosiglitazone
  - Cancer risk – pioglitazone
  - Sodium/water retention – CHF, wt gain
  - Onset
  - Expense-Not on formulary

# Alpha-glucosidase inhibitors

- Acarbose (Precose), Miglitol (Glyset)
- Mechanism
  - Decreased GI absorption
- Efficacy/Evidence
  - Lowers A1c 0.5-1%
  - Diabetes prevention
- Monitoring
  - LFTs
- Concerns/Differences
  - Hypoglycemia corrections
  - Flatulence/diarrhea
  - Binding of other drugs
  - **Expense-Not on formulary**

# Incretin Hormones and Glucose Homeostasis





1. *Endocr Rev*. 1999;20:876–913.
2. *Curr Diab Rep*. 2003;2:365–372.
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4. *Diabetes Metab Res Rev*. 2002;18:430–441.

# Dipeptidyl Peptidase-IV (DPP-4) Inhibitors

- Formulary-saxagliptin (Onglyza), linagliptin (Tradjenta)
- Not on formulary-sitagliptin (Januvia), alogliptin (Nesina)
- MoA
  - Prolongs incretin hormone (GLP-1, GIP) levels
  - Increasing insulin synthesis and release
  - Decreasing glucagon secretion
- A1c decreases 0.5- 0.8%
- Monitoring-renal function (lower dose)
- Concerns/Differences
  - Sitagliptin, saxagliptin-adjust for renal dysfunction
  - Linagliptin-no dosage adjustment in renal dysfunction
  - Pancreatitis
  - HF


Image: www.crlonline.com

# Glucagon like peptide-1 (GLP-1) agonists

- Exenatide (Byetta, Bydureon), liraglutide (Victoza)
- Mechanism
  - Hormone analog
  - Increases insulin secretion
  - Decreases glucagon secretion
- A1C lowering  0.5%–2.0%
- SQ injection
- Concerns/Differences
  - Long acting – dosed once weekly
  - CrCl < 30 – do not use
  - Nausea/hypoglycemia
  - Pancreatitis/thyroid cancer

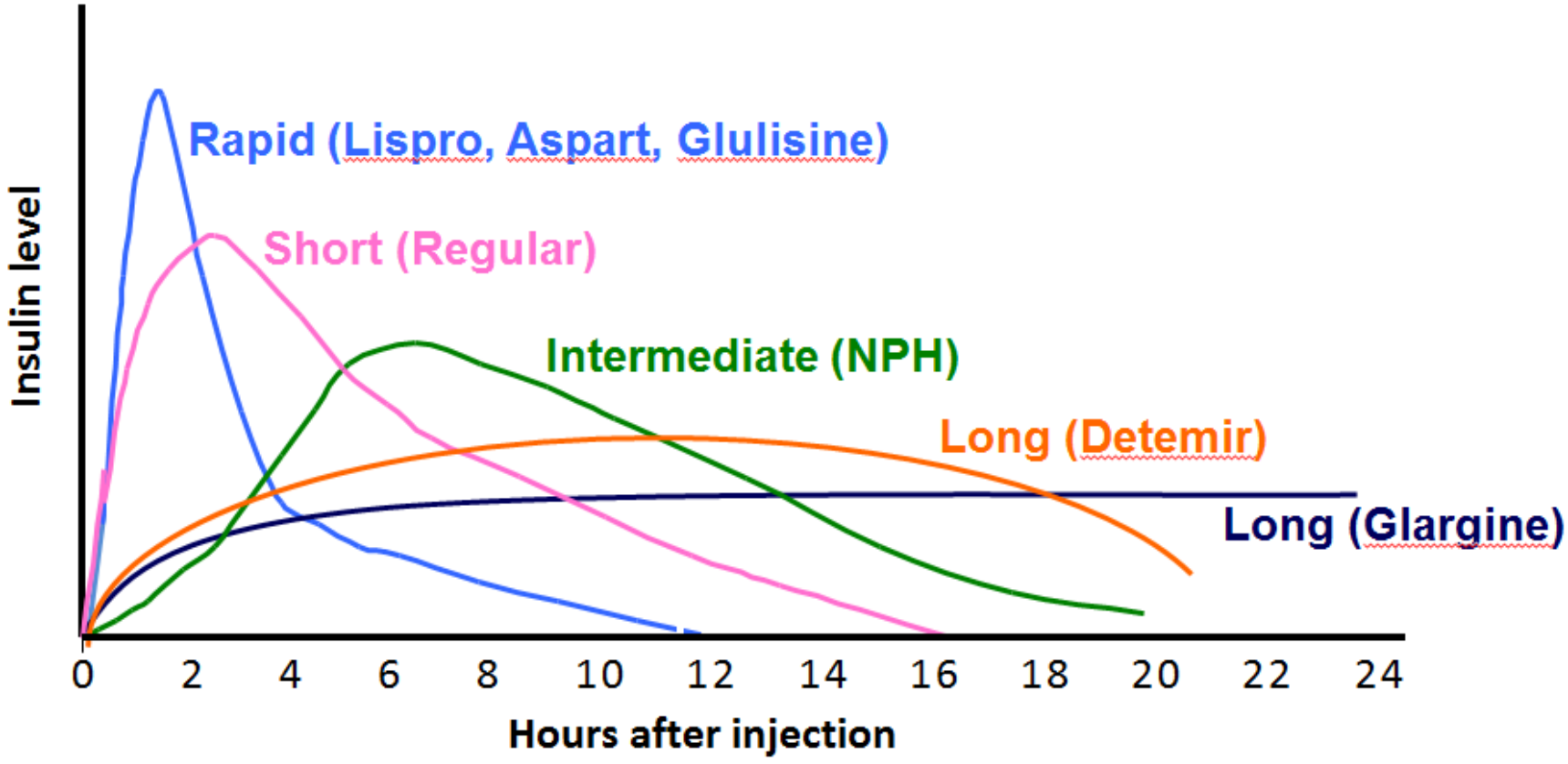

# Newest Oral Agents
# Selective sodium-glucose transporter-2 inhibitors (SGLT-2)

- Canagliflozin, dapagliflozin
- MoA
  - Inhibitors of SGLT2
  - Result in increased glucose excretion and lower plasma glucose
- A1C lowering 0.8%–1.2%
- ADR-hypotension, hyperkalemia, genital mycotic infections, UTIs, increased urination
- Weight loss, no hypoglycemia
- Expensive
- CrCl > 45 ml/min


# Amylin analog—Pramlintide (Symlin)

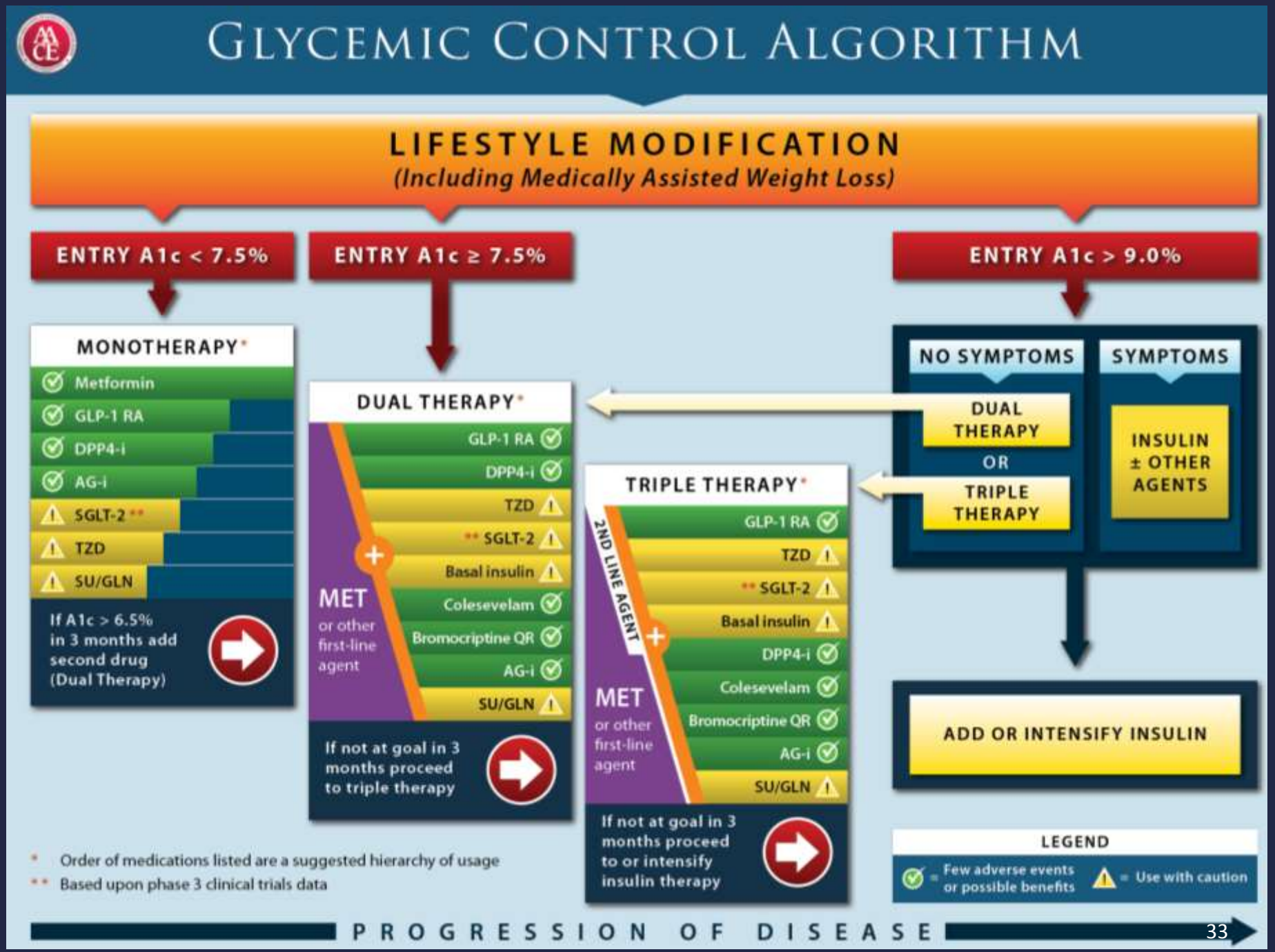
- MoA-synthetic analog of human amylin that causes:
  - Glucose-dependent inhibition of glucagon secretion
  - Reduced rate of gastric emptying
  - Increased satiety
- Efficacy (indicated for patients receiving mealtime insulin)
  - A1C lowering of 0.5%–0.7%
- Dose-different for Type 1 and Type 2
- Adverse effects
  - Nausea, vomiting, hypoglycemia with insulin
- Contraindications
  - Gastroparesis
  - Hypoglycemic unawareness

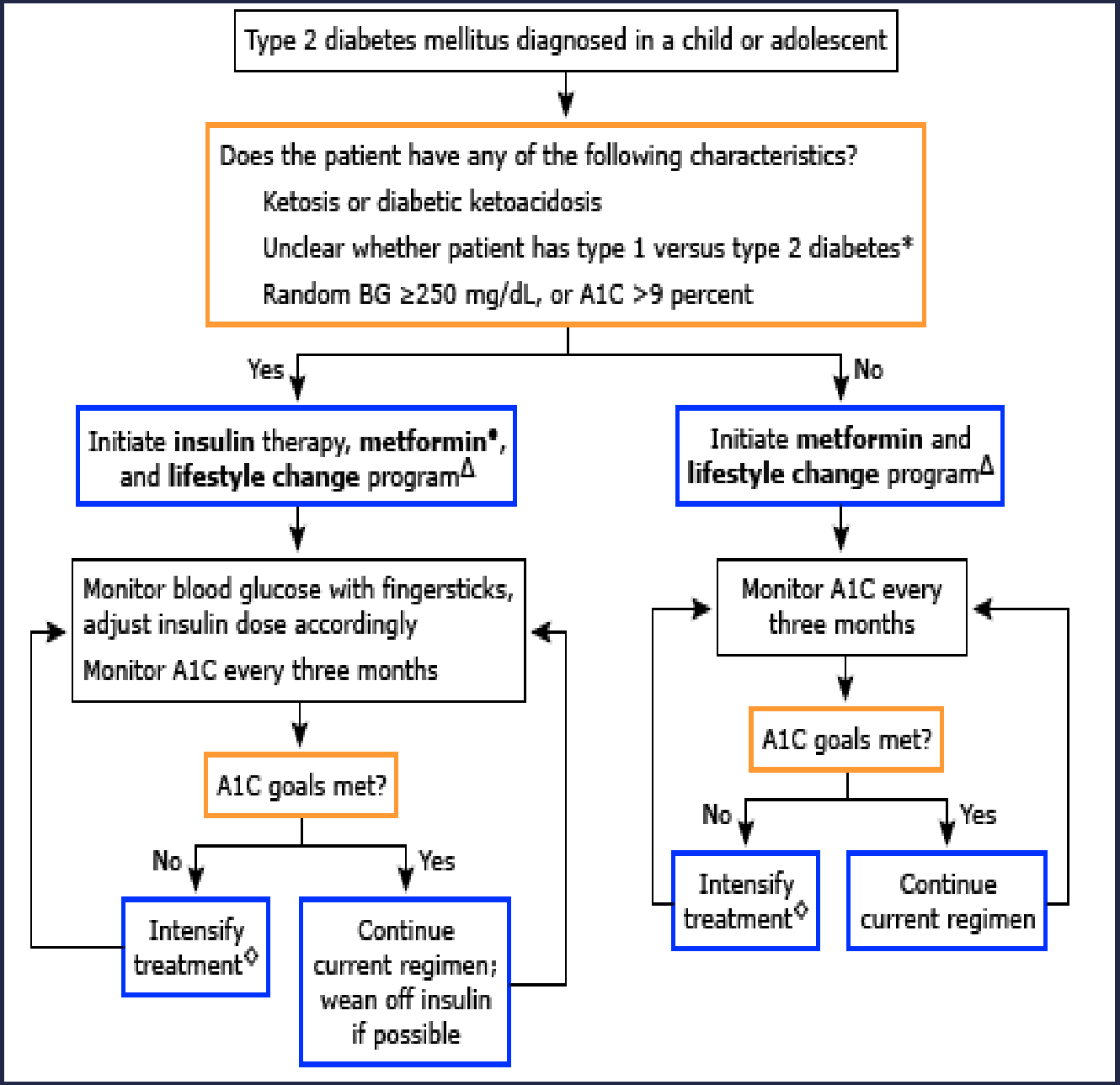
# Comparison of Insulin Profiles



# Drugs and Primary Effects

| Fasting Glucose | Mixed Glycemic Effects | Postprandial Glucose |
| --- | --- | --- |
| • Metformin<br>• Insulin detemir/glargine<br>• NPH insulin | • Sulfonylurea<br>• Mixed insulin<br>• SGLT-2 inhibitor<br>• Liraglutide and weekly exenatide<br>• TZDs | • Regular insulin<br>• Insulin aspart/lispro/ glulisine<br>• Alpha-glucosidase<br>• Meglitinides<br>• DPP-4 inhibitors<br>• Twice daily exenatide<br>• Pramlintide |

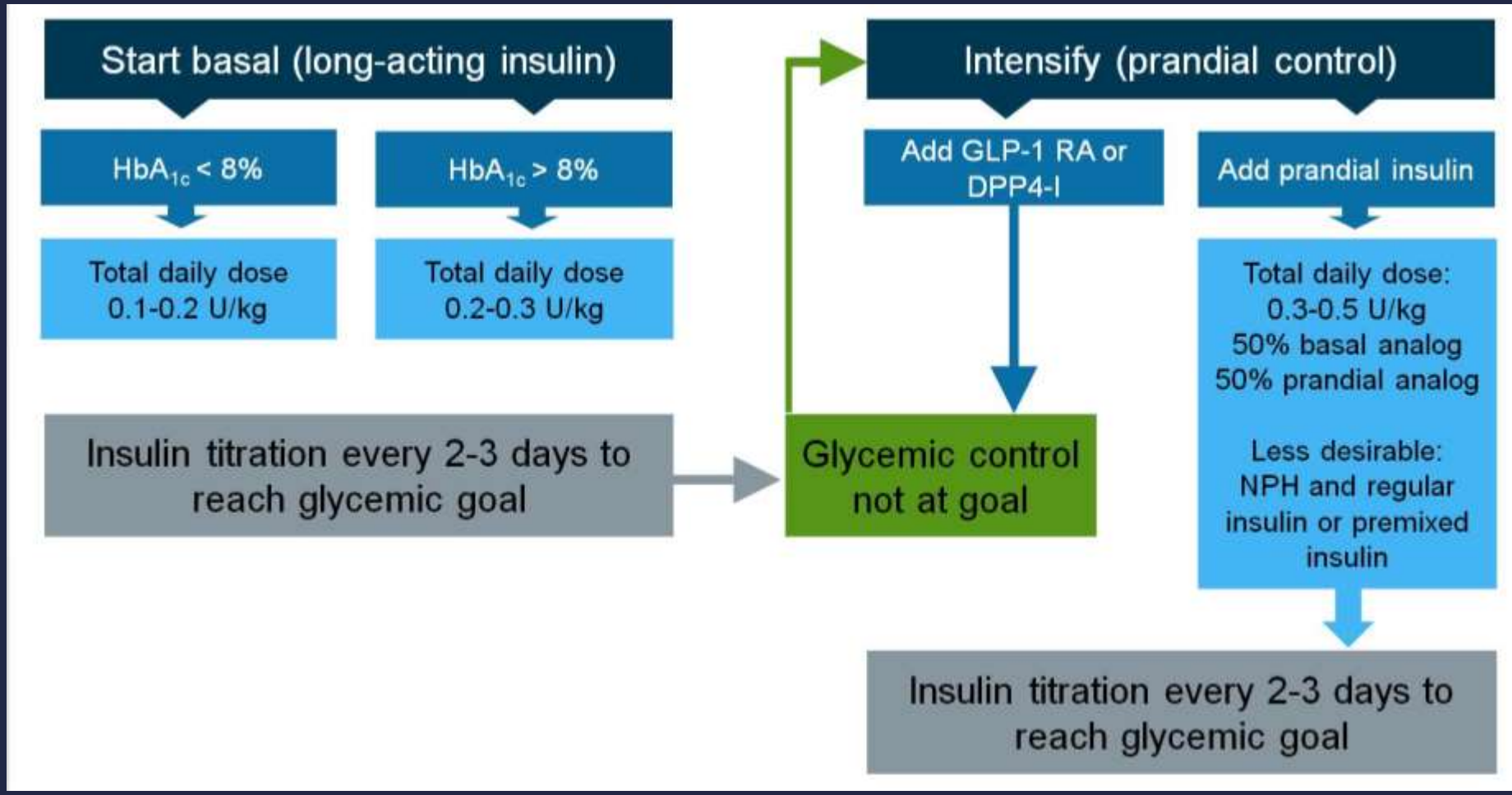

GLYCEMIC CONTROL ALGORITHM
LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)
ENTRY A1c < 7.5%
ENTRY A1c ≥ 7.5%
ENTRY A1c > 9.0%
MONOTHERAPY*
Metformin
GLP-1 RA
DPP4-i
AG-i
SGLT-2 **
TZD
SU/GLN
If A1c > 6.5% in 3 months add second drug (Dual Therapy)
DUAL THERAPY*
MET or other first-line agent
+
GLP-1 RA
DPP4-i
TZD
** SGLT-2
Basal insulin
Colesevelam
Bromocriptine QR
AG-i
SU/GLN
If not at goal in 3 months proceed to triple therapy
TRIPLE THERAPY*
MET or other first-line agent
2ND LINE AGENT
+
GLP-1 RA
TZD
** SGLT-2
Basal insulin
DPP4-i
Colesevelam
Bromocriptine QR
AG-i
SU/GLN
If not at goal in 3 months proceed to or intensify insulin therapy
NO SYMPTOMS
SYMPTOMS
DUAL THERAPY
OR
TRIPLE THERAPY
INSULIN ± OTHER AGENTS
ADD OR INTENSIFY INSULIN
* Order of medications listed are a suggested hierarchy of usage
** Based upon phase 3 clinical trials data
LEGEND
= Few adverse events or possible benefits
= Use with caution
PROGRESSION OF DISEASE




# Management of Type 2 Diabetes in Children and Adolescents

UptoDate Online-Management of newly diagnosed Type 2 Diabetes Mellitus in children and adolsecents Pediatrics 2013; 131 (2):364

# Algorithm for Adding/Intensifying Insulin




Garber AJ. Et al. Endocrine Practice. 2013; 19: 327-336

# What is “Intensive Control” of Diabetes? More than glycemic control

1. Glycemic control (A1C < 7%)
   - Every 3 months
2. Blood Pressure Management (< **140/80)**
   - Every visit
3. Lipid Management (LDL <100, TG < 150, HDL > 50)
   - Yearly
4. Aspirin Therapy
6. Immunizations
   - Influenza – yearly
   - Pneumococcal – at diagnosis
   - Hep B
7. Monitor for complications - yearly
8. Education
   - Self management

# Key Points

- Glycemic targets & BG-lowering therapies must be individualized
- Diet, exercise, & education: foundation of any T2DM therapy program
- Unless contraindicated, metformin = optimal 1st-line drug
- Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain BG control
- Treatment decisions should involve the patient

# References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# Contact Information

Ext 494

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http://diabeteshealth.com/cartoons/general/514.html

| Class | HbA1c lowering | Advantages | Disadvantages | F/NF |
|---|---|---|---|---|
| **Biguanide** | 1-2% | • Extensive experience<br>• No hypoglycemia<br>• Weight neutral<br>• ? ↓ CVD | • Gastrointestinal<br>• Lactic acidosis<br>• B-12 deficiency<br>• Contraindications | F |
| **SUs / Meglitinides** | 1-2%<br>0.5-1.5% | • Extensive experience<br>• ↓ Microvasc. risk | • Hypoglycemia<br>• Weight gain<br>• Low durability<br>• ? Ischemic preconditioning | F/NF |
| **TZDs** | 0.5-1.5% | • No hypoglycemia<br>• Durability<br>• ↓ TGs, ↑ HDL-C<br>• ? ↓ CVD (pio) | • Weight gain<br>• Edema / heart failure<br>• Bone fractures<br>• ? ↑ MI (rosi)<br>• ? Bladder ca (pio) | NF |
| **α-GIs** | 0.5-1% | • No hypoglycemia<br>• Nonsystemic<br>• ↓ Post-prandial glucose<br>• ? ↓ CVD events | • Gastrointestinal<br>• Dosing frequency<br>• Modest ↓ A1c | NF |

*Diabetes Care, Diabetologia.*2012

| Class | HbA1c lowering | Advantages | Disadvantages | F/NF |
|---|---|---|---|---|
| **DPP-4 inhibitors** | 0.5- 0.8% | • No hypoglycemia<br>• Well tolerated | • Modest ↓ A1c<br>• ? Pancreatitis<br>• Urticaria | F |
| **SGLT-2 inhibitors** | 0.8-1.2% | • Weight neutral or loss<br>• No hypoglycemia | •Mycotic infections<br>•Hyperkalemia, hypotension | NF |
| **GLP-1 receptor agonists** | 0.5-2.0% | • Weight loss<br>• No hypoglycemia<br>• ? Beta cell mass<br>• ? CV protection | • GI<br>• ? Pancreatitis<br>• Medullary ca<br>• Injectable | NF |
| **Amylin mimetics** | 0.5%–0.7% | • Weight loss<br>• ↓ PPG | • GI<br>• Modest ↓ A1c<br>• Injectable<br>• Hypo w/ insulin<br>• Dosing frequency | NF |
| **Bile acid sequestrants** | 0.5%? | • No hypoglycemia<br>• Nonsystemic<br>• ↓ Post-prandial glucose<br>• ↓ CVD events | • GI<br>• Modest ↓ A1c<br>• Dosing frequency | F |

# Adverse Effect Profiles

| | MET | DPP-4i | GLP-1 RA | TZD | AGI | SU / GLN | INSULIN | SGLT-2 | PRAML |
|---|---|---|---|---|---|---|---|---|---|
| HYPO | Neutral | Neutral | Neutral | Neutral | Neutral | Moderate/Severe / Mild | Moderate to Severe | Neutral | Neutral |
| WEIGHT | Slight Loss | Neutral | Loss | Gain | Neutral | Gain | Gain | Loss | Loss |
| RENAL/ GU | Contra-indicated Stage 3B,4,5 | Dose Adjustment May be Necessary (Except Linagliptin) | Exenatide Contra-indicated CrCl < 30 | May Worsen Fluid Retention | Neutral | More Hypo Risk | More Hypo Risk & Fluid Retention | Infections | Neutral |
| GI Sx | Moderate | Neutral | Moderate | Neutral | Moderate | Neutral | Neutral | Neutral | Moderate |
| CHF | Neutral | Neutral | Neutral | Moderate | Neutral | Neutral | Neutral | Neutral | Neutral |
| CVD | Benefit | | | Neutral | | ? | | | |
| BONE | Neutral | Neutral | Neutral | Moderate Bone Loss | Neutral | Neutral | Neutral | ? Bone Loss | Neutral |

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects