Antihyperglycemic Agents in Diabetes

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Objectives

- Review 2014 ADA Standards of Medical Care in DM as they pertain to medication therapy and 2012 ADA Management of Hyperglycemia Position Statement
- Review classes anti-hyperglycemic medications
- Discuss side effects and monitoring of DM medications
- Discuss medications effect on blood glucose
- Describe stepwise management of blood glucose

ADA Standards of Medical Care 2014: Hyperglycemia

- General glycemic target: A1c < 7% (B)
  - Consider < 6.5% if (C)
    - Hypoglycemia avoidable
    - Short duration of DM
    - Long life expectancy
    - No CVD
  - Consider < 8 % (B)
    - h/o hypoglycemia: severe, unawareness, inability to self manage
    - Advanced micro/macro complications
    - Long standing difficult to control DM
    - Extensive co-morbid conditions
    - Limited life expectancy

Diabetes Care 2014;37:S14-80

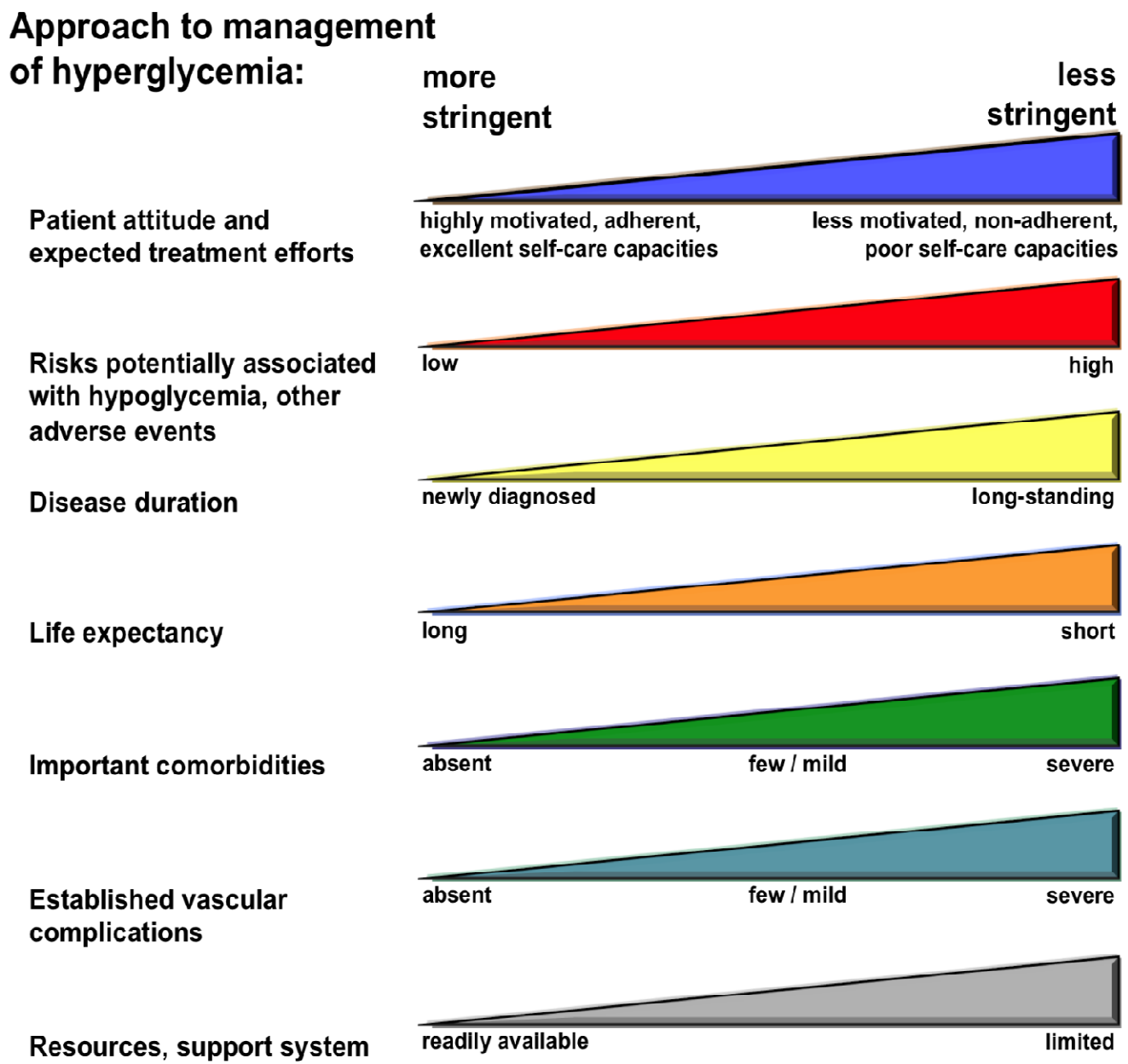


Figure 1 Diabetes Care 2012;35(6):1364-79

ADA Standards of Medical Care 2013: Lipids

- General LDL goals:
  - Without overt CVD
    - < 100 mg/dL (B) or
    - 30-40% reduction (B)
  - With overt CVD
    - Consider < 70mg/dL *with high dose statin
  - Combination therapy has not been shown to provide additional CV benefit above statin therapy alone and is NOT generally recommended. (A)

Diabetes Care 2013;36:S11-66

ADA Standards of Medical Care 2013: Lipids

- Treat with statin at any LDL if
  - Overt CV disease (A)
  - Without CVD, over 40 y/o and 1+ CVD risk factors (A)
- Treat with statin if LDL >100 (C)
  - Without overt CVD, under 40 y/o
- Lifestyle modifications should always be a standard part of lipid therapy (A)

Diabetes Care 2013;36:S11-66

Non-insulin Anti-hyperglycemic Agents

Non-Insulin Anti-hyperglycemic Agents

- Secretagogues
  - Sulfonylureas
  - Glitinides
- Insulin Sensitizers
  - Biguanide
  - TZD
- Carbohydrate Absorption Inhibitors
- Incretin-Based
  - GLP-1 Receptor Agonist
  - DPP-4 Inhibitors
  - Amylin Analog
- SGLT-2 inhibitors
- Others
  - Bile acid sequestrants
  - Dopamine-2 agonists

Insulin Secretagogues

- Sulfonylureas: glimiperide, glipizide, glyburide
  - Glimiperide: peak 2-3 hrs; duration 24 hrs
  - Glipizide IR: peak 1-3 hrs; duration 12 hours
  - Glipizide ER: peak 6-12 hours; duration 24 hours
  - Glyburide: avoid in renal disease; increased hypoglycemia
- Glitinides: repaglinide, nateglinide
  - Repaglinide preferred for more A1c reduction
  - Onset: ~30 min; peak 1 hour; duration 4-6 hours
  - Swing shift workers, erratic schedules, elderly

Insulin Secretagogues

- Do not use SU and glitinides together or with prandial insulin
- Limited durability
- Patient education for secretagogues
  - Take before meals
  - Prevention, recognition, self management of hypoglycemia
  - SU: avoid skipping meals
  - Meglitinides: Skip dose if meal skipped

Insulin Sensitizers

- Metformin
  - Primary: Decreases hepatic glucose production
  - Secondary: Increases peripheral glucose uptake
- Pioglitazone
  - Primary: Increases peripheral glucose uptake
  - Secondary: Decrease hepatic glucose production

Metformin

- Dose titration
  - Starting dose: 500mg QD or BID due to GI side effects
  - Max effective dose 2000 mg/d (1000 mg BID)
    - Intolerant: consider 850mg BID or use extended release metformin
- Patient education
  - Take with meals; low fat to reduce diarrhea
  - GI disturbances usually resolve in 1-2 wks
  - Avoid excessive alcohol (acute and chronic)
- Monitoring
  - Serum Cr (Baseline and periodically)
  - B12 deficiency (symptomatic)

Thiazolidinediones

- Pioglitazone
  - Bladder cancer: most at risk - high doses for long duration
  - Fractures in women
  - Does not appear to have the CV risk associated with rosiglitazone
- Patient Education
  - Maximum effects seen in 4-8 weeks
  - Can be taken any time of day without regard for meals
  - May increase HDL and lower TG
- Monitoring
  - Liver function tests: Baseline then ALT periodically
  - Watch for edema/SOB especially with insulin
  - Can cause CHF exacerbations; Contraindicated in NYHA Class III-IV

Alpha-Glucosidase Inhibitors

- Acarbose (Precose®), miglitol (Glyset®)
  - Initiate a lowest doses and titrate as tolerated
- Patient Education
  - Take with first bite of meal; skip meal, skip dose
  - If given with insulin/secretagogue, may cause hypoglycemia which can only be treated with *glucose*, not complex carbohydrates
  - GI Side effects are significant
- Avoid in GI disease and severe renal disease

Peptide Analogs

- GLP-1 agonist
  - Exenatide IR (Byetta®) and ER (Bydureon®)
  - Liraglutide (Victoza®)
- DPP-4 Inhibitors
  - Sitagliptin (Januvia®)
  - Linagliptin (Tradjenta®)
  - Saxagliptin (Onglyza®)
  - Alogliptin (Nesina®)
- Amylin analog
  - Pramlintide (Symlin®)

Glucagon Like Peptide-1 (GLP-1) Agonists

- Exenatide
  - Initial: 5 mcg SQ bid within 60 minutes before meal
  - Titration: ↑ to 10 mcg bid after 1 month
  - Pen comes in preset 5 mcg or 10 mcg doses
- Exenatide ER
  - Once weekly subQ injection w/o regard to meals
  - Patient must suspend powder w/diluent prior to injection
- Liraglutide
  - Once daily subQ pen injection w/o regard to meals
  - Initial dose: 0.6mg x 1wk, then 1.2mg; max 1.8mg
  - Single pen able to give different doses

Glucagon Like Peptide-1 (GLP-1) Agonist

- Adverse Effects
  - Significant nausea, vomiting
  - Acute renal failure and insufficiency
  - Acute pancreatitis
  - Increased INR w/warfarin (exenatide)
  - Thyroid C-cell cancer in rats (liraglutide, exenatide ER)
- Avoid in severe GI disease
- Patient Education
  - SubQ injection techniques
  - Skip meal, skip dose (Byetta)
  - Do not overeat

Dipeptidyl Peptidase-IV (DPP-4) Inhibitors

- Sitagliptin
  - Decrease dose with renal impairment
- Saxagliptin
  - Decrease dose with CYP3A4 inhibitors and renal impairment
  - ?? Increase HF related hospitalizations
- Linagliptin
  - Duration ~12 hrs
- No dose titration
- Adverse reactions of DDP-4 Inhibitors:
  - HA, abdominal pain, vomiting, nausea
  - Acute pancreatitis

Amylin Analog

- Pramlintide
  - Adjunctive therapy with prandial insulin for T1 and T2 DM
  - Prolongs gastric emptying, decreases pp glucagon secretion, suppresses appetite
- Dose
  - Reduce insulin doses prior to initiating pramlintide
  - T1DM: SubQ15mcg immediately before meals
    - Can increase every 3 days to target dose of 30-60 mcg
  - T2DM: SubQ 60 mcg immediately before meals
    - Can increase to 120mcg after 3-7 days

Amylin Analog (Pramlintide)

- Side Effects
  - Anorexia, n/v, severe hypoglycemia, headache
  - Avoid in gastroparesis
- Appropriate use
  - Patients close to A1c target (Avoid with A1c >9%)
  - For elevated postprandial BG levels
  - Avoid in non-adherent patients to both medications and BG monitoring
  - Avoid with recent, recurrent hypoglycemia, inability to self manage hypoglycemia, previous severe hypoglycemia

Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitors

- Canagliflozin (Invokana®), Dapagliflozin (Farxiga®)
  - Inhibits SGLT-2 in proximal tubule to decrease reabsorption of glucose in the kidneys, increasing urinary glucose excretion
  - Dose:
    - Canagliflozin:
      - 100mg QD 30 min before first meal (Max dose: 300mg/day)
      - 100mg max dose with eGFR 45-60; avoid use if eGFR <45
    - Dapagliflozin:
      - 5 mg qAM with or without meals (Max dose 10mg/day)
      - Avoid initiation if eGFR<60; discontinue if eGFR persistently < 60
        - Loses efficacy, increases renal related adverse effects and bone fractures

Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitors

- Benefits:
  - Weight loss
  - Slight BP reduction (diuretic effect)
- Adverse Effects
  - Genital fungal infections, UTI, pruritus, thirst, constipation, GI upset, dehydration, increased SCr, decreased CrCl, hyperkalemia
  - ?Increased risk of CVA, bladder cancer, breast cancer, bone fractures
- Caution:
  - CKD, urinary incontinence, diuretic use
  - Monitor SCr, K

Comparison of Non-Insulin Agents

Drugs	A1c Reduction	Advantages	Disadvantages
Metformin	1 – 1.5%	Weight neutral CV benefits	GI side effects Avoid in renal dysfx
Sulfonylureas	1 – 1.5%	Rapidly effective Inexpensive	Weight gain Hypoglycemia
Pioglitazone	0.4 -1.8%	Lipids Ok in renal dysfx	CHF, edema Bladder cancer(?)
Meglitinides	0.5 -1.5%	Rapidly effective	Weight gain 3 x day dosing
α-Glucosidase Inhibitor	0.5 - 0.8%	Weight Neutral	GI side effects 3 x day dosing
GLP-1 Agonist	0.5 - 1%	Weight Loss	GI side effects Pancreatitis Long term safety?
DPP-4 Inhibitors	0.5 - 0.8%	Weight Neutral	Pancreatitis Long term safety?
SGLT-2 Inhibitors	0.5-1.5%	Weight Loss BP reduction	Infections; $\uparrow$ K Long term safety?

Assessing Medication Efficacy

Medication	Blood glucose primarily effected
Sulfonylurea	Mixed
Metformin	Fasting
Alpha-Glucosidase Inhibitors	Postprandial
Pioglitazone	Mixed
Glitinides	Postprandial
DPP-IV inhibitors	Postprandial
GLP-1 agonist	Exenatide – IR postprandial; ER Mixed Liraglutide - mixed
SGLT-2 Inhibitors	Mixed

Onset of Medication Efficacy

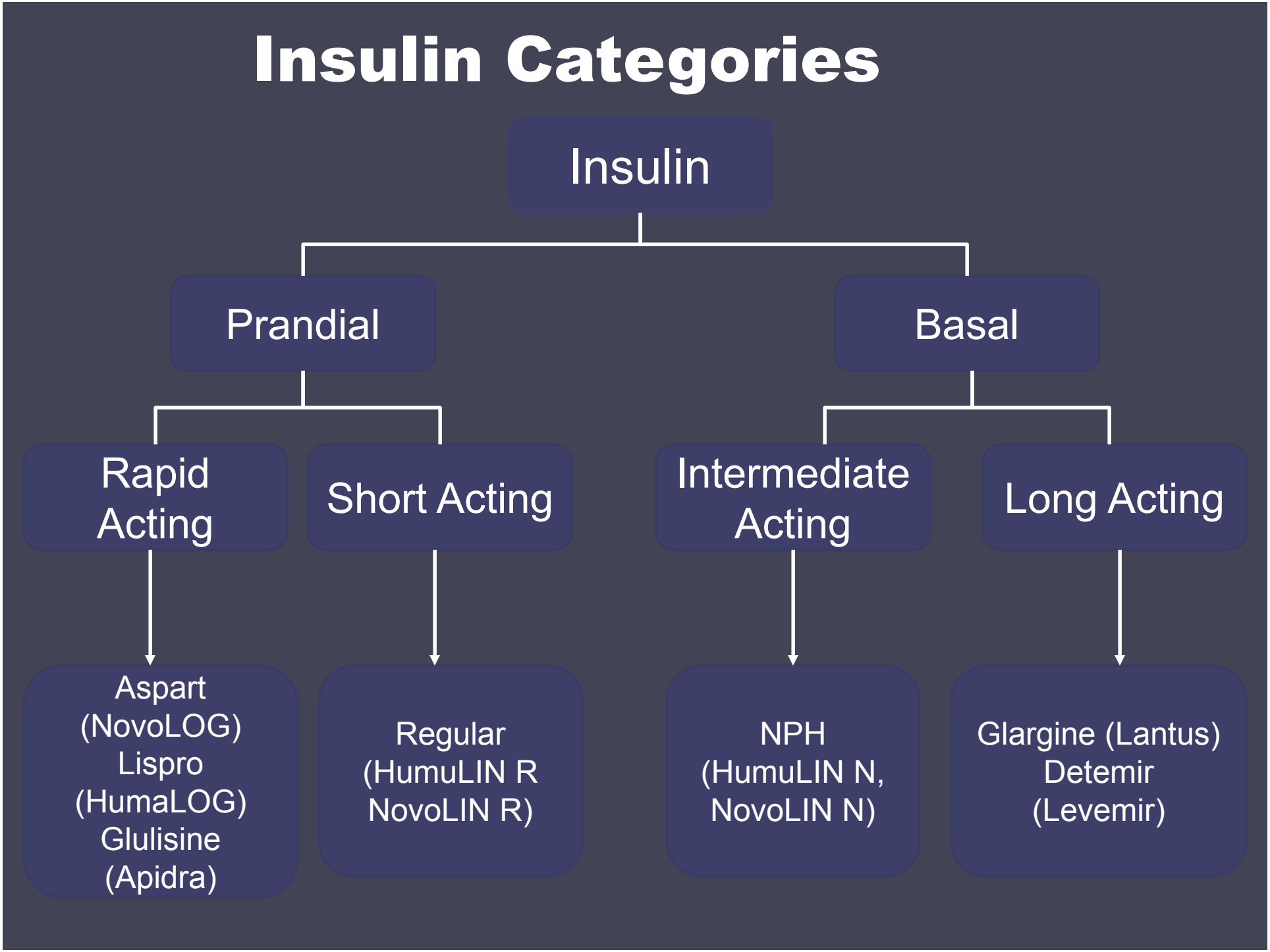
Medication	Time to Lower BG values
Sulfonylurea	Days
Metformin	~2 weeks
Alpha-Glucosidase Inhibitors	Immediate
Pioglitazone	4-6 weeks
Metglitinides	Days
DPP-IV inhibitors	<1 week
GLP-1 agonist	<1 week
SGLT-2 inhibitors	<1 week

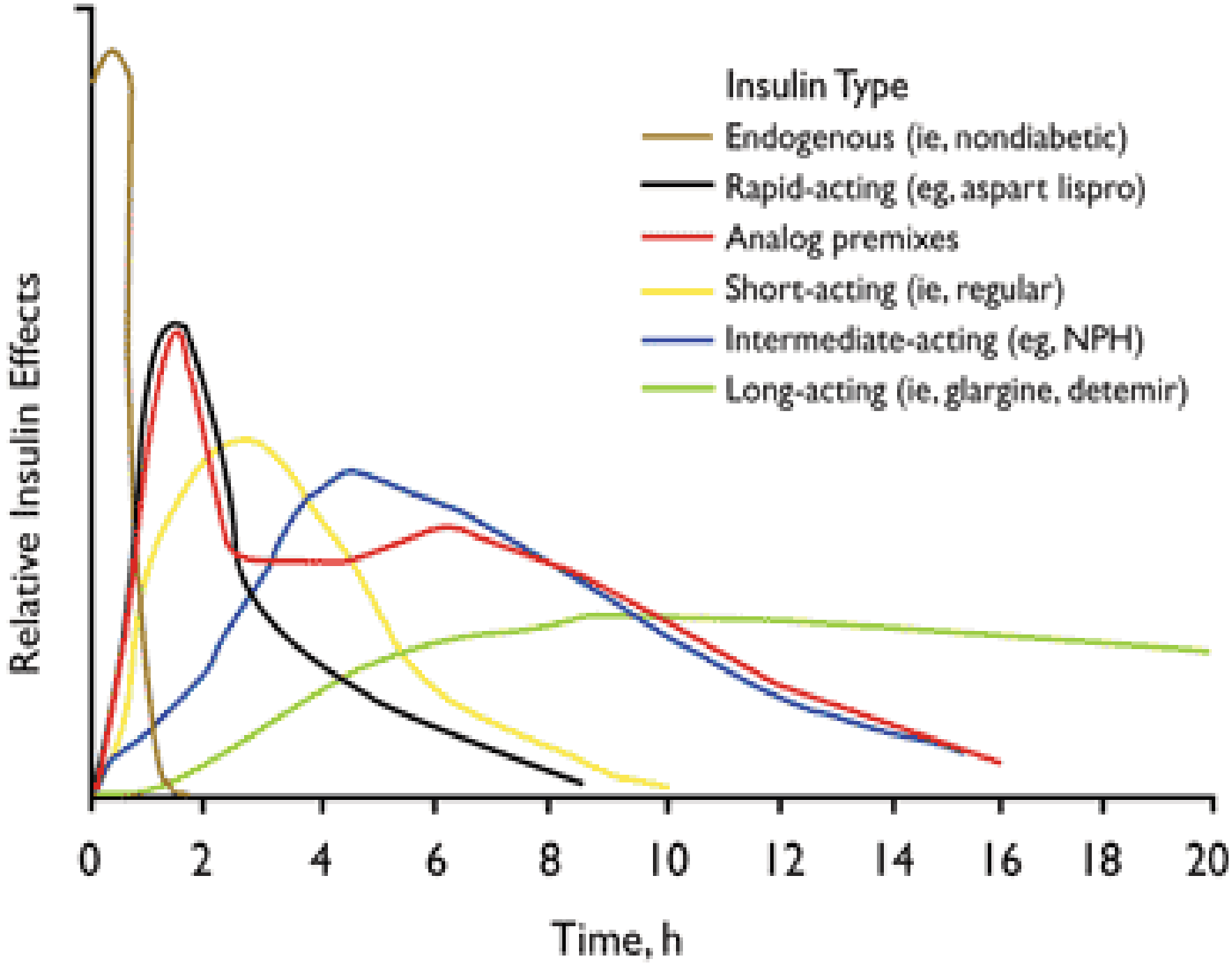
Insulin

Insulin Categories

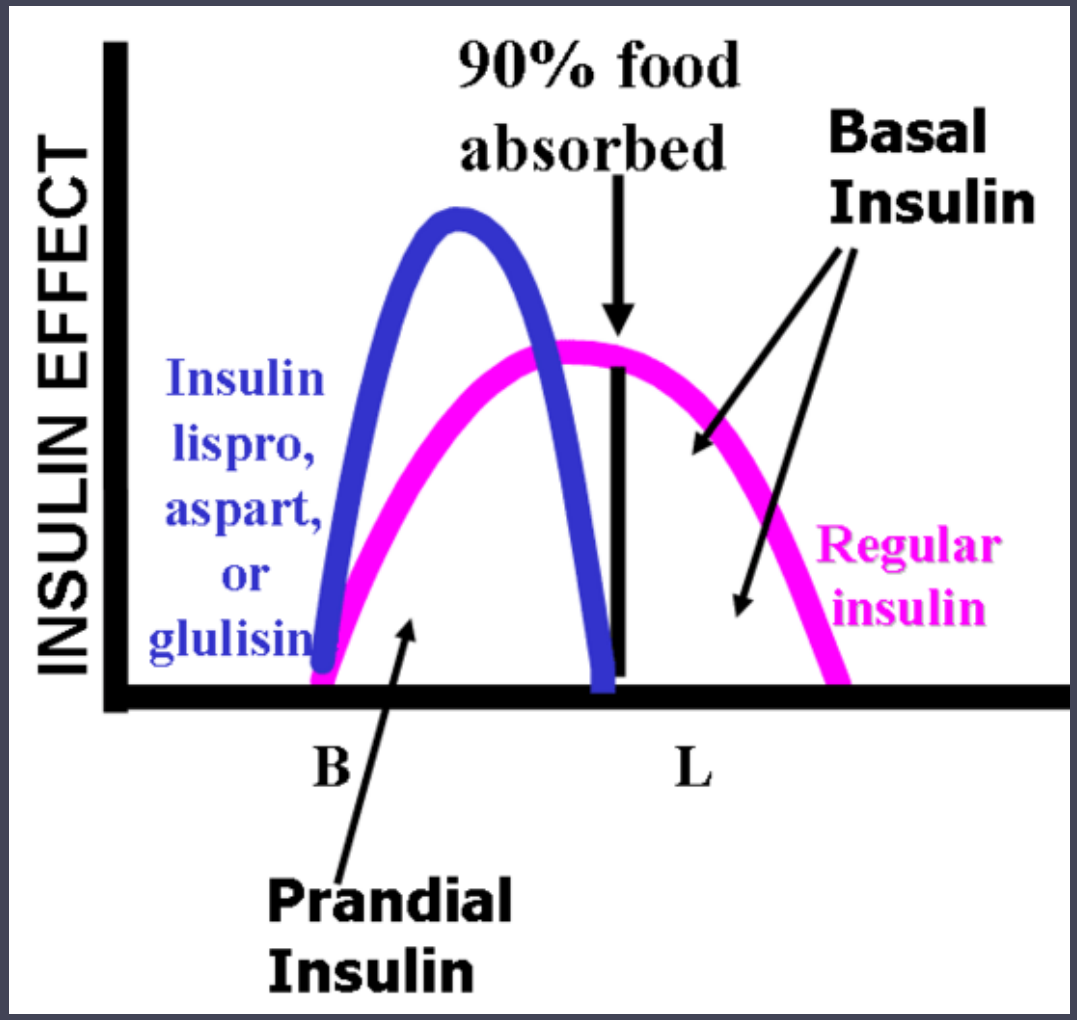
- Human (synthetic)
  - Prandial: Regular
  - Basal: NPH
- Designer or Analog
  - Prandial: Aspart, Lispro, Glulisine
  - Basal: Glargine, Detemir

Insulin Categories




Insulin Type
Endogenous (ie, nondiabetic)
Rapid-acting (eg, aspart lispro)
Analog premixes
Short-acting (ie, regular)
Intermediate-acting (eg, NPH)
Long-acting (ie, glargine, detemir)
Relative Insulin Effects
0
2
4
6
8
10
12
14
16
18
20
Time, h

Prandial Insulin



Timing of Prandial Insulin Doses

- Rapid Acting (NovoLOG, HumaLOG, Apidra)
  - Give no more than 15 minutes before meal
  - Preferably immediately before meal
  - In special cases, may be given immediately after meals
- Short Acting (Regular, NovoLIN R, HumLIN R)
  - Give no more than 60 minutes before a meal
  - Preferably about 30 minutes before a meal
  - Do NOT give after a meal

Timing of Basal Insulin Doses

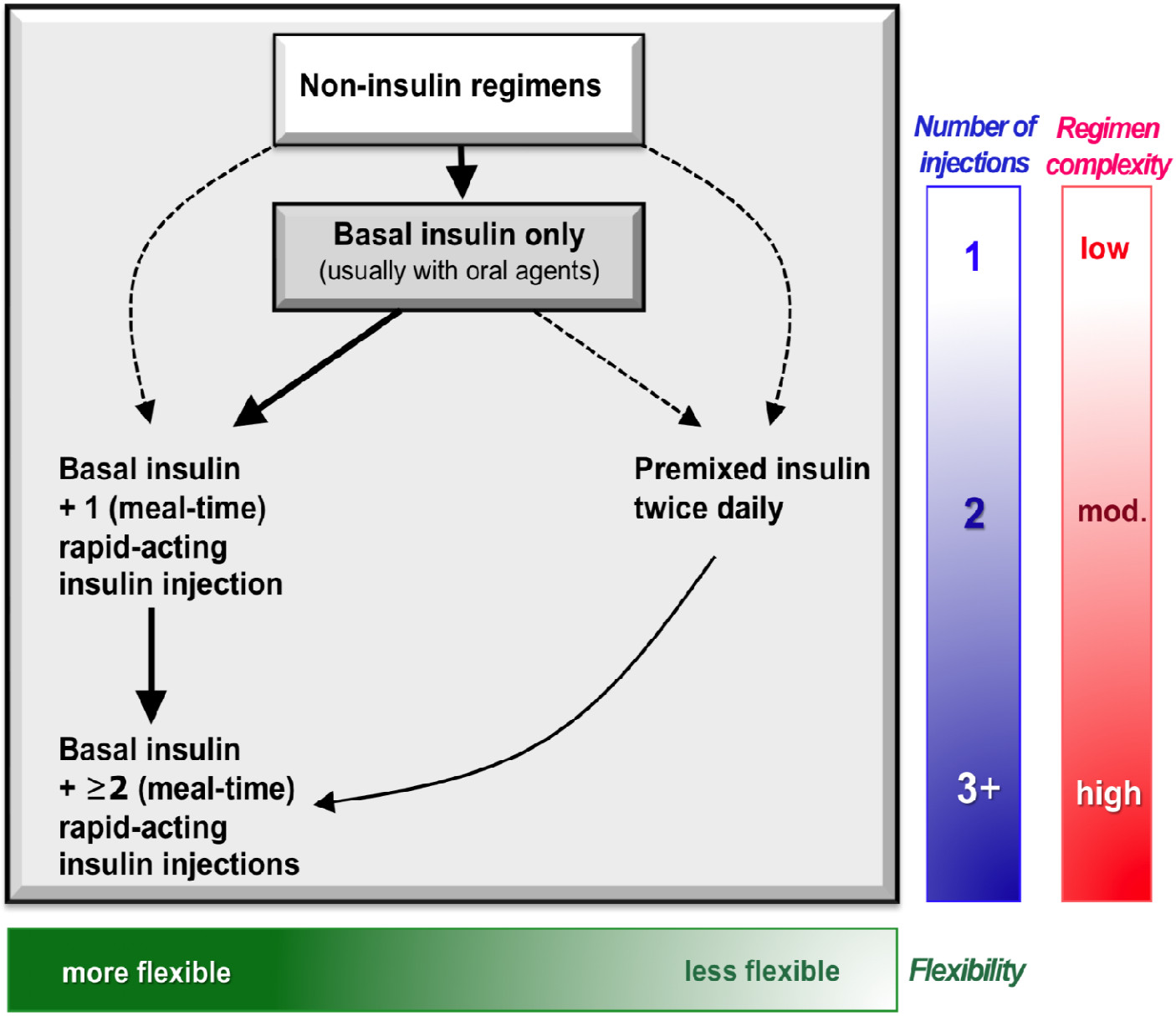
- Lantus (glargine)
  - Generally given once daily; very few may need BID dosing
  - Doses over 80 units should be given in 2 doses

- Novolin N, Humulin N (NPH) and Levemir (detemir)
  - Generally needs to be given BID for full 24 hour coverage
  - If given once daily, give at bedtime (common with orals)
    - Watch for overnight hypoglycemia due to peaks
  - Doses over 80 units should be given in 2 doses
    - Levemir pens max single injection is 60 units

Timing of Premixed Insulin Doses

- NovoLOG 70/30, HumaLOG 75/25, HumaLOG 50/50
  - Give no more than 15 minutes before breakfast and supper
  - Preferably immediately before meal
  - Do **NOT** give at bedtime
- NovoLIN 70/30, HumuLIN 70/30
  - Give no more than 60 minutes before a meal
  - Preferably about 30 minutes before a meal
  - Do **NOT** give after a meal or at bedtime

Premixed insulin should NOT be used as sliding scale or supplemental insulin



Diabetes Care 2012;35:1364–1379

Basal Insulin Initiation & Titration

- Start with
  - If BMI <25: 10 units NPH, glargine or detemir at bedtime
  - If BMI >25: 10-15 units NPH, glargine or detemir at bedtime OR 70/30 before supper
- Then increase by 5 units on weekly basis until fasting BG<200
- Then increase by 2 units on weekly basis until fasting BG <120

- Be careful with patient self-titration
- Avoid patient self-titration at initial visit

Insulin Patient Education

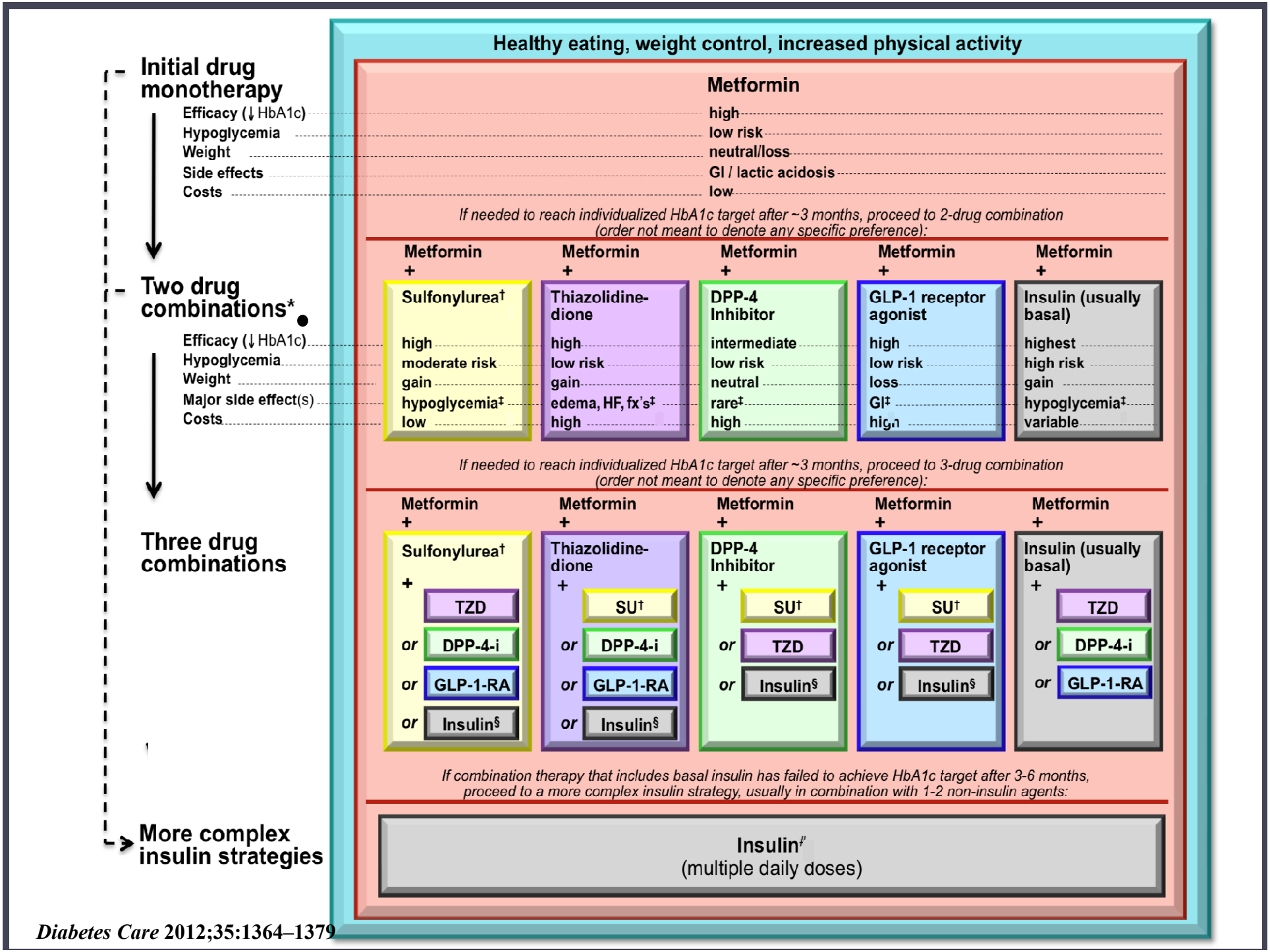
- What does “with meals” or “before meals” mean?
  - Meals vs Food
- Hypoglycemia self management
- Sick days
- What to do for “highs”

Patient-Centered Approach to Managing Hyperglycemia

Blood Glucose Pattern Management

- Identify BG abnormality
  - Priority 1: Hypoglycemia
  - Priority 2: Fasting, premeal, bedtime hyperglycemia
  - Priority 3: 2 hour postprandial hyperglycemia
- Large BG swings: day to day or meal to meal
- If adjusting using A1c alone
  - Assess for adherence
  - First fully assess for hypoglycemia even when >10%
- Always watch for A1c and fingerstick BG mismatches

Clinical Diabetes 2013; 1(31):10-13



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Assess for Hypoglycemia

- Generalized:
  - Assess basal dose
- Isolated:
  - Assess change in diet, delayed meal
- Pattern:
  - Assess most likely insulin/SU dose

Adjusting Basal/Bolus Regimens

Time of glucose check	Insulin dose to change
Pre-Breakfast	Basal insulin
Pre-Lunch	Breakfast
Pre-Dinner	Lunch
Bedtime	Dinner

Check postprandials if preprandial BG are at target, but A1c still above goal

Selecting a Successful Medication Regimen

- Diet history
  - Carb understanding
- Lifestyle pattern
  - Scheduled or variable meals, wake-up, bedtime
- Patient motivation
  - Check BG, multiple doses, change lifestyle
- Patient capabilities
- Hypoglycemia
- Blood glucose/A1c targets

Diabetes Care 2012;35:1364–1379

Pearls

- Always consider insulin dosing/timing errors
  - Be “ok” with missed doses
- Use caution with patient insulin self titration esp w/new diagnosis
- Keep T2DM on metformin even w/prandial insulin
- Be very careful with “pick lists”
- Do not give bolus/supplemental doses of premixed insulins
- Declining renal function increases hypogycemia risk
- Watch for A1c and fingerstick BG mismatch
- Consider dosing insulin in even units (especially pens)