Insulin therapy in type 2 DM

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Session objectives

- Discuss the indications for insulin therapy in DM 2
- Explain the different types of insulin
- Discuss strategies on the initiation of insulin in different patients with type 2 DM
- Discuss a practical approach to the adjustment of insulin in patients on different insulin regimens

Case 1

- A 52-year-old woman with DM 2 for 7 years
- Had education for lifestyle changes
- Metformin 1000 mg bid, Sitagliptin 100 mg qd, Gliclazide MR 60 mg qd, Dapagliflozin 10 mg qd
- No reported diabetes complications
- HbA1c 8.8, normal kidney & liver function
- **How would you approach?**

Glucose targets depend on:

Age

Comorbid conditions

Vascular disease

Patient motivation & adherence

Life expectancy

Risks of treatment

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Individualized A1c targets in DM

<7	→	General (for most adults)
<6.5	→	- Consider if low risk of hypoglycemia - Was shown to reduce the risk of CKD & retinopathy
7 to 8.5	→	- Advanced complications or - Extensive comorbid conditions or - Functionally dependent or - Severe hypoglycemia or - Limited life expectancy

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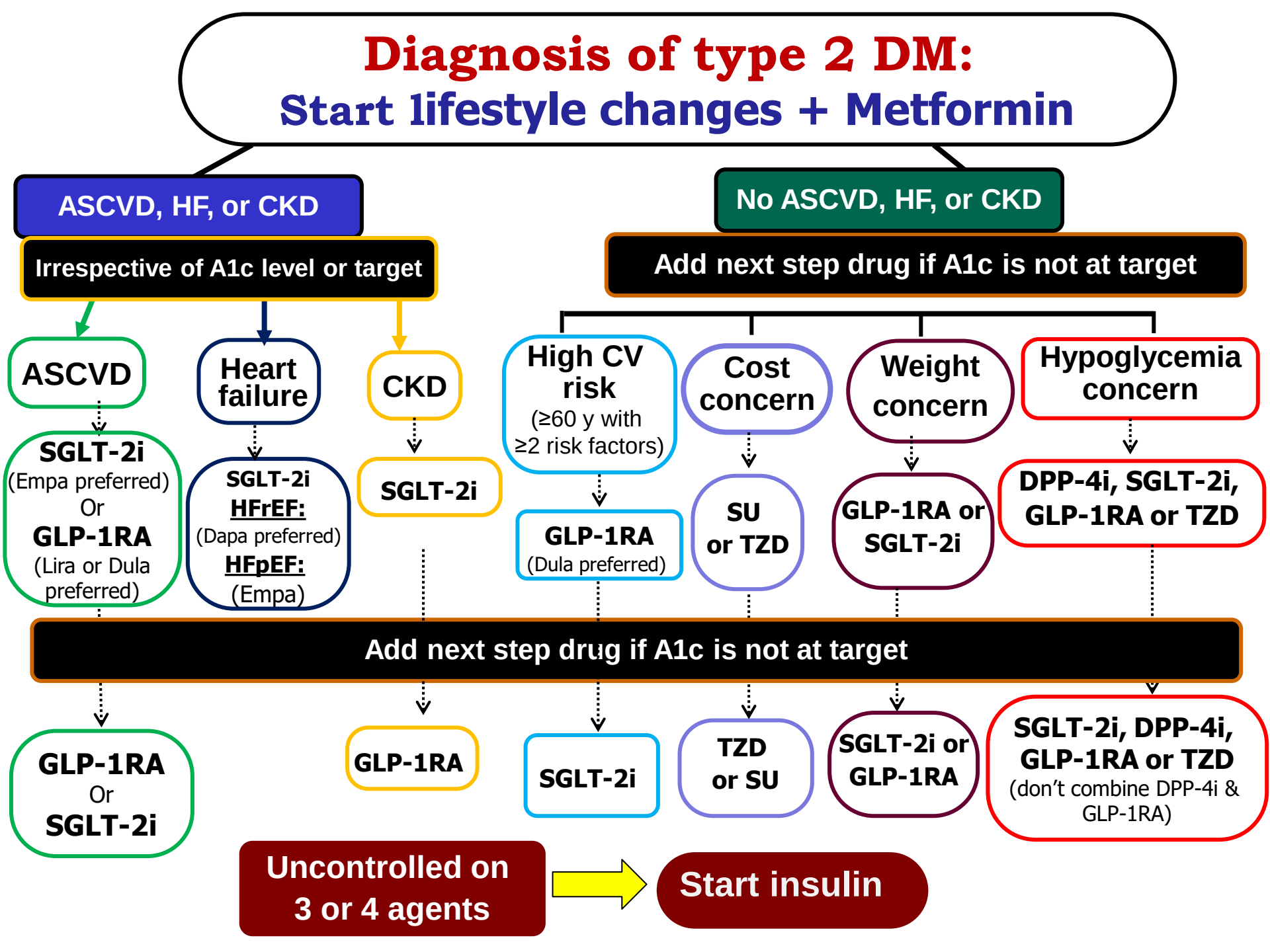
Canadian Diabetes Association. Can J Diabetes 2020;44:S42

A1c lowering power of Non-insulin DM medications

- Most agents ↓ A1c by an average of 1%
- Metformin, SU, GLP-1RA: 1-1.5%
- DPP-4i & SGLT-2i: 0.5-0.7%
- Pioglitazone: variable (0.5-1.5%)

American Diabetes Association. Diabetes Care 2022;45 (suppl 1):S125
Canadian Diabetes Association. Can J Diabetes 2020;44:S42


Diagnosis of type 2 DM:
Start lifestyle changes + Metformin
ASCVD, HF, or CKD
No ASCVD, HF, or CKD
Irrespective of A1c level or target
Add next step drug if A1c is not at target
ASCVD
Heart failure
CKD
High CV risk
(≥60 y with ≥2 risk factors)
Cost concern
Weight concern
Hypoglycemia concern
SGLT-2i
(Empa preferred)
Or
GLP-1RA
(Lira or Dula preferred)
SGLT-2i
HFrEF:
(Dapa preferred)
HFpEF:
(Empa)
SGLT-2i
GLP-1RA
(Dula preferred)
SU
or TZD
GLP-1RA or SGLT-2i
DPP-4i, SGLT-2i, GLP-1RA or TZD
Add next step drug if A1c is not at target
GLP-1RA
Or
SGLT-2i
GLP-1RA
SGLT-2i
TZD
or SU
SGLT-2i or GLP-1RA
SGLT-2i, DPP-4i, GLP-1RA or TZD
(don't combine DPP-4i & GLP-1RA)
Uncontrolled on 3 or 4 agents
Start insulin

Indications for insulin

- Failure of non-insulin glucose-lowering therapy
- Type 1 DM
- Type of DM is not known
- Pregnancy
- Symptomatic hyperglycemia
- Glucose ≥300 mg (16.6 mmol)
- A1c >10 (especially with symptoms)
- In-hospital

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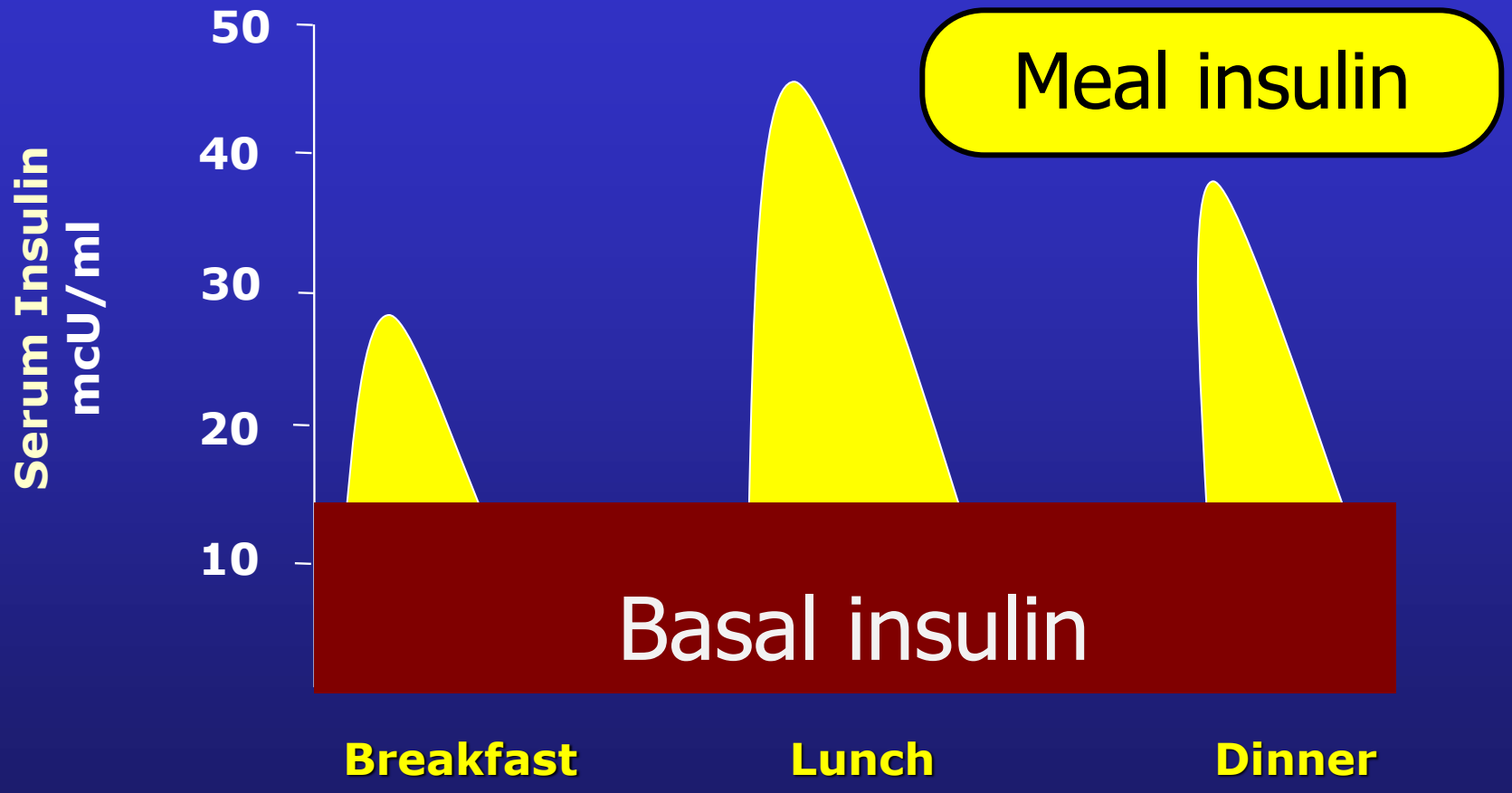
Normal insulin secretion



Polonsky K et al. New Eng J Med 1988;318:1231

Types of Insulin

- Basal insulin
- Meal insulin

Basal insulin

Intermediate –acting:

NPH (Humulin N®, Insulatard®)

Long-acting:

Glargine U-100 (Lantus®)

Glargine U-300 (Toujeo®)

Glargine biosimilar (Basaglar ®)

Detemir (Levemir ®)

Degludec (Tresiba®)

Meal Insulin

- **Short-acting:**
  - Regular (Actrapid®, Humilin R®, Novolin R®)
  - Taken 30 minutes before meal
- **Rapid-acting:** (insulin analogs)
  - Aspart (Novorapid®, Novolog®)
  - Glulisine (Apidra®)
  - Lispro (Humalog®)
  - Taken 0-15 minutes before meals (can be given immediately after meals)

Premixed insulins

- **70/30 (Mixtard 30® or Humulin 70/30®):**

  - Contains 70% NPH & 30% Regular insulin

- **Aspart 70/30 (Novomix 30®):**

  - Contains 70% Aspart Protamine & 30% Aspart

Premixed insulins

- **Lispro 75/25 (Humalog mix 25®):**
  - Contains 75% Lispro Protamine & 25% Lispro
- **Lispro 50/50 (Humalog mix 50®):**
  - Contains 50% Lispro Protamine & 50% Lispro
- **Aspart 50/50 (Novomix 50®):**
  - Contains 50% Aspart Protamine & 50% Aspart

Which insulin to use?

- Basal alone or Basal + Meal

Basal Insulin:

- May be enough to control glucose if A1c <9
- Or Can use if patient is reluctant to starting insulin

(Use initially to break insulin fear)

Starting basal insulin

- **NPH, Glargine, Detemir or Degludec**
- Choice depends on the cost (NPH is the cheapest)
- At bedtime (or AM)
- Starting dose: 0.1 unit/kg (or 10 units)
- If A1c >9: can start with 0.2 units/kg/day
- Home glucose monitoring

Non-insulin medications when starting insulin

- ADA recommends to consider GLP-1RA (if possible) before starting basal insulin
- Keep Metformin
- Can keep DPP-4i, SGLT-2i, GLP-1RA (consider cost)
- We stop Sulfonylurea (some keep it)
- Consider stopping Pioglitazone (can be used but ↑ weight & risk of heart failure)

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Follow up after starting basal insulin

Can patients adjust insulin?

- This study* examined adjusting insulin by the patient or the physician using an algorithm
- Based on fasting home glucose
- ↑ Insulin dose by 2 units every 3 days
- Target glucose <120 mg (6.7 mmol)
- Patient algorithm: ↓ A1c by 1.2%
- Physician algorithm: ↓ A1c by 1.08%

*AT. LANTUS Study. Diabetes Care 2005;28:1282

Use an algorithm to have patients adjust insulin dose

Instructions

- Check your sugar fasting daily (make it easier only once/day)
- Your target sugar is <130 mg (individualize)
- Increase insulin by 2 units every 3 days till fasting <130
- If sugar goes <80 mg, reduce the dose by 2 units
- When sugar at target, check at other times
- Call us if questions

Handout for self-adjusting insulin

- The type of insulin prescribed for you is _____
- The initial dose is: _____ units, timing: _____
- Check your sugar before breakfast daily
- The desired level of sugar is < _____
- ↑ dose by 2 units every 3 days till glucose < _____
- If sugar <80 mg, ↓ dose by 2 units
- When sugar reaches the desired level, check at other times (before and after meals)
- Contact us for any questions at: _____

Handout for self-adjusting insulin

- The type of insulin prescribed for you is Glargine
- The initial dose is: 8 units, timing: at bedtime
- Check your sugar before breakfast daily
- The desired level of sugar is < 130
- ↑ dose by 2 units every 3 days till glucose < 130
- If sugar <80 mg, ↓ dose by 2 units
- When sugar reaches the desired level, check at other times (before and after meals)
- Contact us for any questions at: 4444-4444

خطة علاجية لتعديل جرعات الإنسولين

Handout for self-adjusting insulin

- قرر طبيبك وصف علاج الإنسولين ليساعدك على التحكم بالسكر
- نوع الإنسولين الموصوف لك هو : _____
- الجرعة الأولية هي:_____ وحدات , توقيتها : _____
- قم بإجراء تحليل السكر بالبيت قبل الإفطار يومياً
- مستوى السكر المطلوب (قبل الإفطار) : أقل من 130
- إذا كان مستوى السكر أكثر من 130 لمدة 3 أيام, قم **بزيادة** الجرعة بمعدل **2 وحدة**
- إستمر في زيادة الجرعة كل 3 أيام حتى يصل مستوى السكر إلى المطلوب
- إذا انخفض السكر إلى أقل من 80 , قم **بتخفيض** الجرعة بمعدل **2 وحدة**
- إتصل بنا لأي إستفسارات على : _____

CASE 1: Messages

Basal insulin

- May be enough alone if A1c <9 or use if patient is reluctant to insulin

- Use a patient-driven algorithm to save time and effort

Case 2

- A 55-year-old woman is on insulin Glargine 40 units at bedtime, Metformin 1 gram bid, Sitagliptin 100 mg qd, Glimepiride 6 mg qd
- A1c was 9.6 before starting insulin (4 months ago)
- Today A1c 8.3
- Home glucose pre-meals (mg/dL):

Pre-Breakfast	Pre- Lunch	Pre-Dinner
120	120	-
123	110	180
135	-	165
118	90	170

Case analysis

- Assessing home glucose monitoring
- Look at each column separately
- Is there a pattern (all high, variable?)
- Ask about patterns of meals:
  - Which is the largest meal?
  - Are meals consistent in time and amount?

Analysis of continuous glucose monitoring (CGM) data

- Recommended days CGM device is worn: **14 days**
- % of time CGM device is active: 70% of 14 days
- Components of Ambulatory Glucose Profile (AGP):
  1) Mean (average) glucose
  2) Glucose management indicator
  3) Glycemic variability target
  4) TAR (time above range):
     - % of readings & time >180 mg (10 mmol)
  5) TIR (time in range): % of readings & time 70-180 mg (3.9-10.0 mmol)
  6) TBR (time below range): % of readings & time < 70 mg (3.9 mmol)

Targets for components of CGM (Ambulatory glucose profile: AGP)

1) Mean (average) glucose: <154 mg (8.5 mmol)
2) Glucose management indicator: <7%
3) Glycemic variability target: ≤36%
4) TAR (time above range):
   - High (level 1): [180-250 mg (10-13.9 mmol)]: <25%
   - Very high (level 2): [>250 mg (13.9 mmol)]: <5%
5) **TIR** (time in range): [70-180 mg (3.9-10 mmol)]: >70%
6) TBR (time below range):
   - Low (level 1) :[54-69 mg (3.0-3.8 mmol)]: <5%
   - Very low (level 2): [<54 mg (3.0 mmol)]: <1%

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AGP Report

Name

MRN

GLUCOSE STATISTICS AND TARGETS

26 Feb 2019 - 10 Mar 2019	**13 days**
% Time CGM is Active	**99.9%**

Glucose Ranges	**Targets** [% of Readings (Time/Day)]
Target Range 70-180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial.

Average Glucose	**173 mg/dL**
Glucose Management Indicator (GMI)	**7.6%**
Glucose Variability	**49.5%**

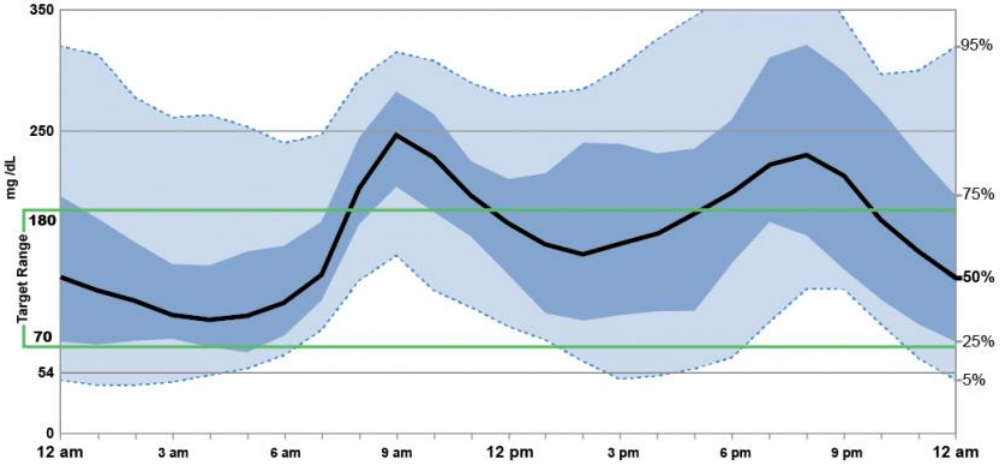
Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

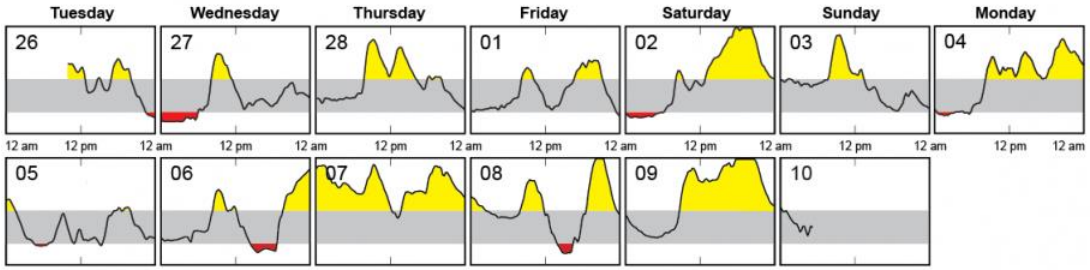
- **Very High** (>250 mg/dL) **20%** (4h 48min)
- **High** (181–250 mg/dL) **23%** (5h 31min)
- **Target Range** (70–180 mg/dL) **47%** (11h 17min)
- **Low** (54–69 mg/dL) **4%** (58min)
- **Very Low** (<54 mg/dL) **6%** (1h 26min)

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



DAILY GLUCOSE PROFILES

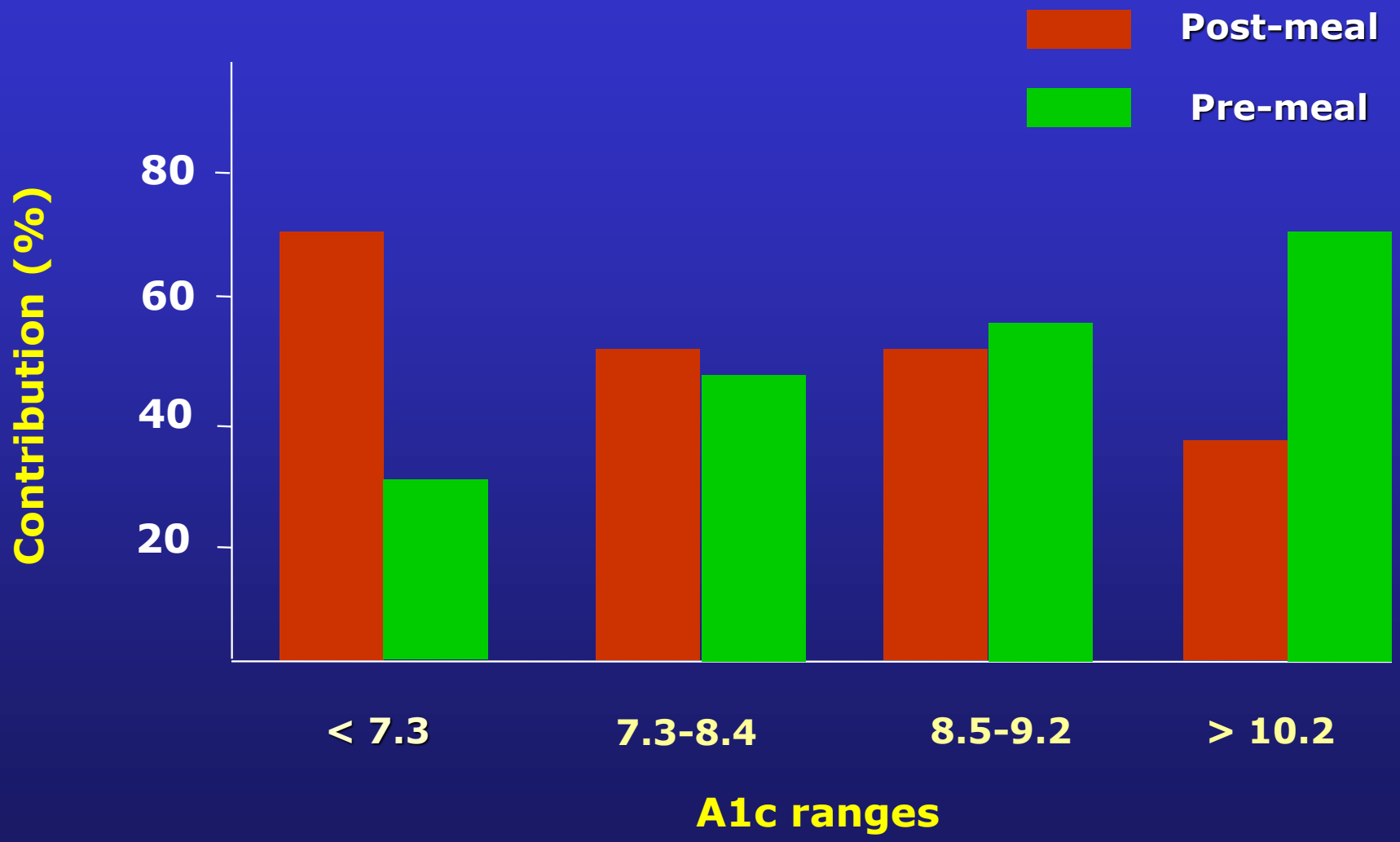


Each daily profile represents a midnight to midnight period.

Patents pending-HealthPartners Institute dba International Diabetes Center-All Rights Reserved. 2019

captürAGP® v 4.0

Contribution of glucose to A1c



Monnier L, et al. Diabetes Care 2003;26:881

Pre- & Post meal glucose

- As A1c gets to <8.5, the contribution of post-meal glucose becomes more
- So, pre-meal may be at target, but post-meal glucose values are high
- Check post-meal glucose

Case 2: Plan

- Check **post-meal** home glucose [mg (mmol)]

Post-Breakfast	Post-Lunch	Post-Dinner
160 (8.9)	260 (14.4)	220 (12.2)
155 (8.7)	245 (13.6)	215 (12.1)
-	195 (10.8)	200 (11.1)
170 (9.4)	200 (11.1)	230 (12.7)

Target post-meal: < 180 mg (10 mmol)

Home blood glucose: general targets

Before meals:

80-130 mg

(4.4-7.2 mmol)

2 hours after meals:

<180 mg

(10 mmol)

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Options when basal insulin alone is not enough

1) **Add meal insulin**
2) **Add GLP-1RA**
3) **Add SGLT-2i** (if not already used)
4) **Add DPP-4i** (if not already used)

Options with basal insulin

1) Add GLP-1 agonist:

- Use before starting meal insulin if possible
- Remember to stop DPP-4i
- When switching from DPP-4i: ↓ A1c 0.3-0.7%
- ↓ Weight, less hypoglycemia

2) Add SGLT-2i:

- ↓ Weight, less hypoglycemia
- ↓ A1c by 0.5-0.7%

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Canadian Diabetes Association. Can J Diabetes 2020;44:575

Options with basal insulin

3) Add DPP-4i:

- ↓ A1c by 0.5-0.7%
- Less weight gain
- Less hypoglycemia

Back to case 2: management plan options

1) Add meal insulin

- Most effective

2) Add GLP-1RA (and stop DPP-4i):

- Can be tried
- May not be enough to achieve target glucose

3) Add SGLT-2i

- Attractive option (if cost is not an issue)

Plan if adding meal insulin

- Start by 1 injection at the main meal
- Rapid-acting insulin or Regular
- Start by 4 units (or more depending on glucose levels)
- Monitor home glucose **2-hour post-meal**
- Adjust dose by 2 units every 3 days
- Target post-prandial glucose:

  < 180 mg (10 mmol)
- Assess need for insulin at other meals by home glucose levels

"Golden rule" of Insulin

Basal insulin → Controls **pre-meal** glucose

Meal insulin → Controls **post-meal** glucose

CASE 2: Message

- Basal insulin alone may not be enough
- Can use SGLT-2i, DPP4i or GLP-1RA + basal insulin
- Can add meal insulin
- Cost should be considered
- Monitor post-meal glucose when using insulin

Case 3

- A 55-year-old man on insulin NPH 40 units at bedtime Metformin 1000 mg bid, Sitagliptin 100 mg qd
- He could not afford SGLT-2i
- A1c 8.8
- Home glucose (mg/dL):

Before breakfast	Before lunch	Before dinner
110	180	-
80	200	182
105	-	175
100	-	166

Case 3

- Premeal glucose reflects action of basal insulin
- High pre-lunch and pre-dinner requires addition of NPH am
- Plan:

  - Add NPH (8-10 units) AM

  - Increase NPH am for target premeal < 130 mg

Case 3: follow up

- After adjusting doses
- Now on NPH 24 AM, 40 bedtime
- A1c 8.2
- Home glucose:

Pre-Breakfast	Pre-Lunch	Pre-Dinner
140	112	-
120	104	170
155	-	155
130	90	162

"Golden rule" of Insulin

Basal insulin → Controls **pre-meal** glucose

Meal insulin → Controls **post-meal** glucose

Case 3: plan

- Do **2-hour post-meal** home glucose:

Post-Breakfast	Post-Lunch	Post-Dinner
160	260	220
155	245	195
-	195	200
144	210	230

Target post-meal: < 180

CASE 3: Plan

- Add meal insulin to lunch & dinner
  - Regular
  - Or Rapid (Aspart, Lispro or Glulisine)
- Start by 4 units before meals
- Advise patient to increase dose by 2 units every 3 days till 2-hour post meal < 180 mg
- Keep same NPH doses

Case 4

- A 38-year-old man with no past medical history
- Reports ↑ urination and thirst for 2 weeks
- Exam: BMI 34.2, acanthosis nigricans
- Father and brother have type 2 DM
- Random glucose 486 mg (27 mmol)
- Normal electrolytes, no ketones, no acidosis
- He is diagnosed with type 2 DM
- **How to approach?**

Case 4: management

- **Insulin is indicated in newly-diagnosed DM 2 if:**
  - Catabolic features (weight loss, ketosis, hyperTG)
  - or symptoms of hyperglycemia (polyuria, polydipsia)
  - or random glucose ≥16.6 mmol (300 mg)
  - or A1c >10%
- Which insulin to use?
  - **Basal + meal**

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Options of Basal + Meal insulin

1) Long Basal + Rapid

   (Glargine, Detemir or Degludec + Rapid)

2) Intermediate Basal + Meal

   (NPH + Regular or Rapid)

3) Premixed Insulin

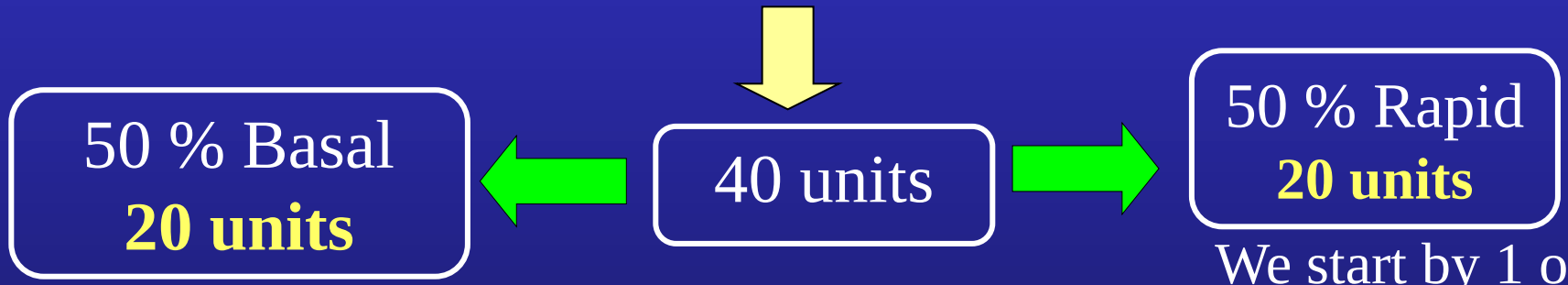
Long basal + meal insulin analogs

- More flexible, available as pens
- But more injections & more expensive
- Usual starting dose: 0.3-0.5 units/kg/day
  - Normal weight, active: start 0.3 units/kg/day
  - Overweight or obese or inactive: start 0.5 units/kg/day
- 50% basal & 50% meal

Example: starting long basal+ meal

Weight 80 kg

- Starting dose: 0.5 units/kg/day



We start by 1 or 2 main meals (discuss with patient)

Example:

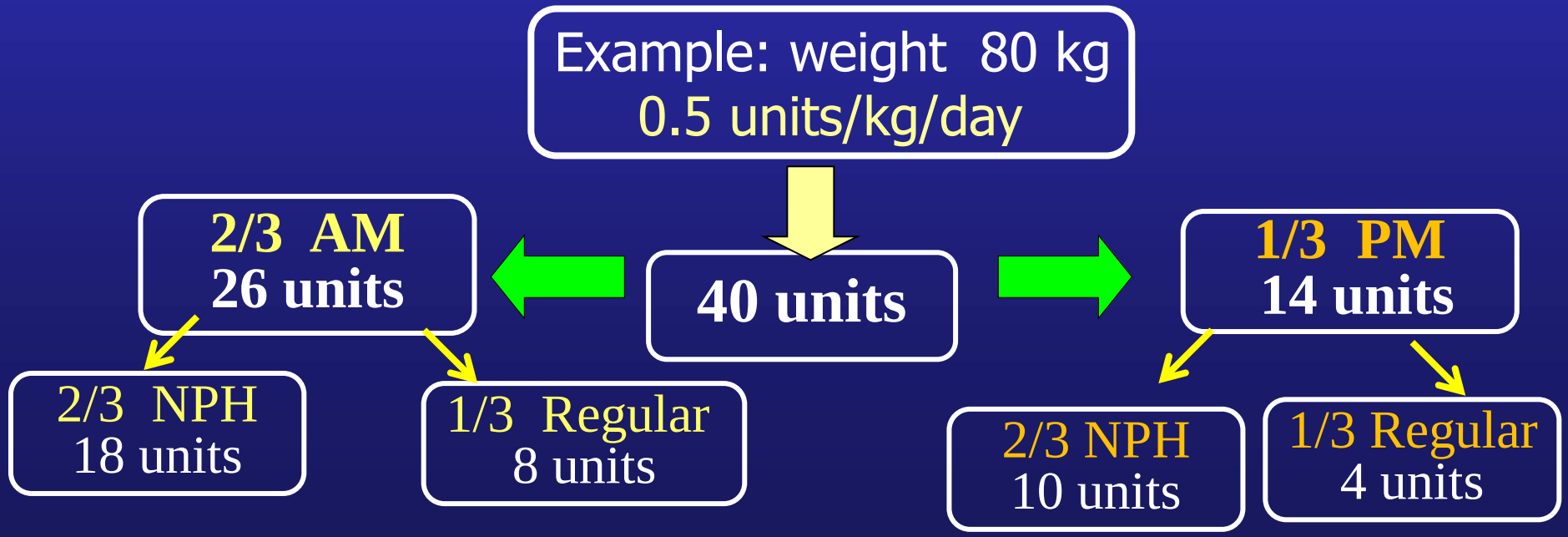
20 at Lunch

or

12 Lunch, 8 PM

Starting NPH +Regular insulin

- More flexible, low cost
- Vial, patient has to mix
- Starting dose 0.3-0.5 units/kg/day: 2/3 am, 1/3 pm
- Then each dose is divided: 2/3 NPH, 1/3 regular



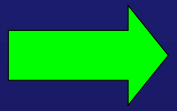
Premixed insulin

- Easier, more convenient for the patient
- Available in pen and vial
- May not work especially if heavy/variable meals
- Dose: 0.3-0.5 units/kg/day: 2/3 AM, 1/3 PM
  - Normal weight, active: start 0.3 units/kg/day
  - Overweight or obese or inactive: start 0.5 units/kg/day

Example: 80 kg

Starting 0.5 u/kg/day

40 units



2/3 AM
[26 units]

1/3 PM
[14 units]

CASE 4: Messages

- Patients with significant hyperglycemia need

  (basal + meal) insulin

- Premixed insulin is an easy option, but may not work

  Or use long basal + meal insulin

  Or NPH + meal insulin

Case 5

- A 55-year-old man with DM 2 for 8 years
- Premixed insulin 70/30 (Mixtard 30®): 40 units AM, 20 units PM, Metformin, Linagliptin, Empagliflozin
- A1c 8.6
- Home glucose (mg/dl):

Pre-Breakfast	Pre-Lunch	Pre-Dinner
105	80	-
80	90	200
110	-	180

Case 5

- Ask the patient to check 2-hour post-meal glucose
- Home glucose (mg/dl):

Pre-Breakfast	**Post-BF**	Pre-Lunch	**Post-lunch**	Pre-Dinner	**Post-D**
105	**150**	80	**250**	-	**270**
80	**142**	90	**262**	200	-
110	**170**	-	**215**	180	**335**

Home blood glucose: general targets

Before meals:

80-130 mg

(4.4-7.2 mmol)

2 hours after meals:

< 180 mg

(10 mmol)

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Case 5: analysis

- **Pre-breakfast** glucose is controlled
  - So, NPH part of premixed at **dinner** is enough
- **Pre-lunch** glucose is controlled
  - So, NPH part of premixed at **AM** is enough
- **Pre-dinner** glucose is high
  - This could be due to high post-lunch glucose

Case 5: analysis

- **Post-breakfast** glucose is acceptable
  - So regular part of premixed is enough
- **Post-lunch** glucose is high
  - So, need to add **meal insulin at lunch**
- **Post-dinner glucose** is high
  - So, need more **meal insulin at dinner**

Case 5: analysis

- The patient needs **more meal** insulin at **dinner** and the addition of **meal** insulin at **lunch**
- But, he is on premixed insulin
  - So, cannot change the dose of meal insulin alone
  - If the dose of premixed is increased:
    - Post-meal glucose will improve
    - But pre-meal glucose will become low
- **So, we need to change the type of insulin**

Options when Premixed insulin 70/30 does not work

1) Long Basal + Meal insulin

2) NPH + Meal insulin

3) Premixed insulin 50/50

Option 1:

Long basal + Meal insulin

Option 1:
Long Basal + Rapid Meal

- **<u>Advantages</u>:**
  - Pen
  - Less nocturnal hypoglycemia
- **<u>Drawbacks</u>:**
  - More injections
  - High cost

Switching from premixed to long basal + rapid meal

- **Calculate the basal insulin dose:**

- Calculate TOTAL dose of NPH
- Premixed insulin 70/30: contains 70% NPH
- 70% of 40 = 28
- 70% of 20 = 14
- Total NPH = 28 + 14 = 42 units
  - When switching to long basal: ↓ total dose by 25%
- So, in this case, long basal will be 30 units once/day
- Another easier way:
  - Half of total insulin dose (half of 40 + 20) = 60 ÷ 2= 30

Switching from premixed to long basal + rapid meal

- **Calculate meal insulin dose:**
- Premixed insulin 70/30: contains 30% regular
- 30% of 40 AM = 12 units regular
- 30% of 20 PM = 6 units regular
- When switching from regular to rapid: same doses

Switching from premixed to long basal + rapid meal

Pre-Breakfast	Post-BF	Pre-Lunch	Post-lunch	Pre-Dinner	Post-dinner
105	**150**	80	**250**	-	**270**
80	**142**	90	**262**	200	-
110	**170**	-	**215**	180	**335**

Assessment and Action:

Current dose:
Regular: 12 am, 6 pm

1) Post-breakfast glucose:

- Controlled
- Give rapid insulin same dose (12 units)

2) Post-lunch glucose:

- High. Add rapid insulin at lunch (start with 4 units)

3) Post-dinner glucose:

- High. ↑ rapid insulin at dinner (to 10 units)

New dose of long basal + meal insulin

(example: Glargine + Aspart)

Glargine	**30 bedtime**
Aspart	**12 am, 4 lunch, 10 pm**

Adjust doses as per home glucose

Option 2:

NPH + Meal insulin

Option 2: NPH + Meal

– **Advantages:**

- Low cost

– **Drawbacks:**

- Person has to mix

- Person has to carry

How to switch from premixed to NPH + Regular insulin?

- Calculate the doses of NPH and Regular
- Premixed 70/30 = 70% NPH & 30% regular
- **70/30: 40 AM & 20 PM**
- 70% is NPH = 28 AM, 14 PM
- 30% is regular = 12 AM, 6 PM
- So, this patient is taking : NPH 28 am, 14 pm
  & Regular 12 am, 6 pm
- Now, adjust doses according to home glucose

Switching from premixed to NPH + Regular

Pre-Breakfast	Post-BF	Pre-Lunch	Post-lunch	Pre-Dinner	Post-dinner
105	150	70	250	-	270
80	142	90	262	200	-
110	170	-	215	180	310

Assessment and Action:

1) Pre-Breakfast glucose:

- Reflects action of NPH at pm
- Controlled
- No change in dose (14)

2) Post-breakfast glucose:

- Reflects action of regular at am
- Controlled. Keep same dose (12)

Current dose:
NPH 28 am, 14 pm
Regular: 12 am, 6 pm

Switching from premixed to NPH + Regular

Pre-Breakfast	Post-BF	Pre-Lunch	Post-lunch	Pre-Dinner	Post-dinner
105	**150**	70	**250**	-	**270**
80	**142**	90	**262**	210	**-**
110	**170**	-	**215**	182	**310**

Assessment and Action:

3) Pre-lunch glucose:

- Reflects action of NPH at am
- Controlled
- No change in dose (28)

Current dose:
NPH 28 am, 14 pm
Regular: 12 am, 6 pm

4) Post-lunch glucose:

- High
- So, we need to add regular insulin at lunch

Switching from premixed to NPH + Regular

Pre-Breakfast	Post-BF	Pre-Lunch	Post-lunch	Pre-Dinner	Post-dinner
105	**150**	70	**250**	-	**270**
80	**142**	90	**262**	210	**-**
110	**170**	-	**215**	182	**310**

Assessment and Action:

5) Pre-dinner glucose:

- Reflects action of NPH
- Wait till post-lunch is better

6) Post-dinner glucose:

- Reflects action of regular at dinner
- ↑ dose gradually by 2 or 4 units till target <180 mg

Current dose:
NPH 28 am, 14 pm
Regular: 12 am, 6 pm

New dose of NPH/R insulin

NPH	28 am, 14 pm
Regular	12 am, 4 lunch, 10 pm

Adjust doses as per home glucose

Option 3:

premixed 50/50

Switching from 70/30 to premixed 50/50

- **Pen**
- **Easier**
- **But, may not control glucose**
- **Dose:**
  - same as 70/30
  - So, this patient gets 40 AM, 20 PM

When will premixed insulin not work?

- Type 1 DM
- Diabetes in pregnancy
- Inconsistent meals or erratic lifestyle
- Many patients with chronic kidney disease

CASE 5: Messages

- Premixed insulin does not work in many patients
- Be ready to change it if needed
- Change to long basal + meal or NPH + Regular

Case 6

- A 58-year-old woman with DM 2 for 12 years
- On Premixed Aspart 70/30 (Novomix®) 60 units AM, 40 units PM, Metformin, Linagliptin
- Tries with lifestyle changes
- BMI 40.2
- A1c 11.2
- Home glucose (mg/dl):

Pre-breakfast	Pre-lunch	Pre-dinner
280	180	-
200	270	360
225	-	400

Case 6: analysis

- Glucose levels are high at all times
- Patient needs more insulin
- She very likely needs insulin at **LUNCH**
- Lifestyle changes alone are unlikely to be enough to control glucose
- Adding SGLT-2i may help, but will not be enough to control glucose

Case 6: action

- Lifestyle changes were reinforced
- SGLT-2i was added
- After 3 months:
  - A1c 10.1
  - Those are home glucose:

Pre-breakfast	**Post-BF**	Pre-lunch	**Post-lunch**	Pre-dinner	Postdinner
180	**250**	140	**350**	-	**270**
190	**280**	120	**370**	360	**250**
160	**270**	-	**295**	355	**305**

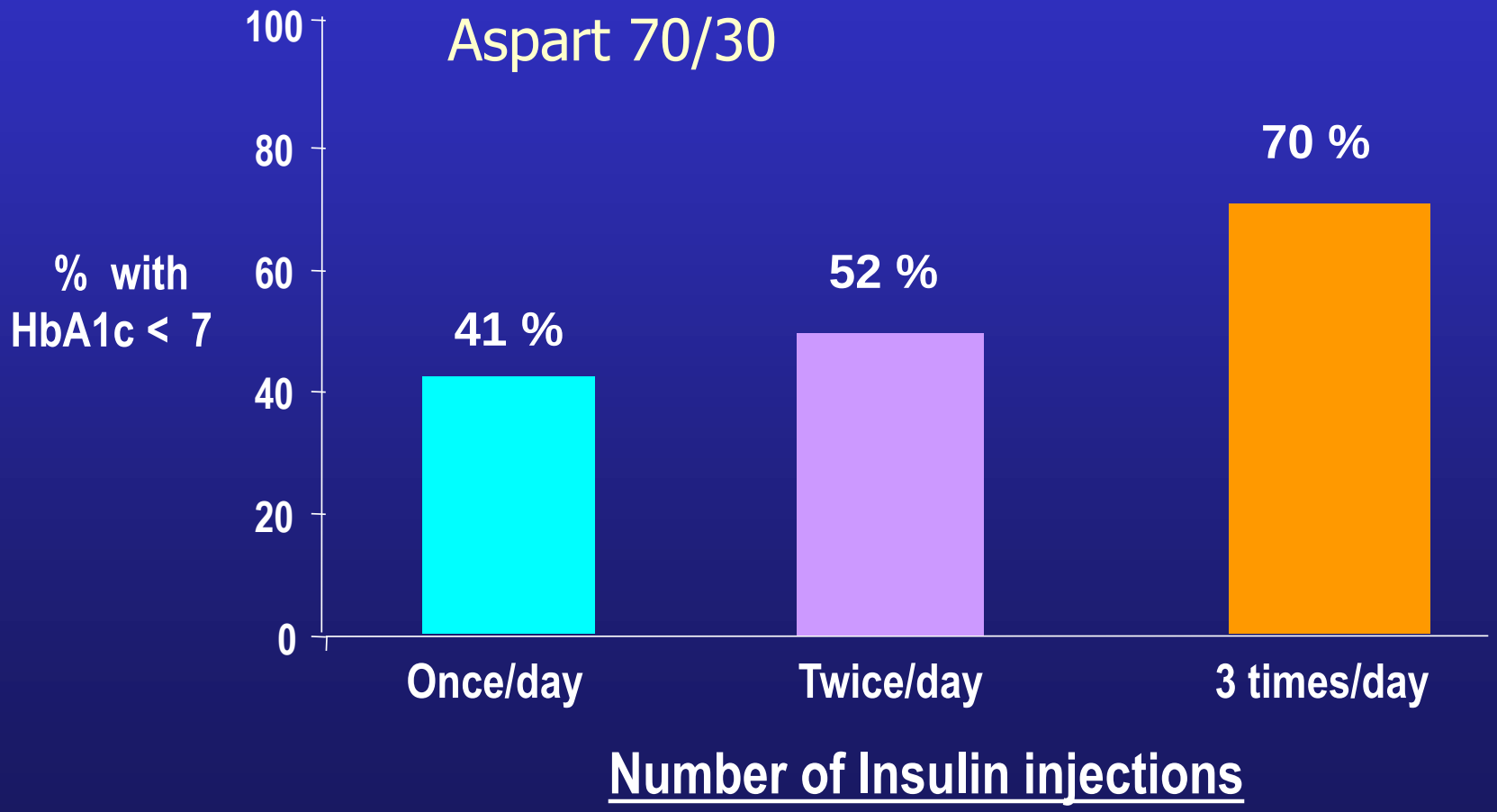
Case 6: analysis & plan

- Most glucose numbers are high
- Post-meal glucose is high (more after lunch), & predinner
- Need to add lunch insulin
- **Plan**:
  - Options:
    1) Another premixed dose at lunch (may or may not work)
    2) OR Switch to long basal + rapid insulin 3 times/day
    3) OR Switch to NPH + Regular 3 times/day

Case 6: Option 1

- **Add premixed insulin at lunch:**
- Several studies showed benefit
- Easier
- Only 1 extra injection
- But it may not control glucose
- Start by 10-15 units

Premixed insulin & glucose control



Garber A, et al. Diabetes Obes Metab 2006;8:58

Case 6: Option 2

- **Switch to NPH + meal insulin:**
- NPH + Regular (or Rapid) insulin
- Total of 3 injections
- Patient has to mix insulin
- Low cost
- More hypoglycemia compared to long basal/meal

Case 6: action

- Premixed was changed to NPH + Regular
- Regular insulin was added at lunch
  - Started with 8 units and titrate
- Target post-meal: <180 mg
- These are the doses after titration:

Regular	36	30	28
NPH	50		36
	AM	L	PM

Case 6: follow up

	AM	L	PM
Regular	36	30	28
NPH	50		36

A_1c 8.8

Fasting	Post-BF	Pre-Lunch	Post Lunch	Pre-Dinner	Post-dinner
115	155	95	150	-	240
125	100	155	162	215	235
110	-	-	-	184	-
100	105	130	148	173	262

Case 6: analysis

- Post-lunch glucose is at target
  - So, regular insulin dose at lunch is good
- Pre-dinner glucose is high
  - You may think this is morning NPH dose
  - NPH at breakfast was increased, but pre-lunch glucose went low
  - Solution: ADD NPH at **lunch**
- NPH may work only for 8-10 hours
- Post-dinner glucose is high:
  - Increase regular insulin at dinner

Case 6: more action

- Add NPH at lunch (start by 4 units)
- Adjust dose according to pre-dinner glucose
  - Target: 80 to 130 mg
- This patient is now better on:

Regular	40	34	36
NPH	50	16	40
	AM	L	PM

Case 6: Option 3

Long basal + rapid meal insulin

- Glargine, Detemir or Degludec + Rapid
- 2 Pens
- Total of 4 injections (Glargine/Detemir cannot be mixed with meal insulin)
- Higher cost than NPH/R

Case 6: action

Aspart	26	40	28	
Glargine				64
	AM	L	PM	bedtime

A_1c 9.2

Pre-breakfast	Post-BF	Pre-Lunch	**Post-lunch**	Pre-Dinner	Post-dinner
120	**255**	180	**150**	-	**195**
110	**290**	174	**170**	240	**215**
100	**270**	-	**145**	210	**250**

"Golden rule" of Insulin

Basal insulin → Controls **pre-meal** glucose

Meal insulin → Controls **post-meal** glucose

Case 6: analysis

- Pre-breakfast glucose is good
  - So, basal insulin dose is enough
- Pre-lunch and pre-dinner glucose are high
  - This represents the action of basal insulin
- Post-lunch glucose is controlled (reflects lunch meal insulin)
- Post-BF & Post-dinner glucose are high:
  - Increase meal insulin doses at both times
- So, here, Glargine is not working for 24 hours:
  - Solution: add 2nd Glargine dose in the morning

Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart

S. G. Ashwell, J. Gebbie and P. D. Home

Diabet. Med. 23, 879–886 (2006)

Assessing insulin effectiveness at the end of the day: Once-daily versus twice-daily insulin glargine injection

Mark R. Burge[1*], Eric R. Schroeder[2], Stephen Mitchell[3]

Journal of Diabetes Mellitus Vol.2, No.2, 203-207 (2012)

Twice-daily insulin glargine for patients with uncontrolled type 2 diabetes mellitus

Mohsen Eledrisi*, Noor Nabeel Suleiman, Obada Salameh, Mohammad Khair Hamad, Omar Rabadi, Ahmed Mohamed, Rana Al Adawi, Abdul Salam

Journal of Clinical & Translational Endocrinology 15 (2019) 35–36

Twice-daily insulin Glargine (Largest series)

- Total of 82 patients with type 1 DM
- Switched from NPH to Glargine (at bedtime)
- Need for extra AM Glargine determined by:
  - AM hypoglycemia with pre-dinner hyperglycemia
- 24 % required Glargine twice/day
- Glargine dose was split equally

Albright E, et al. Diabetes Care 2004;27:633

Case 6: Plan

- Add a 2nd Glargine dose AM
- Done in 2 ways:
  - Split the dose equally:
    - In this case: 35 AM, 35 PM (easier than at bedtime)

      Or

    - Add 6-8 units AM
  - No studies on which one is better
  - Most do the split

Case 6: question

- **How about using Glargine U-300 or Degludec daily instead of twice-daily Glargine U-100?**
- No studies so far
- Based on clinical experience, many patients still need Glargine U-300 or Degludec twice daily
- Remember that premixed Degludec/Aspart is used frequently twice daily

Case 6: Another option

Metabolic (Bariatric) surgery

- **Indications in type 2 DM:**

1) **BMI ≥40 (≥37.5 in Asian Americans)** [recommended]

2) **BMI 35-39.9 (32.5-37.4 in Asian Americans)**: who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with non-surgical methods [**recommended**]

American Diabetes Association. Diabetes Care 2022;45 (suppl 1):S113

Metabolic (Bariatric) surgery

- **Indications in type 2 DM:**

3) BMI 30-34.9 (27.5-32.4 in Asian Americans):

who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with non-surgical methods **[consider]**

American Diabetes Association. Diabetes Care 2022;45 (suppl 1):S113

Which insulin regimen should I use here?

- **Long basal + rapid meal achieved the <u>SAME</u> glucose control compared to NPH + meal**
- Analogs have less **<u>nocturnal</u>** hypoglycemia
- But number of injections (4 or 5 vs 3)
- Cost difference is significant
- **<u>So, discuss with the patient</u>**

Singh S,et al. CMAJ 2009;180:385; Cochrane Database Syst Rev 2007;(2):CD005613

CASE 6: Messages

- Give **enough** insulin
- Many patients need **lunch** insulin
- Options: long basal + Meal (4-5 injections/day)

  or NPH + Meal (3 injections/day)

Case 7

- A 28-year-old lady presented with DKA 6 months ago
- She was started initially on insulin
- Insulin was stopped 2 months ago
- Switched to metformin and glimepiride
- Home glucose range 110-250 mg
- HbA1c 7.2
- **Do you agree with plan?**

Which type of diabetes does she have?

Type 1?

Type 2?

How to differentiate type 1 from type 2 DM?

- Physical exam:
  - Obese: more likely to be DM 2
  - Thin: more likely to be DM 1
  - Acanthosis nigricans: associated with DM 2
- Family history:
  - More with DM 2, but occurs also with DM 1
- Presence of complications:
  - Chronic complications suggest undiagnosed DM 2
  - DKA can occur in DM 1 and DM 2

Tests to differentiate type 1 from 2 DM

1) Autoantibodies:

- **GAD** (Glutamic acid decarboxylase) antibodies (mostly ordered)
- **IAA** (Insulin Autoantibodies)
- **IC** (Islet cell) Antibodies
- **IA-2A** (protein tyrosine phosphatase antibodies)

2) Fasting serum C-peptide

Interpretation of antibodies

High

↓

Type 1

Normal

↓

Idiopathic type 1

or

Type 2

Interpretation of serum C-peptide

Normal or High

Type 2
or
Type 1

↓

Follow

Low

Type 1
or
Late Type 2

↓

Insulin

Follow up of those with normal or high C-peptide level

- These patients may have type 1 DM (in honeymoon phase) or type 2 DM
- Continue insulin with home monitoring
- Observe if patients need less insulin
- May do home ketones (urine or capillary)
- If insulin dose is reduced and home glucose remains stable and no ketones, may consider a trial of stopping insulin with close follow up
- If glucose gets high or with ketones, resume insulin

Summary: key points

- Start with basal insulin alone if A1c <9
- Basal + meal insulin if A1c >9 or symptomatic hyperglycemia
- If uncontrolled glucose with basal, add meal insulin
- If uncontrolled on premixed insulin: switch to basal/meal
- Many need intensive basal + meal (4-5 injections)
- Home glucose is very important to adjust insulin