Treatment of patients with type 2 diabetes: from text book therapy to personalized medicine

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Type 2 diabetes is a complex disease
Diabetes can ruin your life completely

- Most important cause of blindness in adults
- 2-6x increased risk for coronary heart disease and stroke
- Amputations 15x as often
- Most important cause of kidney failure and dialysis

Type 2 diabetes: a complicated way to get cardiovascular disease and die young

- Overweight/Obesity
- Abnormal Lipid Metabolism:
  - LDL ↑
  - ApoB ↑
  - HDL ↓
  - Triglycerides ↑
- Genetics
- Age
- Insulin Resistance Syndrome:
  - Lipids
  - BP
  - Glucose
- Insulin Resistance
- Smoking, Physical Inactivity, Unhealthy Eating
- Hypertension
- Cardiometabolic Risk
- Global Diabetes/CVD Risk
- Age, Race, Gender, Family History
- Inflammation, Hypercoagulation

Don't forget depression

www.diabetes.org/CMR

Type 2 diabetes: the challenge

- Current therapies not ideal
- Address insulin sensitivity
- Patient compliance with multiple therapies
- Preserve beta cell function
- Glucose
- Lipids
- Blood pressure
- Obesity
- Maintenance of glycaemic control in the long term
- Prevent/delay microvascular complications
- Prevent/delay macrovascular complications

"THE CHALLENGE"

Strict glycaemic control with sulphonylurea* or insulin reduces complications!

* chlorpropamide, glibenclamide

Reduction (%)

- Intensive (HbA1c 7.0%) vs conventional (HbA1c 7.9%)

P=0.052
UKPDS epidemiologic study: 
better glycaemic control means fewer complications

Complications

1% HbA1c ↓ = 33% ↓

eyes, kidney

heart/bloodvessels

% Hba1c (%)

600 500 400 300 200 100

6, 7, 8, 9, 10, 11

UKPDS 1998

ADA/EASD goals HbA1c < 7.0%

UKPDS 10 year follow-up

The effects of BG control do seem to persist, those of BP control not

Holman et al. NEJM 2009
UKPDS longest study, but still controversial

- Conventional (411)
- Intensive (951)
- Metformin (342)

Proportion of patients with events

Years from randomisation

M v I
p=0.0034

M v C
p=0.0023

recently diagnosed diabetes and obesity

Question 1

Diabetes treatment may become very complex. How many different drugs is an average person with type 2 diabetes usually taking?

1. 2 - 3
2. 4 - 6
3. 6 - 9
4. 9 - 12
Multifactorial therapy has enormous consequences

- An average type 2 diabetes patient will use:
  - one or two drugs lowering blood glucose, eventually insulin
  - cholesterol-lowering treatment ('statin for all')
  - blood pressure lowering treatment: ACE-inhibitor + at least one other drug
  - probably aspirin
  - any other drug related to co-morbidity (CVD, COPD, arthrosis, osteoporosis)

2-3
1
2
1
2-3?
6 - 9!

Please do not be fooled by your patients!

How many patients with type 2 diabetes are really taking the prescribed medication?

<table>
<thead>
<tr>
<th>Type of drug</th>
<th>% Adherent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral BG lowering agents</td>
<td>50.0</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>50.0</td>
</tr>
<tr>
<td>Lipid lowering drugs</td>
<td>69.7</td>
</tr>
<tr>
<td>Platelet aggregation inhibitors</td>
<td>77.5</td>
</tr>
<tr>
<td>All medications</td>
<td>35.4</td>
</tr>
</tbody>
</table>

Depression may interfere with optimal type 2 diabetes treatment

Depression has a complex of complaints

- Depressive symptoms
- Loss of pleasure or interest in other people
- Feelings of guilt or low self-esteem
- Pessimism linked to feelings of disease, sometimes suicidal ideas
- Significant loss of body weight or sometimes increase
- Sleeplessness or increased need for sleep
- Agitation, slow
- Fatigue, loss of energy
- Disturbed attention, memory
Depression will lead to poor self-management

- Less physical exercise
- Less dietary adherence
- Less compliant with taking medication
- Skip self-monitoring of blood glucose and adjustment of insulin
- More difficult to stop smoking
- Skipping doctor’s appointments

Prevalence of depression as co-morbidity

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Depressive symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>11 %</td>
<td>31 %</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>14 – 19 %</td>
<td>33 %</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute heart disease</td>
<td>20 %</td>
<td>31 %</td>
</tr>
</tbody>
</table>

It is important to recognize depression, as this may strongly interfere with treatment!

Van der Feltz-Cornelis, 2006
Screening for depression

Look for signs of depression
- poor control
- dissatisfied
- missing appointments
- emotional eaters

Take depression questionnaire:
- BDI: Beck depression inventory
- PHQ9: Patient Health Questionnaire

Psychological support
Medication

Current trend:
increasing focus on treatments which do NOT cause hypoglycaemia
Glycaemic targets in guidelines

ADA / EASD
- For microvascular disease prevention, HbA1c goal for adults in general is < 7%
- For selected patients, providers may suggest even lower HbA1c goals, if this can be achieved without significant hypoglycaemia
- Less stringent control may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced complications ...

Diabetes Care 2009; 32 (suppl.1): S6-12; IDF Global Guideline for Type 2 Diabetes

Macrovascular outcomes in ACCORD and ADVANCE: no difference between 'standard' and 'intensive'
ACCORD showed high incidence of severe hypo

Also cross-sectional studies show increased all-cause mortality in those with lowest HbA1c

Primary care database on diabetes treatment in England:
1. Those on insulin had more c.v. disease & renal insufficiency
2. With very low HbA1c, we observe an increase in mortality
**Same HbA1c, different numbers of hypoglycaemia**

Patient 1:
- type 2 diabetes for 5 years
- metformin 2dd 1000 mg, sitagliptin 100mg
- HbA1c 6.5%
- no hypoglycaemia

Patient 2:
- type 2 diabetes for 8 years
- metformin 2dd 1000 mg, glargin 44 U at bedtime
- HbA1c 6.5%
- 3 mild hypo's per week
- 1 severe hypoglycaemia per person per year

**We know a lot about metabolic effects of various diabetes treatments, but almost nothing about their long-term effects!!**
There are many choices in the treatment of type 2 diabetes

Lifestyle intervention (healthy food, weight reduction, physical activity)
Metformin (metabolic control, less c.v. events, no hypoglycaemia, no weight increase)

<table>
<thead>
<tr>
<th>Second line drug</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylurea</td>
<td>hypo, weight gain</td>
</tr>
<tr>
<td>Glinides</td>
<td>hypo, safe in renal insuff.</td>
</tr>
<tr>
<td>Thiazolidines</td>
<td>edema, c.v.d., bladder</td>
</tr>
<tr>
<td>α-Glucosidase inh.</td>
<td>pp. BG, GI side-effects</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>no hypo, neutral weight</td>
</tr>
<tr>
<td>GLP1 agonists</td>
<td>injections, weight loss</td>
</tr>
<tr>
<td>Insulin</td>
<td>injections, weight gain, BG measurements</td>
</tr>
</tbody>
</table>

Progression of type 2 diabetes makes treatment choices / regimens more complicated

Lifestyle

Metformin → Combi tablets → GLP1

Simple insulin → Complex insulin
Each treatment regimen should take into account lifestyle and other activities

* active elderly
* cab driver
* unemployed
* house wife
* researcher
* secretary

The case of Mr. A., 44 years

Type 2 diabetes
Cab driver
Weight 90 kg
BMI 30 kg/m²
Metformin 2g
Simvastatin 40mg
Lisinopril 20mg

Goal: improving glycaemic control without hypoglycaemia
Start sitagliptin 100 mg

Weight 88 kg
BMI 29.3

* cab drivers do not want to become hypoglycaemic
The case of Mr. D., 49 years

Type 2 diabetes since 2005
Unemployed, sedentary lifestyle, arthrosis of the knees
BMI 39.7 kg/m²
2010: failure of therapy on glimepiride 4 mg + metformin 1000 mg tid
Goal: improving glycaemic control & weight reduction
Starting Exenatide 2 dd 5 → 10 mcg

Was able to stop glimepiride
No hypoglycaemia
Reduction of weight 4 kg, BMI now 38.4 kg/m²

Question 2

For a patient with type 2 diabetes, intolerant to metformin, failing gliclazide + sitagliptin, HbA1c 7.9%, BMI 30 kg/m², I would prescribe:

1. a GLP1 agonist like exenatide
2. basal insulin (glargine)
3. twice daily premix insulin (LisPro mix 25)
4. multiple daily insulin injections
The case of Mrs. E., 59 years

Type 2 diabetes
Weight 90 kg
BMI 30 kg/m²
intolerant to metformin
Gliclazide + sitagliptin
Simvastatin
Normal blood pressure

Goal: improving control
but wants to lose weight

Start of exenatide bid,
pays for herself
100 Euro per month

Weight 75 kg
(BMI 25)

Insulin or GLP1 agonist as a first step after failure on oral agents?

501 patients DM2
age 30-75 years
HbA₁c 7-11% (SU+MF)
BMI 25 – 40 kg/m²

Randomized study
13 countries

Type 2 diabetes is a progressive disease - eventually all patients need insulin treatment.
Are combinations of insulin plus GLP1 agonist feasible and / or approved

- Combination of GLP1 agonist and insulin may limit weight increase due to insulin use and appetite stimulation
- Possibly there is better postprandial control by GLP1 effect on insulin secretion and on stomach emptying
- Exenatide is approved by EMA & FDA as adjunct to long-acting insulin (Lantus)
- A study on exenatide vs. humalog on top of insulin glargine is still ongoing, the results expected beginning of 2013
- Combination of GLP1 agonist and basal-bolus insulin therapy currently not approved

Progression of type 2 diabetes makes treatment choices / regimens more complicated

- Failure on oral agents (OA)
  - MF+OA+GLP1ag
  - MF+OA+basal insulin
  - MF+PreMix Insulin
    - MF+GLP1ag+basal insulin
    - MF+GLP1ag+BasalBolus
      - MF+GLP1ag+BBT (?) Not approved yet
Address patient reluctance: patients who perform self-monitoring of blood glucose will more rapidly switch from tablets to insulin.

What do we want to achieve with insulin therapy?

- Reduce hyperglycaemic complaints
- Achieve (near) normoglycaemia: BG between 5 and 8 mmol/l
- Prevent complications
- Avoid hypoglycaemia, especially in the elderly

- Can be easily adjusted in specific circumstances
  - driving car, eating out, on holidays
- Can be easily administered by nurse if in nursing home
What is success?

For the doctor:
- treatment is simple to explain
- is based on ‘evidence’
- normalizes blood glucose
- leads to beautiful HbA1c*
- prevents complications
- gives no hypoglycaemia
- gives no increase body weight

For the patient:
- it is a simple treatment
- has no side effects
- I can eat and drink all
- no injections please, and no fingerpricks
- I don’t know what hypo is, but surely do not want ‘it’
- ‘I still want to visit my grandchildren’

‘my neighbour went blind after starting insulin’

1. Bring some simplicity
2. Discuss misconceptions and misbelieves
Summary of factors for success in insulin therapy

• Education:
  - discuss expectations
  - discuss 'insulin resistance' and teach SMBG
  - discuss weight gain and hypoglycaemia (and how to avoid it)

• Tailoring:
  - choose two or three starter regimens, gain experience with them, and adjust if needed
  - encourage insulin regimen which 'fits' the patient and can be adjusted to long-term goals and lifestyle

Insulin treatment options in type 2 diabetes

<table>
<thead>
<tr>
<th>Prandial / Intensified insulin therapy</th>
<th>Conventional insulin therapy</th>
<th>Basal insulin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short acting insulin (analog) prandially + long-acting / NPH insulin</td>
<td>Usually 2 injections mix of short-acting insulin (analog) and long-acting insulin</td>
<td>long-acting / NPH insulin +/- oral agents</td>
</tr>
</tbody>
</table>
What kind of treatments is Europe giving when starting insulin therapy in type 2 diabetes? Results from the INSTIGATE study.

<table>
<thead>
<tr>
<th>Country</th>
<th>Basal Only</th>
<th>Premixed Only</th>
<th>Short Acting Only</th>
<th>Basal-Bolus</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>40%</td>
<td>20%</td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>France</td>
<td>40%</td>
<td>20%</td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>UK</td>
<td>40%</td>
<td>20%</td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Greece</td>
<td>40%</td>
<td>20%</td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Spain</td>
<td>40%</td>
<td>20%</td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Smith H. et al. Diabetologia 2008; 51 (suppl. 1): S443

The case of Mr. G., 40 years

Academic researcher
Daughter with type 1 diabetes
Working to loose weight
But: Type 2 diabetes, recently diagnosed
Weight 85 kg
BMI 27.5 kg/m²
Metformin 3x1000 mg

Start of glargin 8U at bedtime uptitrated till 24 U
Metformin 2 dd 1000 mg

<table>
<thead>
<tr>
<th>7</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>17</th>
<th>19</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0</td>
<td>9.9</td>
<td>11.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.7</td>
<td>12.7</td>
<td>5.9</td>
<td>6.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.9</td>
<td>9.8</td>
<td>4.3</td>
<td>10.7</td>
<td>7.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The case of mrs. U., 68 years

In 2008 partial resection of pancreas, benign
Post-operative hyperglycaemia, started with insulin
Uses LisPro Mix 25,
  22U before breakfast, 10U before dinner
Also perindopril, thiazide, simvastatin, acetylsalicylic acid
(after a small stroke)

Leads a stable but active life, lives 5-6 months per year in Thailand
Does not want to go to multiple injections!
Occasional hypoglycaemia, with good awareness
Self-monitoring: see next slide

<table>
<thead>
<tr>
<th>Controls</th>
<th>7 am</th>
<th>11 am</th>
<th>3 pm</th>
<th>8 pm</th>
</tr>
</thead>
<tbody>
<tr>
<td>LisPro Mix 25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 U before breakfast</td>
<td>10 U before evening meal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Self-monitoring:

Date: 6-12
N: 9
H: 9.6
V: 0.8
L: 10
A: 9.4

Date: 11-12
N: 9.7
H: 3.1
V: 3.0
L: 4.7
A: 4.4

Date: 3-12
N: 3.9
H: 3.2
V: 3.0
L: 4.7
A: 4.8

Date: 15-1
N: 5.9
H: 5.4
V: 5.1
L: 5.6
A: 5.9

Medication:

- LisPro Mix 25
- 22 U before breakfast
- 10 U before evening meal

HbA1c: 5.7 mmol/mol

Weight: 68 kg
Systolic blood pressure: 120 mmHg

Last HbA1c: 37 mmol/mol

Last test: 2011-08-09

Self-monitoring: see next slide.
Question 3

You have a patient with type 2 diabetes, BMI 29, who was failing on metformin and a sulphonylurea. He started insulin glargin once daily at bedtime. He is now in stable control, with FBG 5-7 mmol/l, HbA1c fell from 8 to 6.5%. How long will it take (on average) before his HbA1c again is > 7.0%?

1. 10 - 12 months
2. 14 - 16 months
3. 18 - 20 months
4. longer than 24 months

LisPro Mix 25 gives better glycaemic control than long-acting analogue Glargine* (DURABLE study)

* after 24 weeks of study

adapted from: Wolffensbuttel et al. Diabetologia 2008 (A059)
Long-term efficacy of insulin regimens is limited (DURABLE study)

On average, it will take 14 months before HbA1c again rises to > 7.0%

<table>
<thead>
<tr>
<th>Months of Maintaining HbA1c Goal &lt; 7.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0  2  4  6  8  10  12  14  16  18  20  22  24  26  28  30</td>
</tr>
<tr>
<td>1.0 0.8 0.6 0.4 0.2 0.0</td>
</tr>
<tr>
<td>LisPro Mix 25</td>
</tr>
<tr>
<td>Giargine</td>
</tr>
</tbody>
</table>

p=0.04 between treatment difference

Wolffenbuttel BHR, et al. EASD 2010

The case of mrs. D., 64 years

Still active, works as secretary
In 1999 type 2 DM, glibenclamide 3dd 5 mg, metformin 3dd 500 mg (diarrhoea with higher dose)
Insulin since 2005, because of tablet failure
Started with Humalog Mix 25, 20 – 0 – 16 U

Occasional hypoglycaemia with sports, also wanted to loose weight. Therefore went to NPH insulin and LisPro

Currently using 12 – 6/8 – 6/8U LisPro, 24U NPH; adjusts LisPro according to BG values and meal size

Weight 83 kg, height 1.68 m, weight before insulin was 80 kg.
HbA1c 8.3 → 6.6% at present
The case of Mrs. D., 64 years

2005: Type 2 diabetes, max. oral agents
Weight 80 kg, BMI 27.5 kg/m²
HbA1c 8.3 %

2012: NPH uptitrated to 24 U
LisPro 12 – 6/8 – 6/8 U
Weight 83 kg, HbA1c 6.6%

The postprandial state in type 2 diabetes (study design)

Pre-meal insulin lispro
MM 50/50 + metformin

LM bid + metformin

insulin glargin + metformin

Sub-group (n=46) of 315 patients randomized

Test meal*

-6 ± 2 0 12 24 Week

* McDonald’s® breakfast
[fat 39 g, CHO 78 g, protein 24 g, kcal 750]

adapted from: Tan et al. Diabetologia 2006: Abstract 0989
Better postprandial blood glucose profiles with higher percentage of fast-acting insulin analogue

46 patients with type 2 diabetes taking a McDonald’s® breakfast [fat 39 g, CHO 78 g, protein 24 g, kcal 750]

adapted from: Tan et al. Diabetologia 2006: Abstract 0989

hs-CRP follows postprandial BG excursions

adapted from: Tan et al. Diabetologia 2006: Abstract 0989
Are ultrafast-acting insulin analogues better than regular insulin in type 2 diabetes?

- Injection directly before a meal
- Possible to inject after a meal when meal size is unknown
- Faster normalization when blood glucose is too high
- Better control of postprandial blood glucose *
- Smaller postprandial increase of inflammation markers *
- Lower incidence of nocturnal hypoglycaemia
- Overall similar HbA1c
- Very limited data on effects of complications
- Price ???

In The Netherlands, 95% of fast-acting insulin is an insulin analogue (aspart, lispro)

Higher PPBG coincide with higher postprandial levels of IL6 and TNFα

There are only few studies on the long-term effects of type 2 diabetes therapy.

4T: three year effects of 3 treatment regimens

82% need to add fast-acting insulin

Holman R, et al. NEJM 2009
More intensive insulin treatment associated with higher body weight, insulin dose and hypoglycaemia

<table>
<thead>
<tr>
<th>Change in BW (kg)</th>
<th>Insulin dose (U)</th>
<th>Hypo &amp;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>+1.9 ± 4.2</td>
<td>42 (28 to 72)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>+4.7 ± 4.0 *</td>
<td>48 (30 to 71)</td>
</tr>
<tr>
<td>Prandial</td>
<td>+5.7 ± 4.6 **</td>
<td>56 (34 to 78)</td>
</tr>
</tbody>
</table>

* ≥ Grade 2 events/patient/year

Specific situations

**Type 2 diabetic and wanting to become pregnant**

- Type 2 diabetes increasingly is occurring in younger people
- Many of them want to have children
- Poorer glycaemic control is associated with higher risk of congenital malformations and eclampsia

**Type 2 diabetic and wanting to become pregnant**

- Pregnancy in type diabetes means 'planning':
  - education about all aspects of a safe pregnancy
  - risk of eclampsia and premature delivery
  - switch from oral agents to insulin
  - multiple injection regimen to be preferred, incl. NPH-insulin and fast-acting insulin analogue (LisPro, Aspart)
  - long-acting analogues not approved for pregnancy
  - try to achieve HbA1c 6.5% or below for a number of months before becoming pregnant
  - start with folic acid supplementation
People with diabetes are allowed not to fast. Nevertheless, many will participate fully (pride, peer pressure, etc.).

- Ramadan means breakfast before sunrise (which is early in July, approx. 5.30 am !!), and dinner after sunset (10 pm !!)
- Dinner usually large and rich in carbohydrates
- Goal is to maintain reasonable blood sugar levels without hypoglycaemia
Ramadan (July 20-August 18, 2012!)
Some simple rules for adjustment of medication

Oral agents:
- Tolbutamide, gliclazide & glibenclamide:
  morning half dose, evening before dinner full dose
- Glimepiride:
  take tablets in evening
- Metformin:
  morning half dose, evening full dose

Insulin:
- Once daily long-acting:
  Take at / with evening meal
- Twice-daily premix insulin (like LisPro Mix25):
  Fast-acting in morning, premix at dinner
- Multiple injections:
  Fast-acting in morning and evening, long-acting at bedtime

Summary
HbA1c target depending on risk evaluation

- Young < 40 years
- Middle-aged 40-70 years
- Elderly > 70 years

Complications

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6.0</td>
<td></td>
<td>&lt;6.5</td>
<td></td>
<td>&lt;7.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6.5</td>
<td></td>
<td>6.5-7.0</td>
<td></td>
<td>7.0-8.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Aim for more strict control when without complications
2. Risk of hypoglycaemia varies with type of drugs
3. Less strict control in elderly, those with complications or reduced life expectancy

Summary of effects of insulin regimens

<table>
<thead>
<tr>
<th>Prandial / Intensified (basal-bolus)</th>
<th>Conventional (premixed)</th>
<th>Basal (NPH / long-acting)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>↓↓↓↓</td>
<td>↓↓↓ (if OAs continued)</td>
</tr>
<tr>
<td>PPBG control</td>
<td>better</td>
<td>better</td>
</tr>
<tr>
<td>regimen</td>
<td>difficult</td>
<td>slightly difficult</td>
</tr>
<tr>
<td>hypoglycaemia</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>weight gain</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>complications</td>
<td>↓?</td>
<td>?</td>
</tr>
</tbody>
</table>
## Summary of insulin therapy

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Benefits/Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive BG-lowering</td>
<td>Benefit microvascular; dangerous in long-term diabetics &amp; w. severe CVD</td>
</tr>
<tr>
<td>Fast-acting analogs</td>
<td>Better ppBG control than regular insulin, may reduce c.v. complications</td>
</tr>
<tr>
<td>Combination with metformin</td>
<td>Reduces insulin dose and mitigates weight increase</td>
</tr>
<tr>
<td>Intensive insulin treatment</td>
<td>More hypoglycaemia, weight gain</td>
</tr>
<tr>
<td>Simple starter insulin regimen</td>
<td>Needs intensification within 14 to 18 months, because HbA1c increase</td>
</tr>
</tbody>
</table>

## Take home messages

- Depression may interfere with optimal diabetes therapy
- Currently there is increasing focus on treatments which do not cause hypoglycaemia, but they are more expensive
- There are only few studies on the long-term effects of insulin therapy (in fact on effects of all treatments)
- Situations like pregnancy & ramadan ask a lot of effort from patient and doctor

**Diabetes therapy = personalized medicine**