When and how to start insulin: strategies for success in type 2 diabetes

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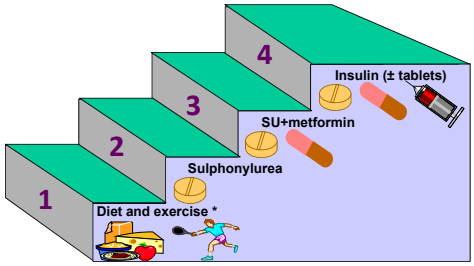
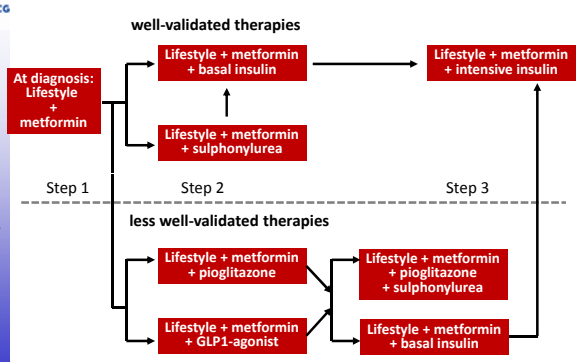
Insulin therapy

Treatment of type 2 diabetes in 1990: with each step treatment gets more complex



Insulin therapy

2008 ADA/EASD type 2 diabetes algorithm



Insulin therapy

Imagine your outpatient-clinic next week: the first patient in front of you is . . .

- A 56-year old male
- Type 2 diabetes since 1999, borderline hypertension, statin user, mildly obese
- Failing oral therapy (SU + metformin), HbA1c 8.9%
- FBG of 9-10 mmol/l, p.p. BG up to 15 mmol/l
- Teacher at a junior high school
- Sedentary work during the week, but likes to bicycle in the weekends

Insulin therapy

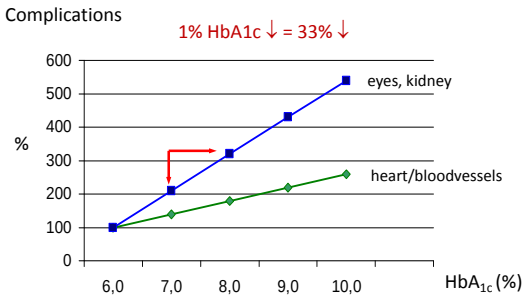
Imagine your outpatient-clinic next week: the second patient in front of you is . . .

- A 82-year old female
- Type 2 diabetes since 1989, hypertension, triple antihypertensives, myocardial infarction in 2004, statin and aspirin user, mildly obese
- Failing oral therapy (SU + metformin), HbA1c 8.9%
- FBG of 9-10 mmol/l, p.p. BG up to 15 mmol/l
- Sedentary lifestyle
- Likes to go to the zoo with her grandchildren

Insulin therapy

UKPDS epidemiologic study:

better glycaemic control means fewer complications



ADA/EASD goals HbA1c < 7.0%

UKPDS 1998

What do doctors want to achieve with insulin therapy ?

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- Reduce hyperglycaemic complaints (if any)
- 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 ?

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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

Insulin treatment options in type 2 diabetes

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Prandial / Intensified insulin therapy	Conventional insulin therapy	Basal insulin therapy
Short acting insulin (analog) prandially + long-acting / NPH insulin	Usually 2 injections mix of short-acting insulin (analog) and long-acting insulin	long-acting / NPH insulin +/- oral agents

Choices, choices, choices ...

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Prandial / Intensified insulin therapy	Conventional insulin therapy	Basal insulin therapy
Short acting insulin (analog) prandially + long-acting / NPH insulin	Usually 2 injections mix of short-acting insulin (analog) and long-acting insulin	long-acting / NPH insulin +/- oral agents
NPH-insulin? Glargine / Levemir? Regular or analog?	**25/75? 30/70? 50/50?**	**NPH-insulin? Glargine / Levemir?**

Continue which oral agents? SU? Metformin? TZD?

Choices, choices, choices ...

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Prandial / Intensified	Conventional	Basal insulin therapy

more than 200 combinations of insulin and oral agents are possible;

so be smart, use only a few starter regimens in your daily practice, and gain experience with them,

while adjusting when needed by the patient

Once daily insulin: basal injection always combined with oral agents

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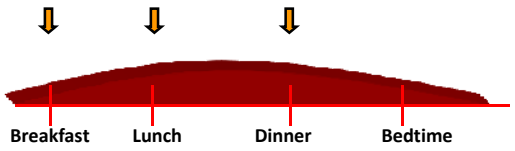
metformin 3 dd 850 mg*
gliclazide 2-3 dd 80 mg



*** or 2 dd 1000 mg**

Once daily insulin: basal injection always combined with oral agents

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Insulin therapy

metformin 3 dd 850 mg → beneficial for weight gain and/or insulin dose

gliclazide 2-3 dd 80 mg → may increase risk hypo

* or 2 dd 1000 mg

Twice-daily insulin mixture: for instance Humalog Mix 25^{R} / NovoMix 30^{R}

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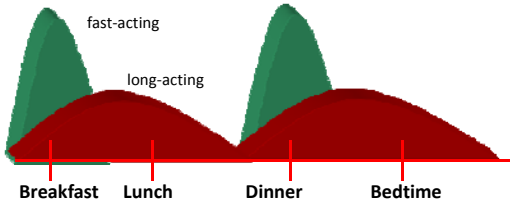
Insulin therapy

metformin 3 dd 850 mg



Pre-prandial insulin injections

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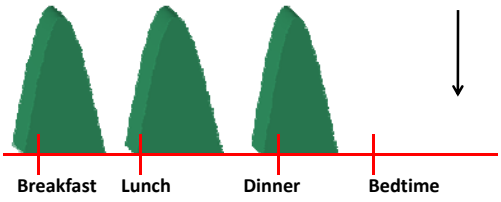
Insulin therapy

Insulin aspart/lispro

fast- fast- fast-acting

Cán work, but frequently basal insulin needed



Basal - bolus insulin therapy: 4 injections daily

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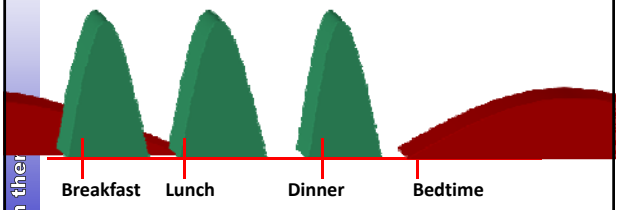
Insulin therapy

Insulin aspart/lispro fast- fast- fast-acting

NPH/ Glargine/Detemir long-acting



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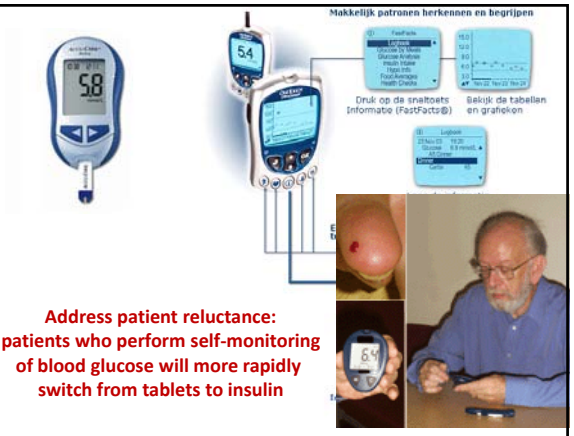
Insulin therapy



Address patient reluctance: patients who perform self-monitoring of blood glucose will more rapidly switch from tablets to insulin

Insulin therapy regimen should take into account lifestyle and other activities

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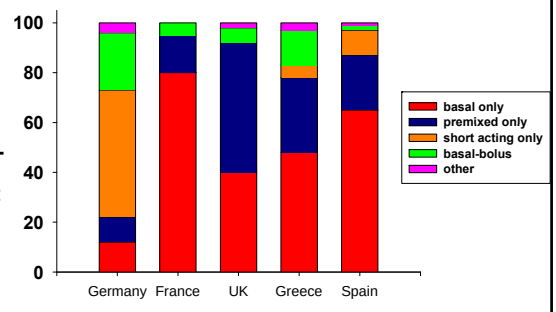
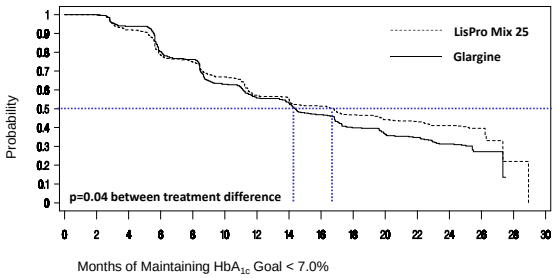
Insulin therapy

Starter insulin regimen in type 2 diabetes vary across Europe - Results from the INSTIGATE study



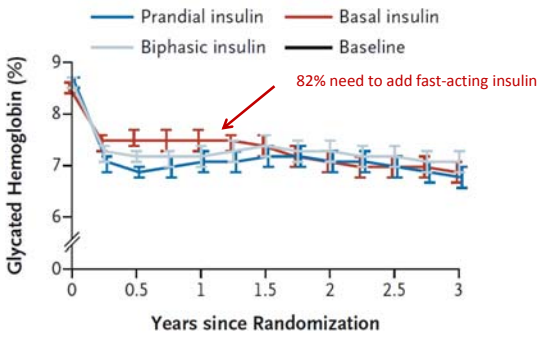
Smith H, et al. Diabetologia 2008; 51 (suppl. 1): S443

Simple starter regimens need intensification over time: lessons from DURABLE study



Wolffenbuttel BHR, et al. EASD 2010

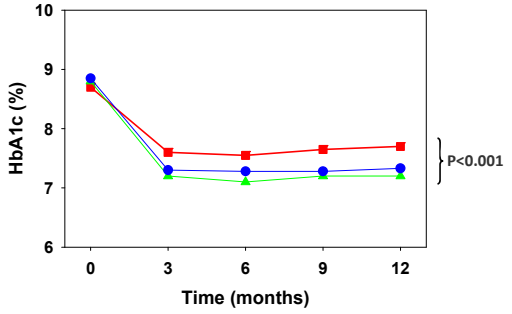
4T: long-term effects



Holman R, et al. NEJM 2009

4T: intensified insulin regimen gives lowest HbA1c

		Δ
Basal	7.6±1.0 %	-0.8±1.0
Biphasic	7.3±0.9 %, *p=0.08 vs. biphasic*	-1.3±1.1
Prandial	7.2± 0.9 %, *p<0.001 vs. biphasic/prandial*	-1.4±1.0



adapted from: N Engl J Med 2007; 357: 1716-30

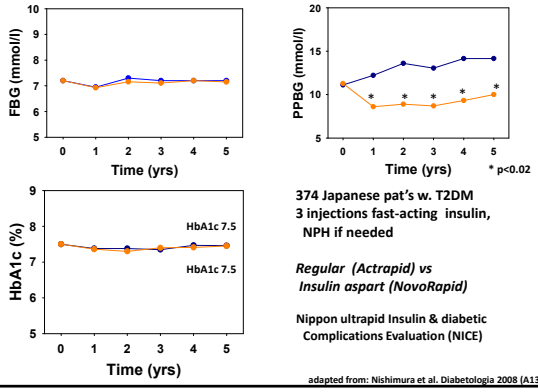
but at a price of higher body weight, insulin dose and hypoglycaemia

	Change in BW (kg)	Insulin dose (U)	Hypo &
Basal	+1.9 ± 4.2	42 (28 to 72)	2.3
Biphasic	+4.7 ± 4.0 *	48 (30 to 71)	5.7 *
Prandial	+5.7 ± 4.6 *#	56 (34 to 78)	12.0 *#

& ≥ Grade 2 events/patient/year

N Engl J Med 2007; 357: 1716-30

NICE: better postprandial BG control with ultrafast-acting insulin analog . . . .



374 Japanese pat's w. T2DM
3 injections fast-acting insulin,
NPH if needed

Regular (Actrapid) vs
Insulin aspart (NovoRapid)

Nippon ultrapid Insulin & diabetic Complications Evaluation (NICE)

adapted from: Nishimura et al. Diabetologia 2008 (A1349)

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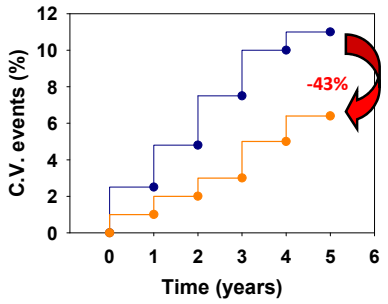
Insulin therapy

. . . does reduce c.v. events !!

(MI, angina, PCI/CABG, TIA/CVA)

But all patients had short duration of diabetes !



Nippon ultrapid Insulin & diabetic Complications Evaluation (NICE) ClinicalTrials.gov NCT00575172

adapted from: Nishimura et al. Diabetologia 2008 (A1349)

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Insulin therapy

Insulin treatment options in type 2 diabetes

Prandial / Intensified insulin therapy	Conventional insulin therapy	Basal insulin therapy
Short acting insulin (analog) prandially + long-acting / NPH insulin	Usually 2 injections mix of short-acting insulin (analog) and long-acting insulin	long-acting / NPH insulin +/- oral agents

Summary of all studies

What are the main differences ?

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Insulin therapy

Some general issues on insulin regimens - 1

- Long-acting insulin analogs vs. NPH-insulin: fewer hypo's with better HbA1c reduction, and less variation of fasting glucose
- Fast-acting insulin analogs give better ppBG control than regular insulin
- Combination with metformin reduces insulin dose and mitigates BW increase
- Simple starter insulin regimens need intensification within 14 to 16 months, because of HbA1c increase

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Insulin therapy

Some general issues on insulin regimens - 2

	Prandial / Intensified (basal-bolus)	Conventional (premixed)	Basal (NPH / long-acting)
HbA1c	↓↓↓↓	↓↓↓ (if OA's continued)	↓↓ (30-50% HbA1c ≤ 7.0%)
PPBG control	better	better	worse
regimen	difficult	slightly difficult	easy, continue OA's
hypoglycaemia	+++	++	+
weight gain	+++	++	+
complications	↓?	?	?

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Insulin therapy

Is intensified insulin therapy harmful ?

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Insulin therapy

In 2008, several long-term clinical trials have reported their results

ADVANCE

ACCORD

VADT

What did they study?

1. Can strict glycaemic control prevent cardiovascular complications ?

2. Do we need to aim for HbA1c < 6.5% ?

Macrovascular outcomes in ACCORD and ADVANCE: no difference between 'standard' and 'intensive'

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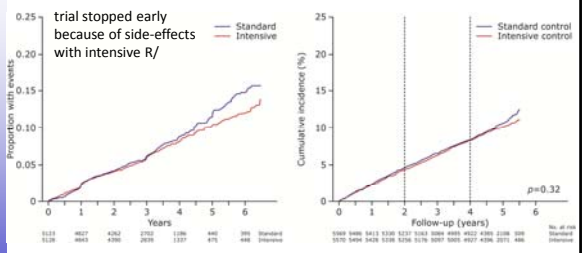
Insulin therapy

trial stopped early because of side-effects with intensive R/



ACCORD ADVANCE

Speculations on cause of increased mortality in ACCORD is answered in VADT substudy

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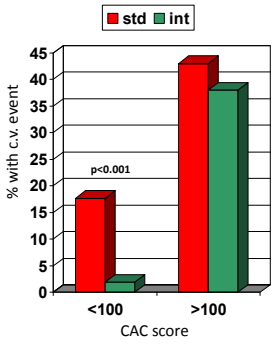
Insulin therapy

- Coronary artery calcification (CAC) score measured in 301 VADT participants
- 40% had CAC score > 400
- CAC predicted new events
- Intensive therapy is especially effective in low CAC score

CAC=5,000 (very high risk)



RACED: Risk Factors, Atherosclerosis and Clinical Events in Diabetes
adapted from: Reaven. ADA presentation VADT, June 2008

Diabetes duration determines the risk of c.v. events during intensive (insulin) therapy (VADT)

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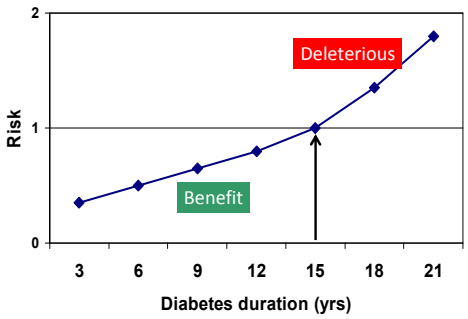
Insulin therapy



adapted from: Duckworth. ADA presentation VADT, June 2008

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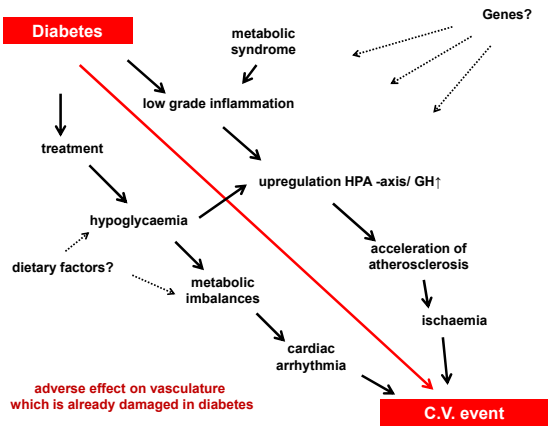
Insulin therapy



Is intensified insulin therapy harmful ?

No, if started early in course of disease
No, but don't use in those with severe c.v. disease

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Insulin therapy

Factors for success in insulin therapy

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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 therapy = personalized medicine

Once daily insulin: basal injection always combined with oral agents

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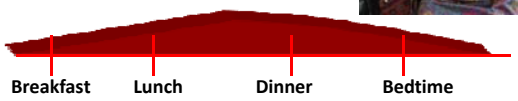
Insulin therapy

metformin 3 dd 850 mg (2 dd 1000 mg)
gliclazide 2-3 dd 80 mg



1. continue oral agents
2. add 8-10 E long-acting insulin at bedtime of breakfast
3. titrate on fasting BG
4. if hypoglycemia, reduce sulphonylurea dose
5. if daytime hyperglycemia, add 2nd injection of insulin

Twice-daily insulin mixture: for instance Humalog Mix 25

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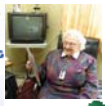
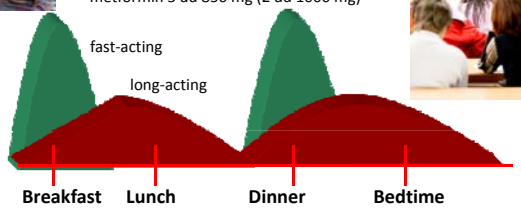
Insulin therapy



metformin 3 dd 850 mg (2 dd 1000 mg)



1. continue metformin
2. give 2/3 of insulin at breakfast and1/3 at dinner
3. titrate on BG before main meals / at bedtime, slower in the elderly
4. self-monitoring mandatory
5. reduce dose in weekend when bicycling

Pre-prandial insulin injections

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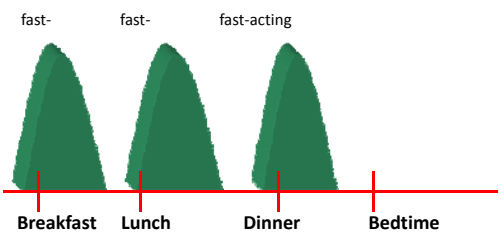
Insulin therapy

Insulin aspart/lispro



1. continue metformin
2. give insulin at 40% breakfast, 25% lunch, 35% dinner
3. titrate on BG before main meals / at bedtime, slower in the elderly
4. self-monitoring mandatory
5. frequently need for long-acting insulin at bedtime

Basal - bolus insulin therapy: maximal flexibility

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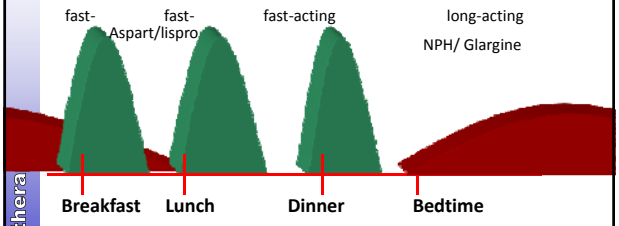
Insulin thera

metformin 3 dd 850 mg (2 dd 1000 mg)



1. give 30-40% of insulin as long-acting at bedtime
2. titrate on BG before main meals / at bedtime, later on p.p. BG
3. self-monitoring mandatory
4. reduce dose when exercising / eating less

Insulin injection regimens in type 2 diabetes

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Insulin therapy

Continue oral agents
Add long-acting insulin bedtime

Add fast-acting insulin when significant hyperglycemia

Add 2nd fast-acting insulin when significant hyperglycemia

Continue metformin
Twice-daily 25/75 mixture

Change % fast-acting in mixtures when postprandial hyperglycemia

Add fast-acting insulin at lunch when afternoon hyperglycemia

Fast-acting insulin before meals
Long-acting at bedtime

Insulin injection regimens in type 2 diabetes

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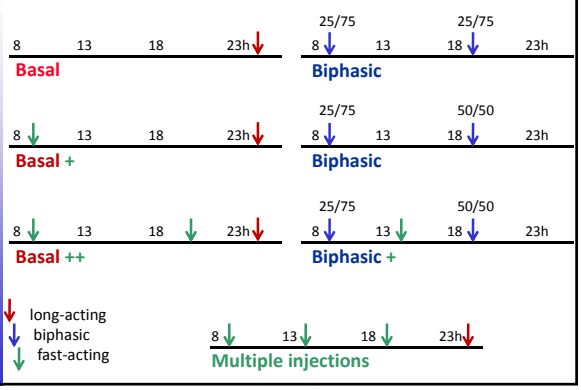
Insulin therapy



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Insulin therapy

Take home messages on insulin therapy

- *Intensive BG-lowering*: dangerous in long-term diabetics and those with severe c.v. disease
- *Long-acting analogs* vs. NPH-insulin: fewer hypo's with better HbA1c reduction, and less variation of fasting glucose
- *Fast-acting analogs*: better ppBG control than regular insulin, which may reduce c.v. complications
- *Intensive insulin treatment*: more hypoglycaemia, weight gain
- *Simple starter insulin regimen*: intensification within 14 to 16 months, because HbA1c increase