



Diabetes Centre  
Groote Schuur Hospital/UCT

## Advancing to insulin in type 2 diabetes

Prof Peter Raubenheimer  
Divisions of Endocrinology and General Medicine  
Groote Schuur Hospital/UCT

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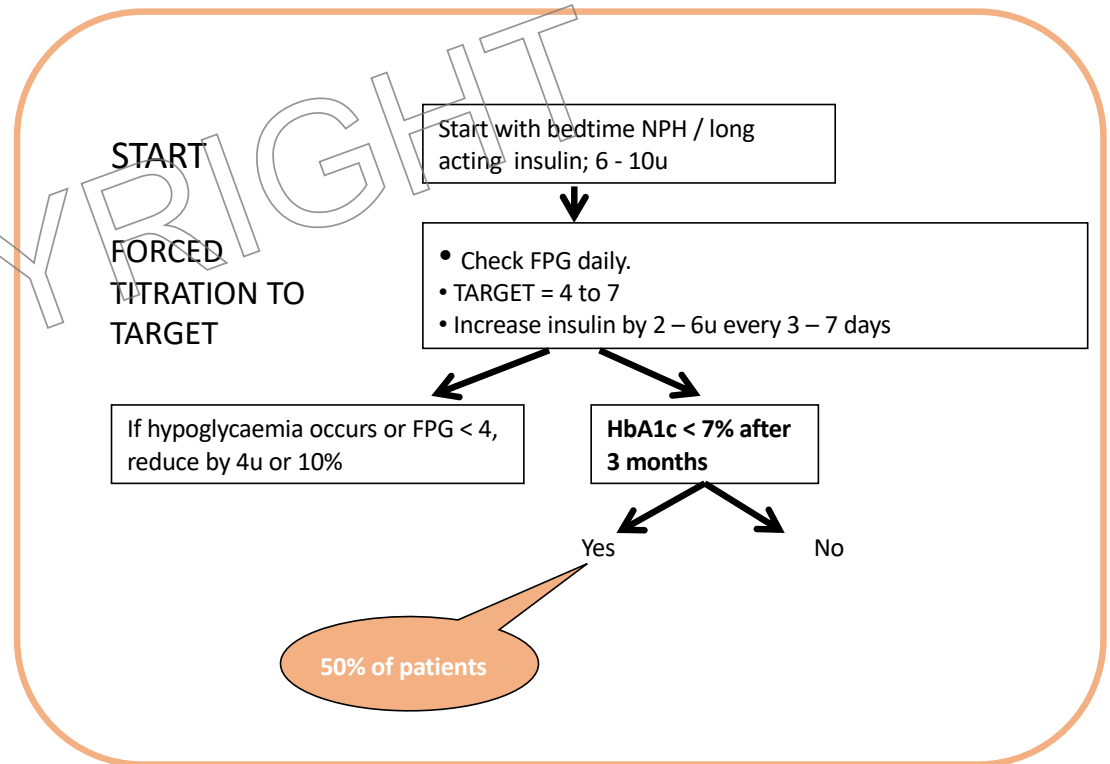
- No conflicts of interest to declare

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# Initiating insulin in T2DM

- Easy, safe, effective
- Start low, titrate fast
- Expect doses of between 0.5 – 1u/kg at 3 months



# Initiation (and Intensification) of Insulin Therapy in Patients with Type 2 Diabetes

- This presentation will discuss:
  - The context and rationale for optimal glucose control
  - The rationale for insulin therapy in T2DM
    - The rationale for EARLY insulin therapy in T2DM
    - Safety of insulin
  - The practical reality of glucose control in T2DM
  - Therapeutic inertia
    - Physician and patient barriers
  - Insulin formulations and clinical trials in T2DM
  - Practical guidelines – keep it simple



BUT...

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# Only 1:7 people in Africa requiring insulin have access to it

## One Hundred Years of Insulin for Some

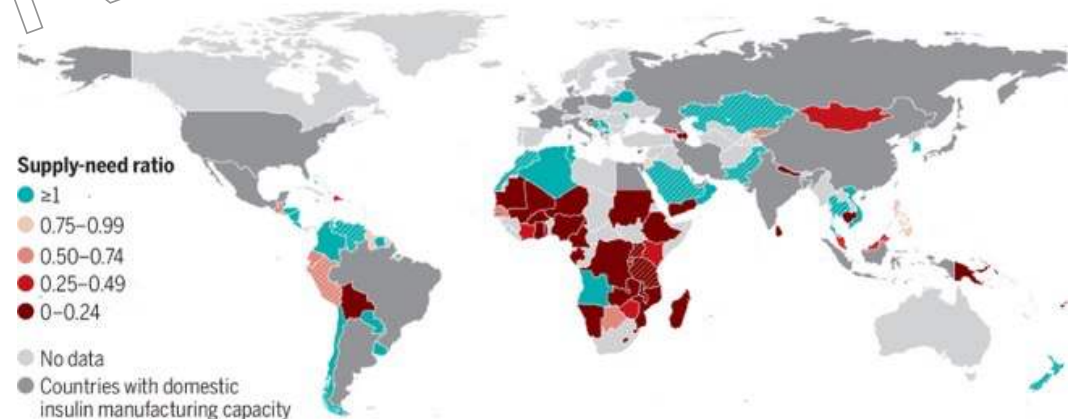
Author: Amy Moran-Thomas, Ph.D. [Author Info & Affiliations](#)

Published July 17, 2021 | N Engl J Med 2021;385:293-295 | DOI: 10.1056/NEJMp2105697 | VOL 385 NO 4



### Global distribution of median insulin supply-need ratios, 2012 to 2018

Eighty-two study countries (solid) and 22 "test" countries (striped) are shown, as well as 20 countries with domestic insulin manufacturing capacity (dark gray). Teal color marks countries with ratios  $\geq 1$ , and red colors mark those with ratios  $< 1$ . See supplementary materials for details.



Sharma A. Insulin imports fail to meet many countries' needs. *Science* 373,494-497(2021).



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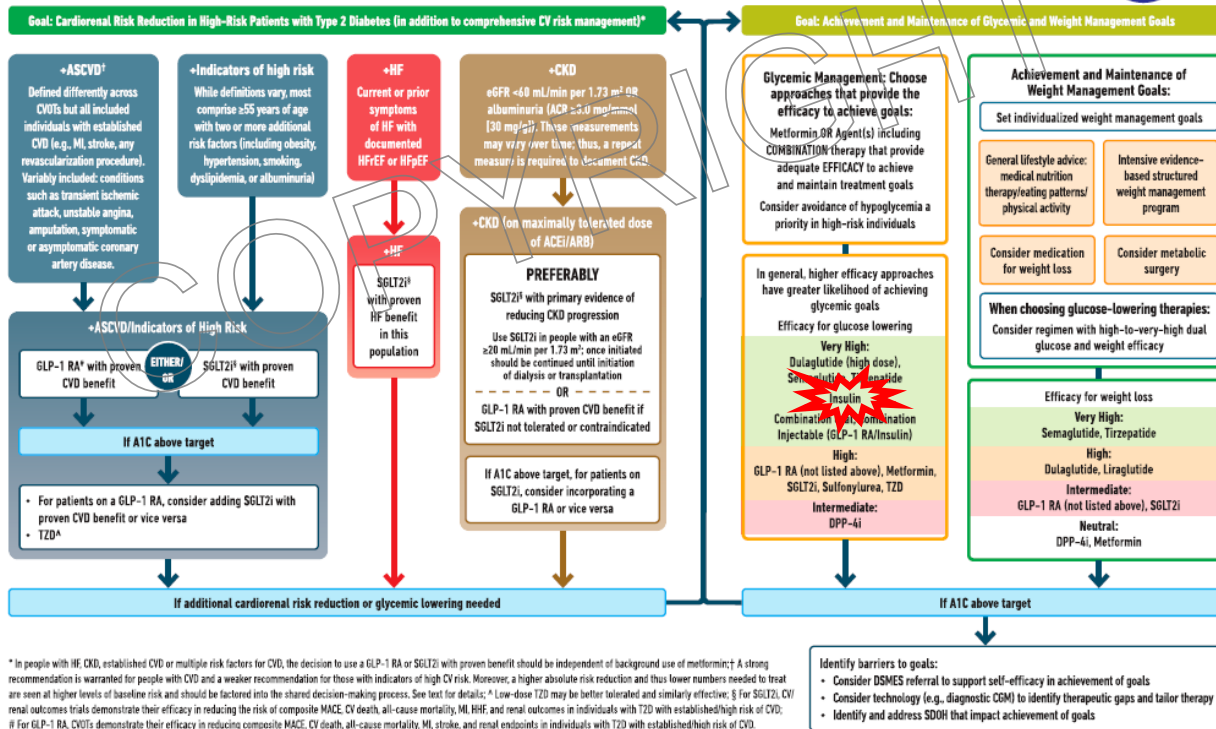
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# ADA-EASD insulin de-emphasised in T2DM

## USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)



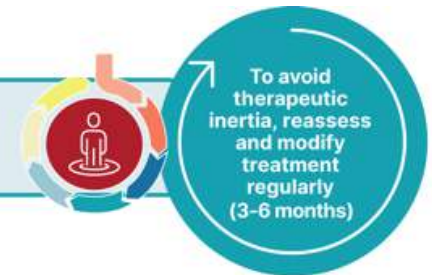
\* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ‡ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HF, and renal outcomes in individuals with T2D with established/high risk of CVD; ¶ For GLP-1 RA, CVDs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.



# BUT...

*Offer a GLP-1 receptor agonist ahead of insulin in stable non-pregnant adults when glycaemic control is no longer achievable with oral glucose-lowering medications. [1A]*

Use principles in Figure 9.3, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES, to meet individualized treatment goals



If injectable therapy is needed to reduce A1C<sup>1</sup>

Consider GLP-1 RA or dual GIP and GLP-1 RA in most individuals prior to insulin<sup>2</sup>

**INITIATION:** Initiate appropriate starting dose for agent selected (varies within class)  
**TITRATION:** Titrate to maintenance dose (varies within class)

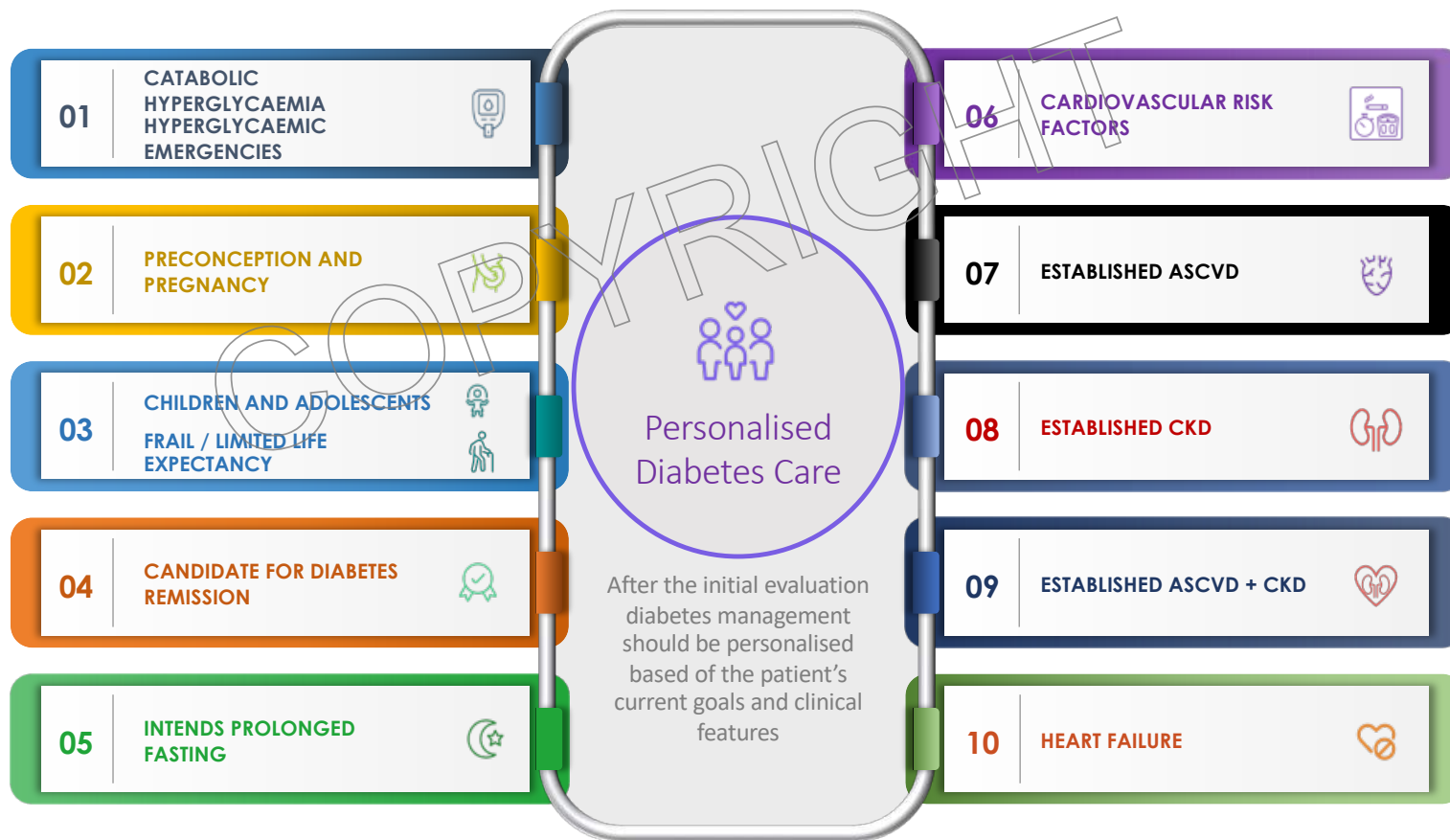
If already on GLP-1 RA or dual GIP/GLP-1 RA, or if these are not appropriate, or if insulin is preferred



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# Personalised diabetes care



# Insulin in T2DM

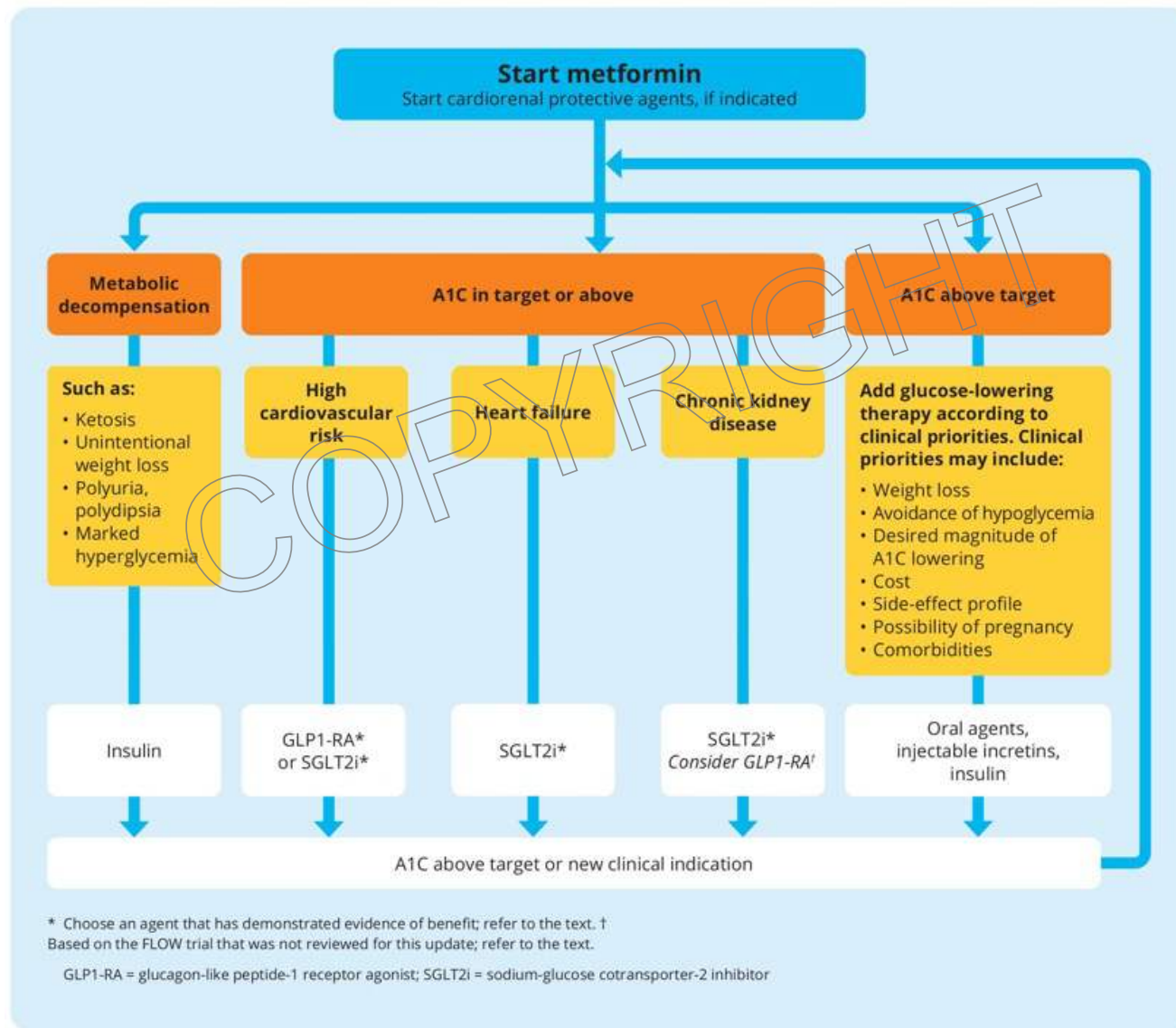
- The **indications** for insulin in type 2 diabetes:
  - Diabetes in pregnancy
  - Acute metabolic decompensation
  - Catabolic hyperglycaemia
  - Severe insulin deficiency phenotype
  - Suboptimal glycaemic control with non-insulin therapies



# Insulin in T2DM

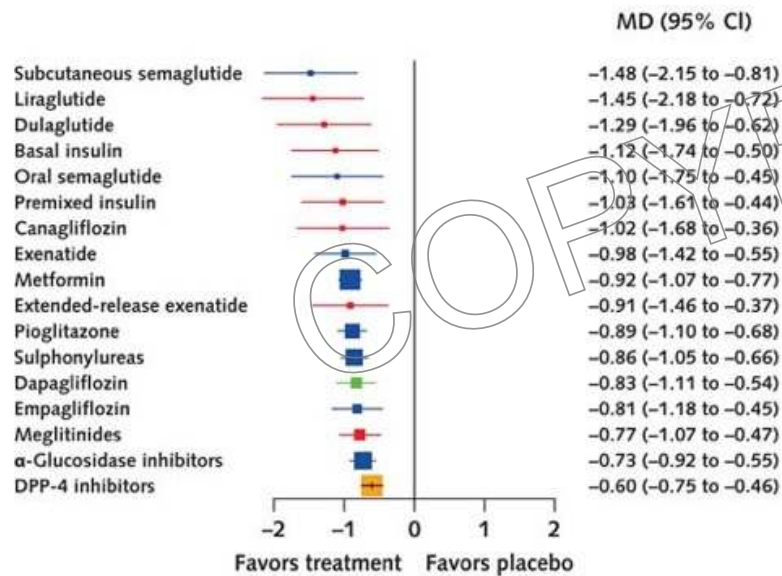
- The **indications** for insulin in type 2 diabetes:
  - Diabetes in pregnancy
  - Acute metabolic decompensation
  - Catabolic hyperglycaemia
  - Severe insulin deficiency phenotype
  - **Suboptimal glycaemic control with non-insulin therapies**



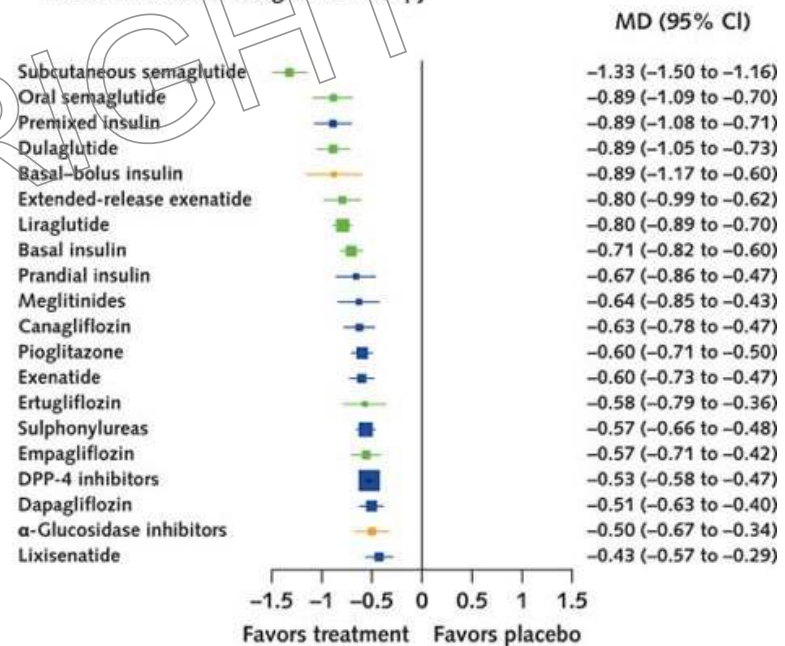


# Insulin not recommended as first line ( or 2<sup>nd</sup> line ) therapy for most people with type 2 diabetes

A. Change in Hemoglobin A<sub>1c</sub> Level in Drug-Naive Patients



B. Change in Hemoglobin A<sub>1c</sub> Level in Patients Receiving Metformin-Based Background Therapy



Tsapas A, et al. *Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes: A Systematic Review and Network Meta-analysis.* Ann Intern Med.2020;173:278-286.

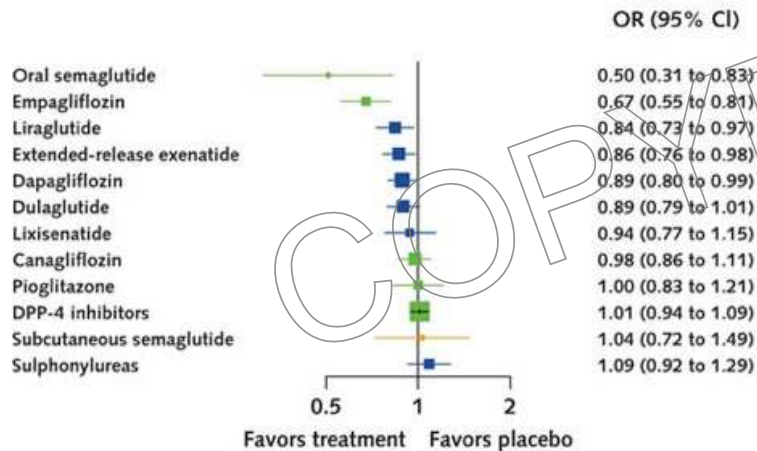


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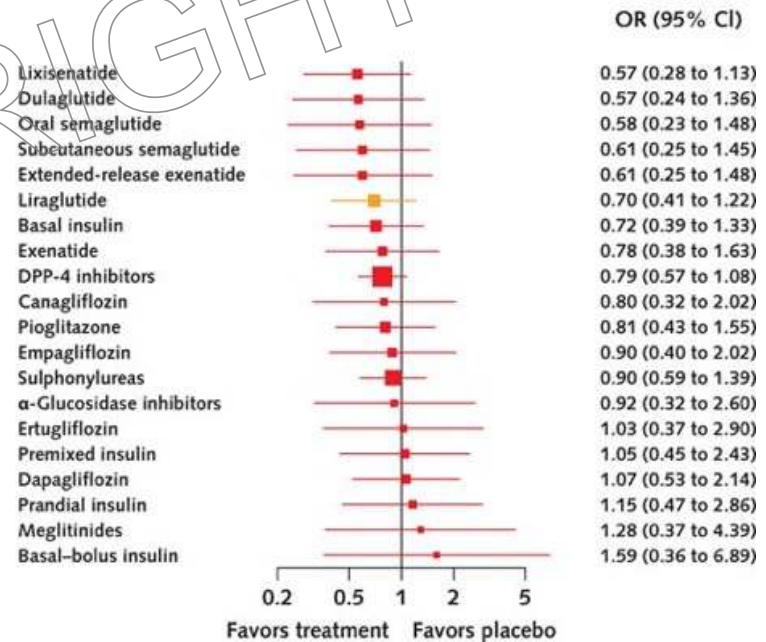
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# Insulin not recommended as first line ( or 2<sup>nd</sup> line ) therapy for most people with type 2 diabetes

C. All-Cause Mortality in Patients at Increased Cardiovascular Risk Receiving Metformin-Based Background Therapy



D. All-Cause Mortality in Patients at Low Cardiovascular Risk Receiving Metformin-Based Background Therapy

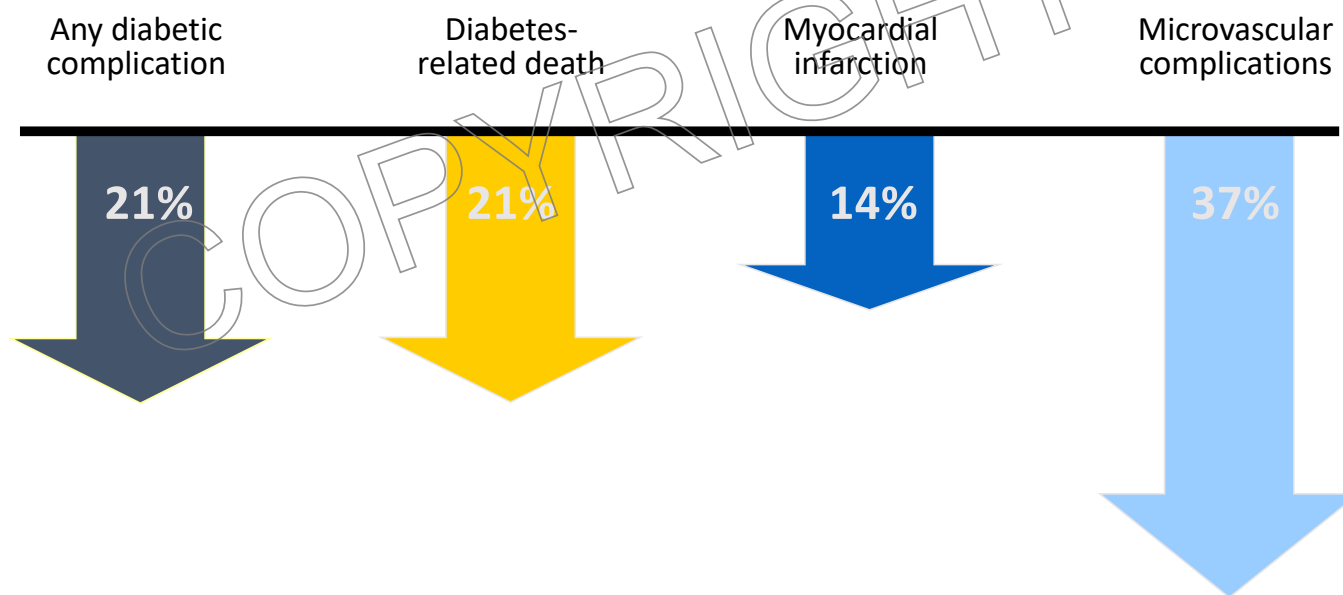


Tsapas A, et al. *Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes: A Systematic Review and Network Meta-analysis.* Ann Intern Med. 2020;173:278-286.



# The rationale for glycaemic control in T2DM

**Every 1% decrease in HbA1c**

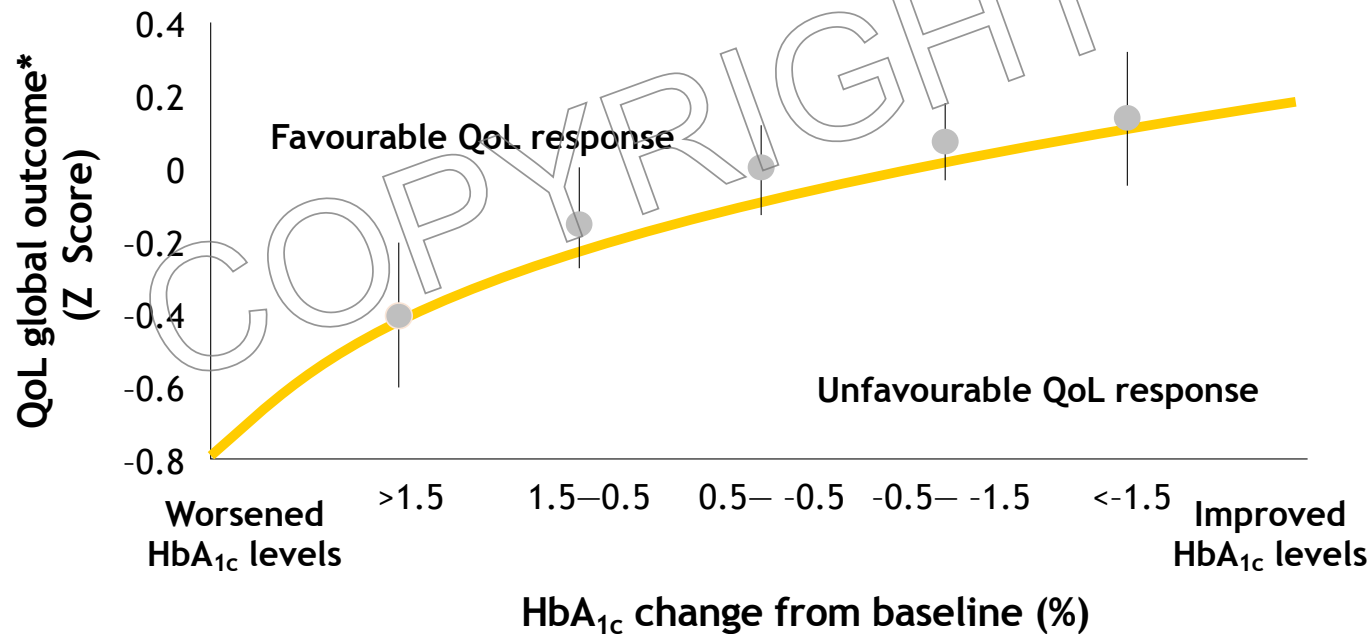


UKPDS 35. BMJ 2000;321:405-12.



# The rationale for glycaemic control in T2DM

***Improved glucose control improves patient QoL***



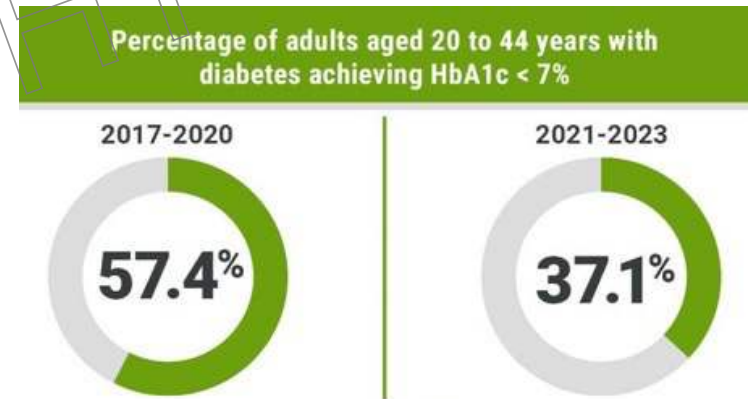
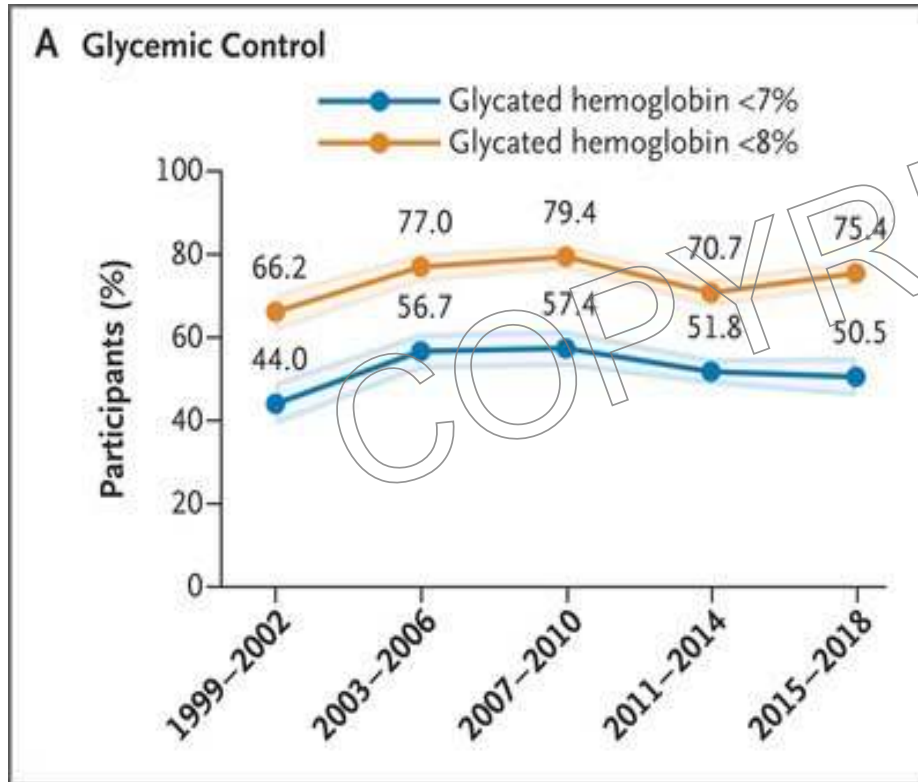
Testa MA, Simonson DC. JAMA 1998;280:1490-1496



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# The practical reality of glucose control in T2DM

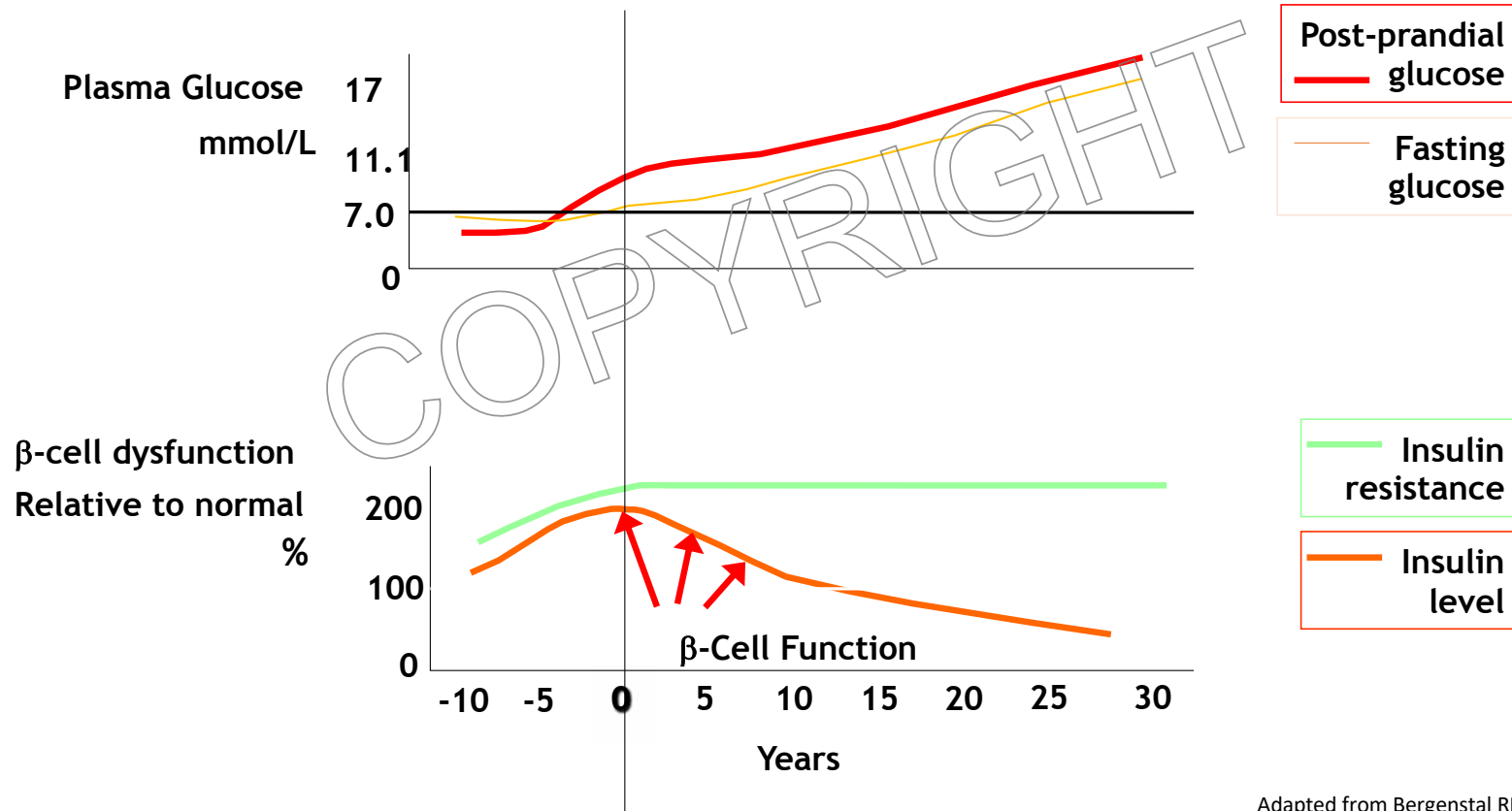


Fang, M., Wang, D., Coresh, J., Selvin, E.: Trends in diabetes treatment and control in U.S. adults, 1999-2018. *New Eng. J. Med.* **384**(23), 2219-2228 (2021)

Inoue K, et al. Prevalence and Control of Diabetes Among US Adults, 2013 to 2023. *JAMA*. Published online February 27, 2025.



# The natural history of T2DM



Adapted from Bergenstal RM, International Diabetes Centre.

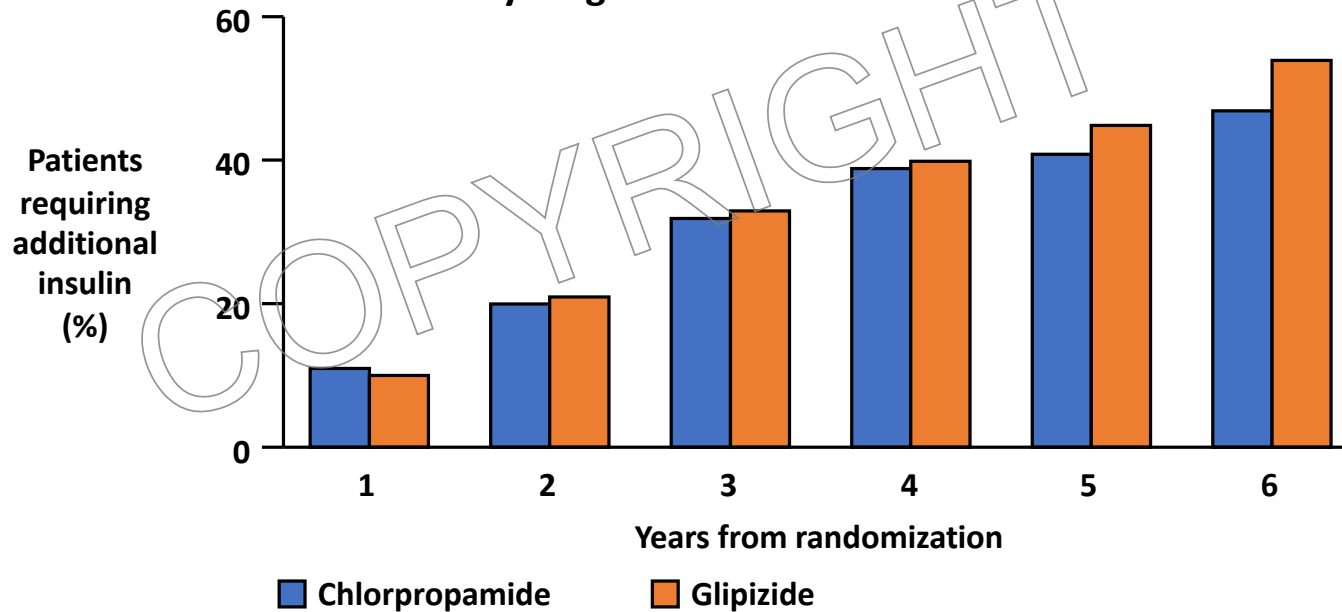


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# Need for insulin increases over time

UKPDS 57: N = 826 with newly diagnosed T2DM



**~53% of patients required additional insulin therapy by year 6**

Wright A et al. *Diabetes Care*. 2002;25:330-6.



# Stepwise Management of Type 2 Diabetes: “Wait-for-Failure” Approach

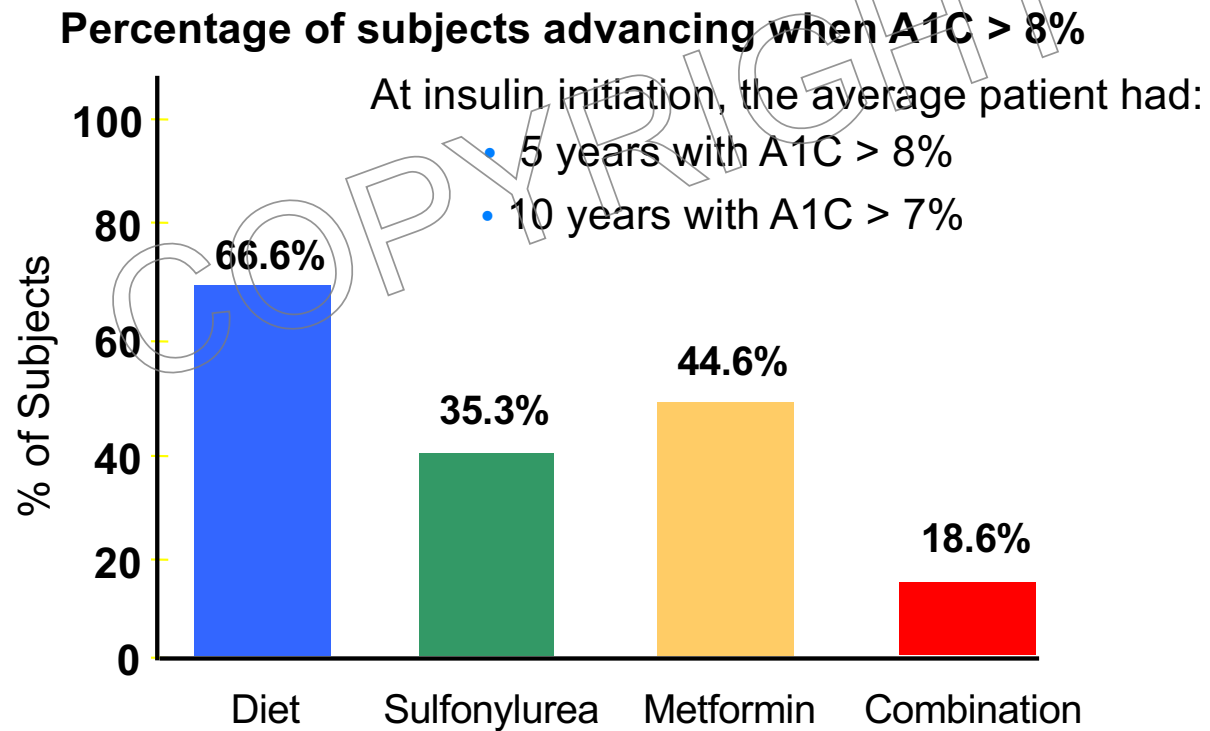
Diet, exercise, lifestyle monotherapy...  
When failure confirmed...

Combination therapy... When failure confirmed...

Based on failure of previous therapies, consider:  
Insulin / 3 OHA combination therapy . . .



# Clinical Inertia: Failure to Advance Therapy When Required

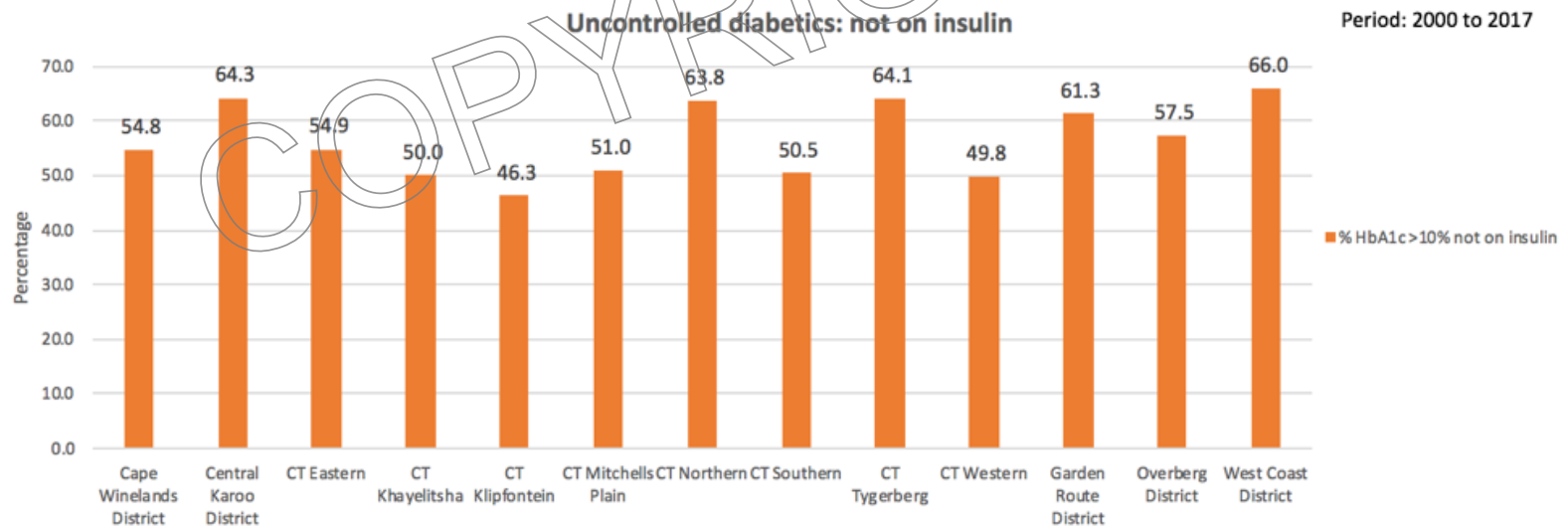


Brown JB et al. Diabetes Care 2004;27:1535-1540.



# Clinical Inertia: Failure to Advance Therapy When Required

**Western Cape Public Sector: % Patients with DM and HbA1c > 10% not on insulin:**



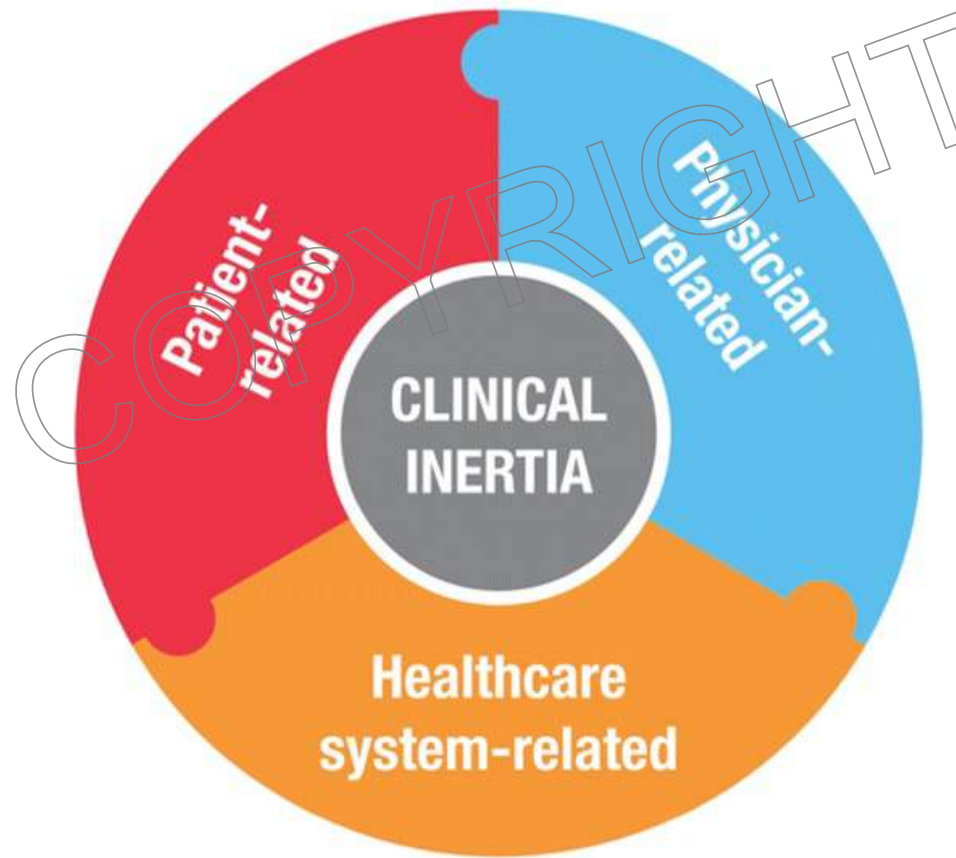
WCG PHDC DM Audit data.



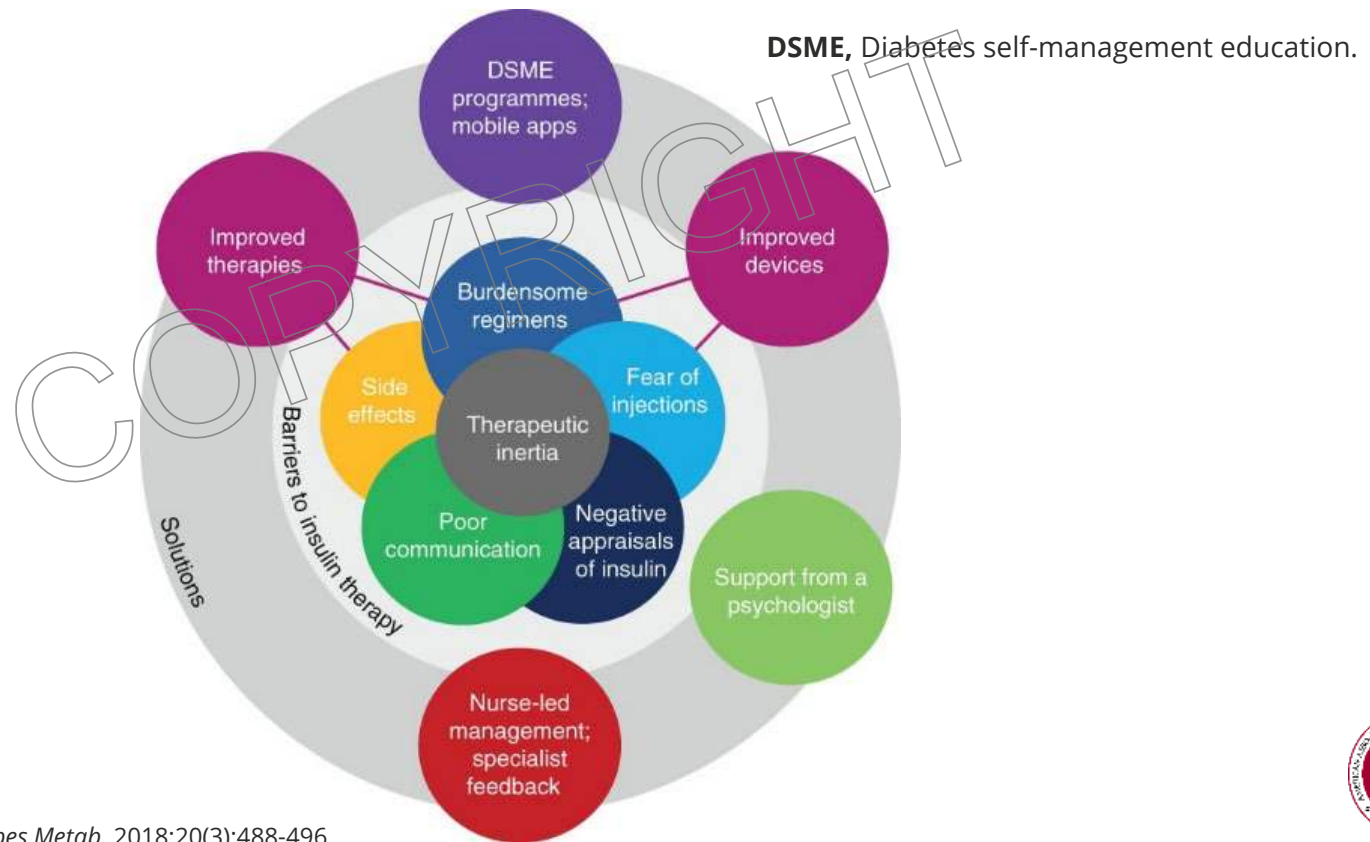
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# Clinical Inertia



# Barriers to Insulin Therapy and strategies to Overcome Them



Russell-Jones D, et al. *Diabetes Obes Metab.* 2018;20(3):488-496.



# Barriers to use of insulin



Despite the valiant efforts of many research groups  
the insulin suppository still has one major problem

# Barriers to use of insulin

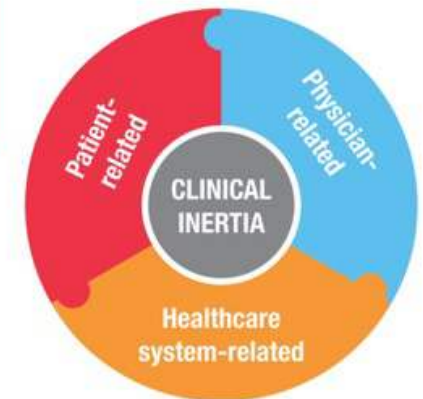
UKPDS: 27% initially refused insulin

DAWN: >50% anxious when starting insulin therapy

## Patient barriers

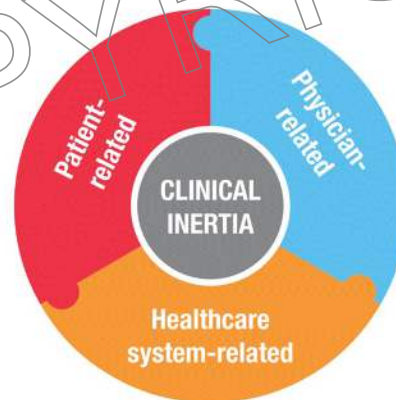
- Lack of awareness or knowledge
- Anxiety
- Fear of hypoglycaemia
- Negative perceptions of outcome
- Needle phobias
- Social stigma
- Lack of self-efficacy or confidence
- Treatment costs

- Denial of disease
- Lack of awareness of progressive nature of disease leading to feeling of 'failure'
- Lack of awareness of implications of poor glycaemic control
- Fear of side effects (hypoglycaemia, weight gain)
- Concerns over ability to manage more complicated treatment regimens
- Too many medicines
- Treatment costs
- Poor communication with physician
- Lack of support
- Lack of trust in physician



# Clinical Inertia

- Denial of disease
- Lack of awareness of progressive nature of disease leading to feeling of 'failure'
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- Too many medicines
- Treatment costs
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- Lack of trust in physician



- Time constraints
- Lack of support from e.g. nursing staff
- Concerns over costs of treatment/testing etc.
- Reactive rather than proactive care
- Underestimation of patient's needs
- Difficulties navigating guidelines and algorithms
- Lack of information or understanding of new treatment options and potential benefits
- Lack of information on side effects/fear of causing harm (ie. hypoglycemia)
- Lack of clear guidance on individualizing treatment
- Concerns over patient's ability to manage more complicated treatment regimens
- Concerns over patient adherence

- No clinical guidelines
- No disease registry
- No visit planning
- No active outreach to patients
- No decision support
- No team approach to care
- Poor communication between physician and staff

# Strategies to tackle “insulin resistance”

- Information & education on progressive nature of disease
- Explore reasons for reluctance to start insulin
  - Ignorance
  - Social stigmas
  - Cultural barriers
  - Irrational beliefs and misconceptions
  - Anxiety
- Offer the opportunity to experiment
- Show devices and discuss starting regimen
- Adopt empowerment approach

## Greyhound motto

*“We ’ll do the driving ”*

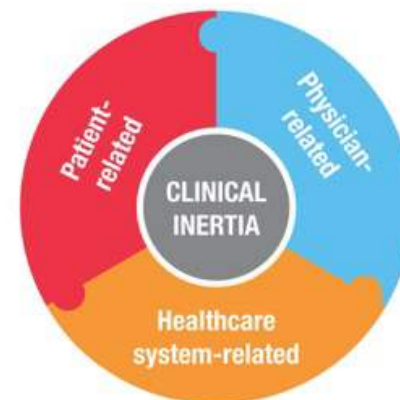
## Hertz motto

*“We’ ll put you in the driving seat”*

# Barriers to use of insulin

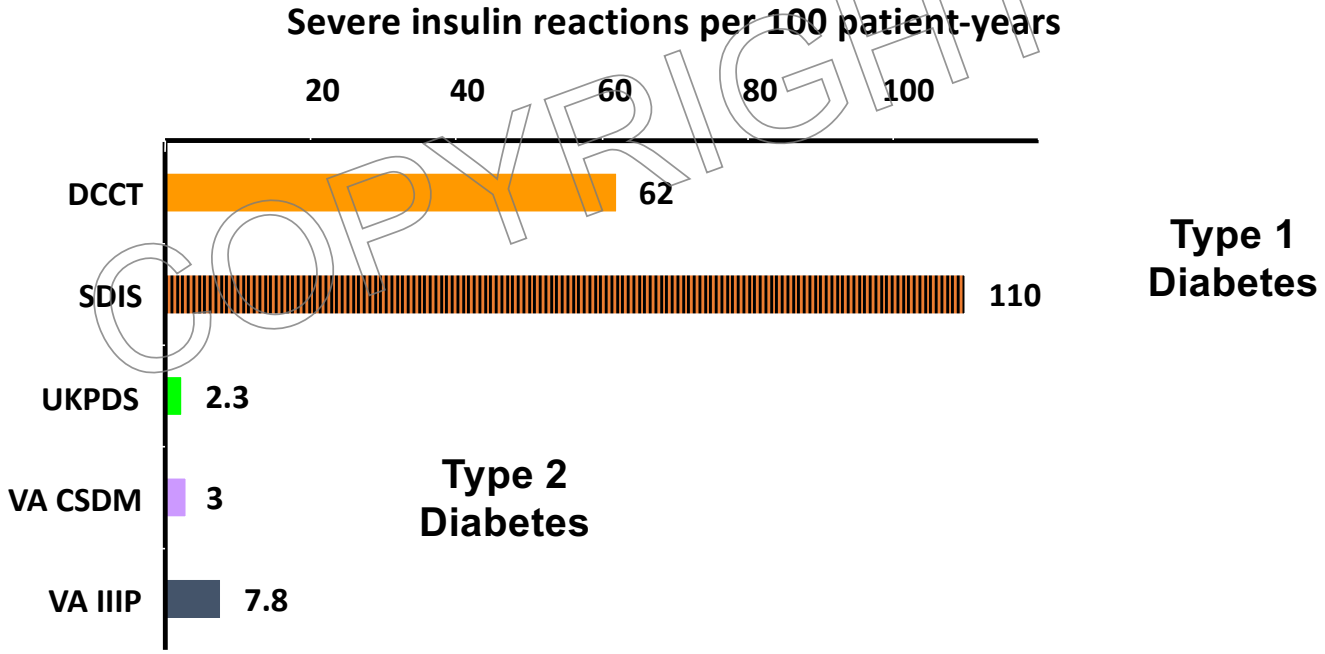
## Physician barriers

- Perception of poor clinical efficacy
- Perception that it is asking too much of some patients
- Poor confidence in patient's abilities
- Fear of inducing hypoglycaemia
- Too demanding for the staff
- Lack of experience



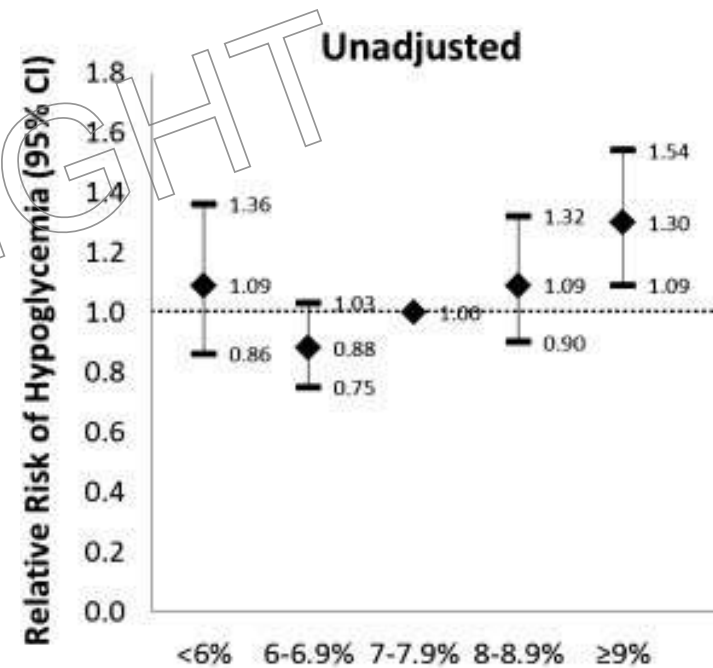
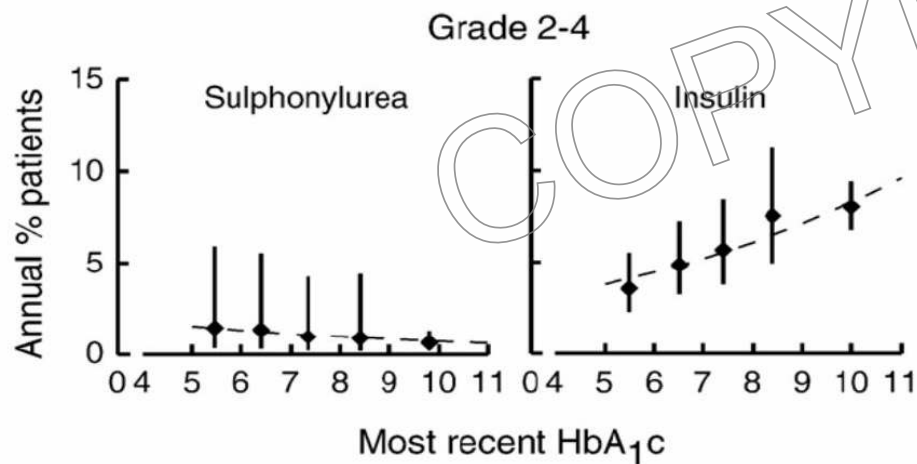
- Time constraints
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- Concerns over patient adherence

# Barriers to use of insulin: hypoglycaemia

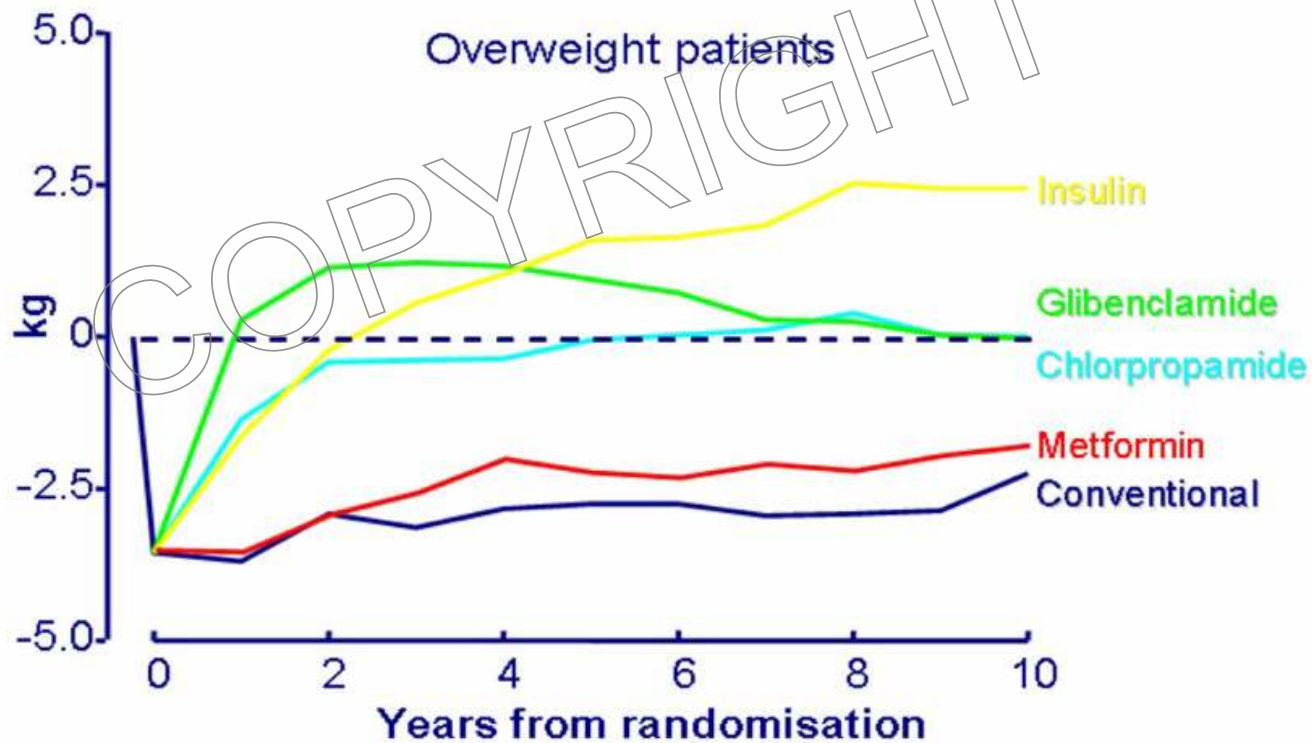


Adapted from McCall A. In: Leahy J, Cefalu W eds. *Insulin Therapy*. New York, NY: Marcel Dekker; 2002:193

# Barriers to use of insulin: hypoglycaemia



# Barriers to use of insulin: weight gain



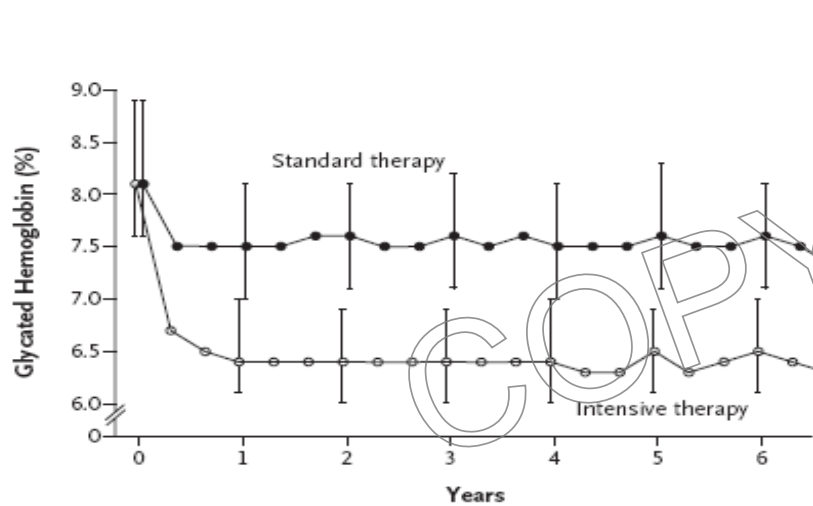
## Weight gain: Combined Effects of Metformin with Insulin Therapy in T2DM

**Table 1. Studies showing the benefits of using metformin with insulin in type 2 diabetes\***

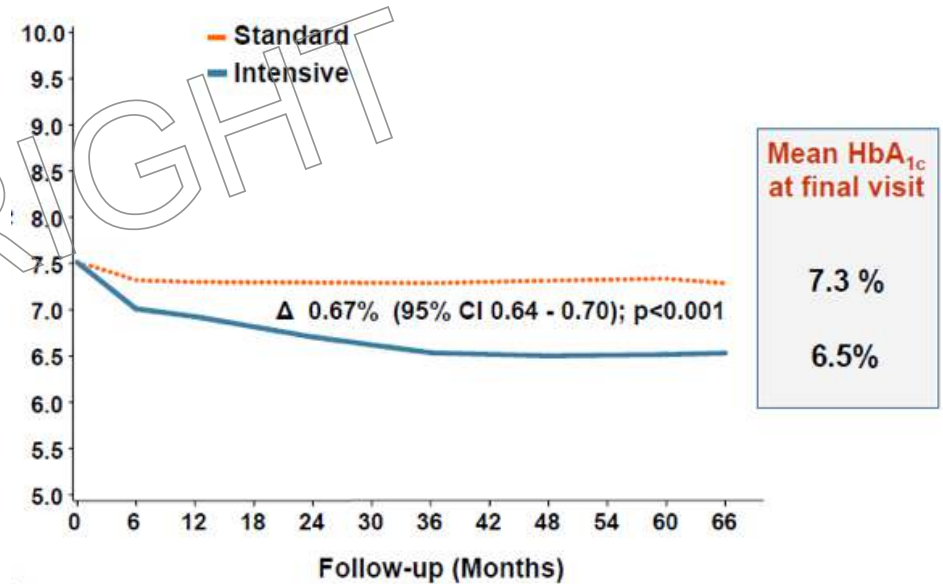
	Yki-Järvinen <i>et al.</i> [26]		Avilés-Santa <i>et al.</i> [29]		Strowig <i>et al.</i> [30]		Wulffelé <i>et al.</i> [31]	
	Insulin	Insulin + metformin	Insulin	Insulin + metformin	Insulin	Insulin + metformin	Insulin	Insulin + metformin
Subject, <i>n</i>	24	19	22	21	31	27	182	171
Duration, <i>mo</i>	12	12	6	6	4	4	4	4
Insulin dose at end, <i>U</i>	53	36	120	92	135	82	71	64
HbA <sub>1c</sub> at end, %	7.9	7.2	7.6	6.5	7.0	7.1	7.6	6.9
Weight gain, <i>kg</i>	4.6	0.9	3.2	0.5	4.4	0.5	1.2	-0.4

\*All of the studies compared subjects on insulin versus metformin and insulin. All found less weight gain, a lower insulin dosage, and mostly a lower HbA<sub>1c</sub>.  
HbA<sub>1c</sub>—hemoglobin A<sub>1c</sub>.

# Sustainable longterm control is possible



No. at Risk	0	1	2	3	4	5	6
Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471



The ACCORD study group. *New Eng J Med* 2008;358:2545-59

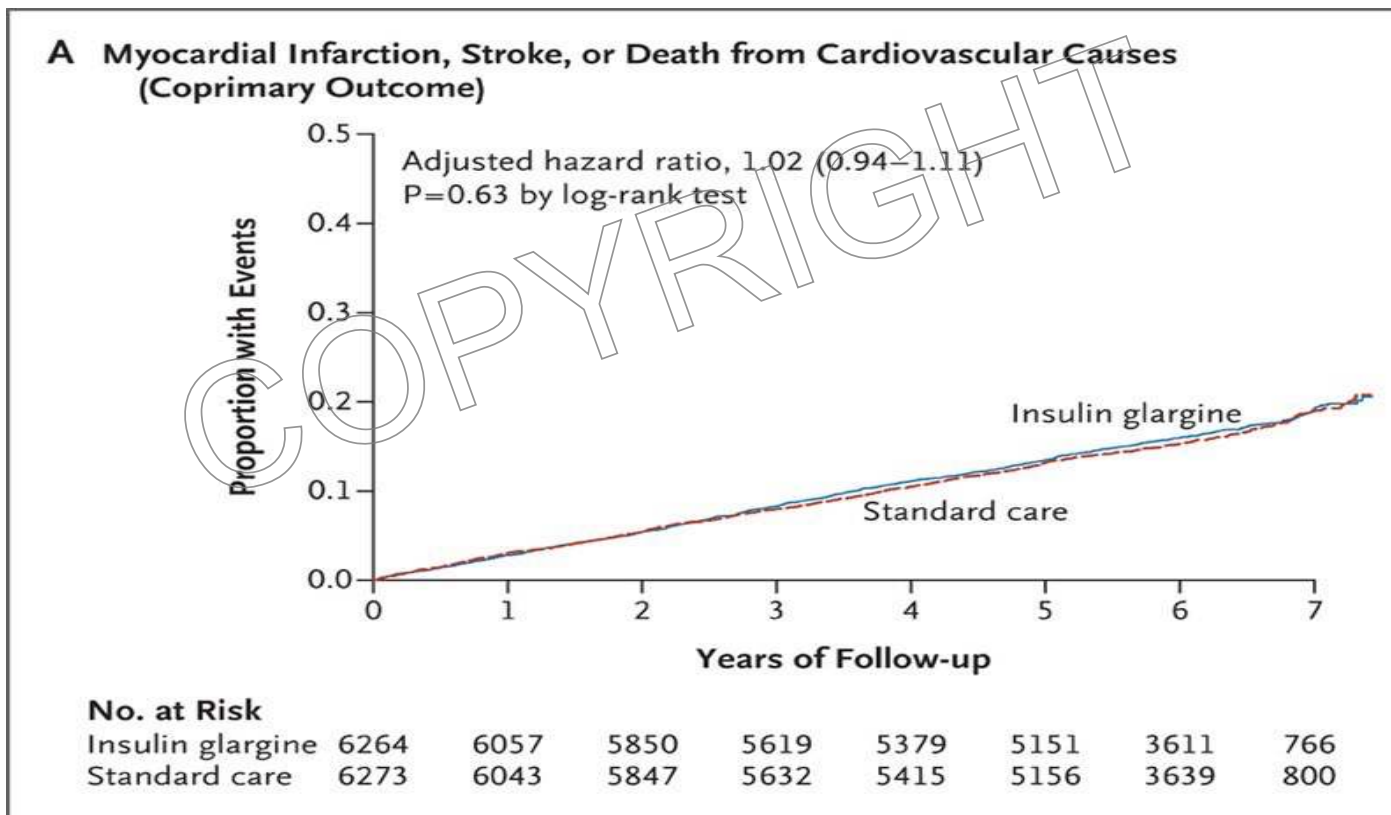
The ADVANCE study group. *New Eng J Med* 2008;358:2560-72



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# Insulin's CV safety established



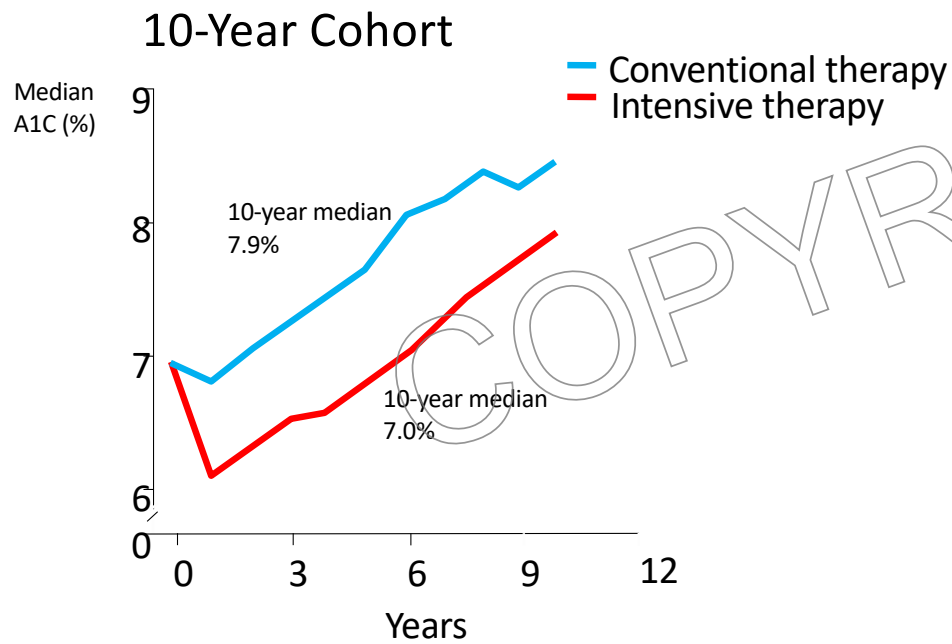
*N Engl J Med* 2012; 367:319-328



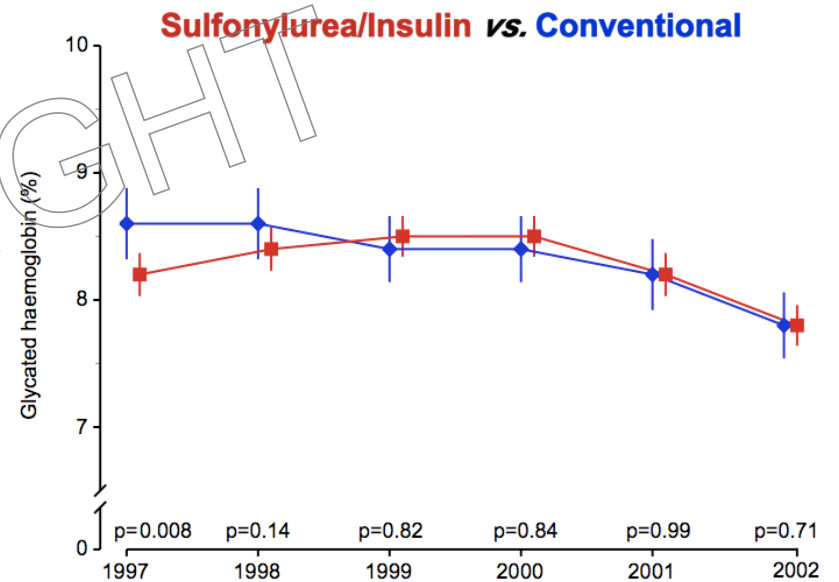
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# Treat to target early – “metabolic memory”



UKPDS Group. *Lancet*. 1998;352:837-853



UKPDS Group. *N Eng J Med* 2008;359:



## Treat to target early – “ metabolic memory”

*After median 8.5 years post-trial follow-up*

<b>Aggregate Endpoint</b>	<b>1997</b>	<b>2007</b>
Any diabetes related endpoint	RRR: 12% P: 0.029	9% 0.040
Microvascular disease	RRR: 25% P: 0.0099	24% 0.001
Myocardial infarction	RRR: 16% P: 0.052	15% 0.014
All-cause mortality	RRR: 6% P: 0.44	13% 0.007

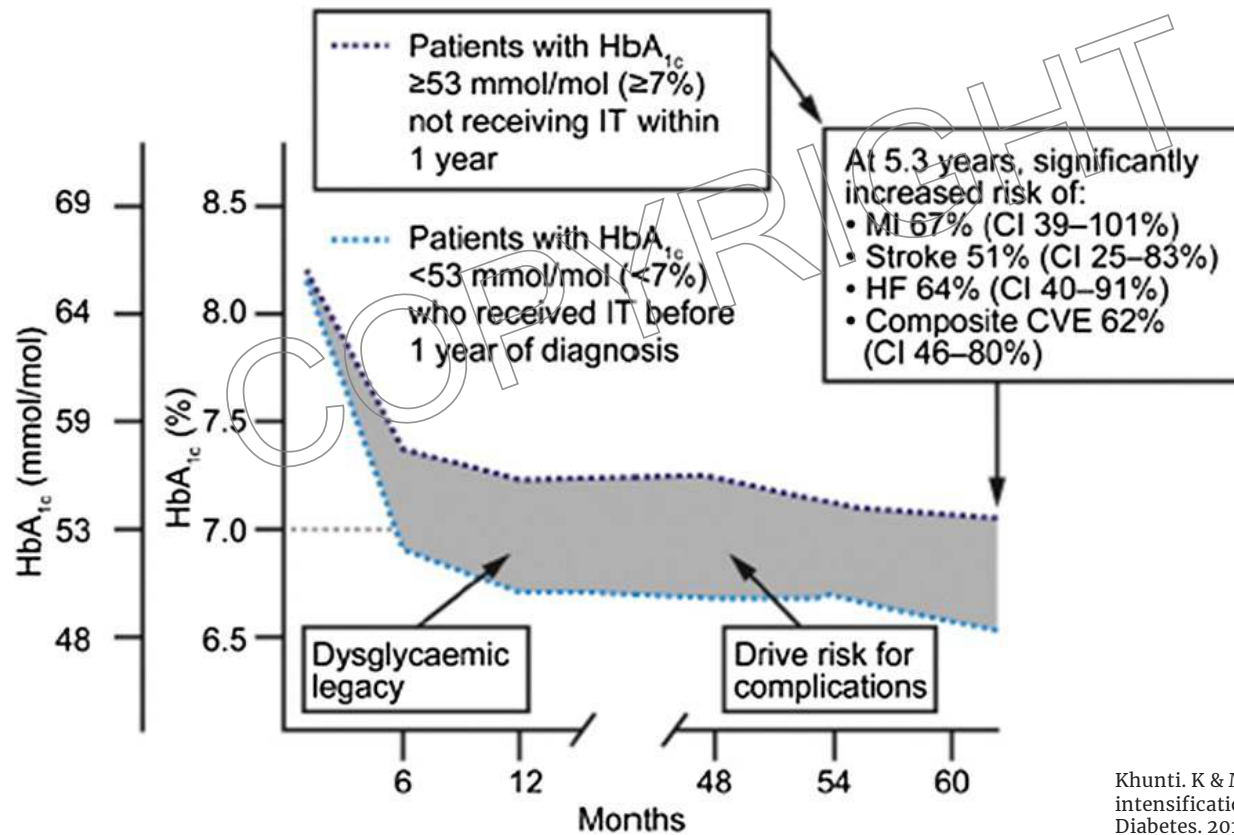
*RRR = Relative Risk Reduction, P = Log Rank*



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# Treat to target early – “metabolic memory”



Khunti. K & Millar-Jones. D. Clinical inertia to insulin initiation and intensification in the UK: A focused literature review. Primary Care Diabetes. 2017, 11: 3–12



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# Summary

- Reducing HbA1c of benefit. There is No HbA1c threshold – aim low.

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# Summary

- Reducing HbA1c of benefit. There is No HbA1c threshold – aim low.
- T2DM is a progressive disease – this will need constant stepwise addition of medication; many/most will need insulin
  - Can control longterm with such an approach
  - Overall insulin safe



# Summary

- Reducing HbA1c of benefit. There is No HbA1c threshold – aim low.
- T2DM is a progressive disease – this will need constant stepwise addition of medication; many/most will need insulin
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# Summary

- Reducing HbA1c of benefit. There is No HbA1c threshold – aim low.
- T2DM is a progressive disease – this will need constant stepwise addition of medication; many/most will need insulin
  - Can control longterm with such an approach
  - Overall insulin safe
- Risk is hypoglycaemia/drug side effects – individualize target
- Treat to aggressive target “early” – easier and the “legacy” will persist; less aggressive later acceptable.

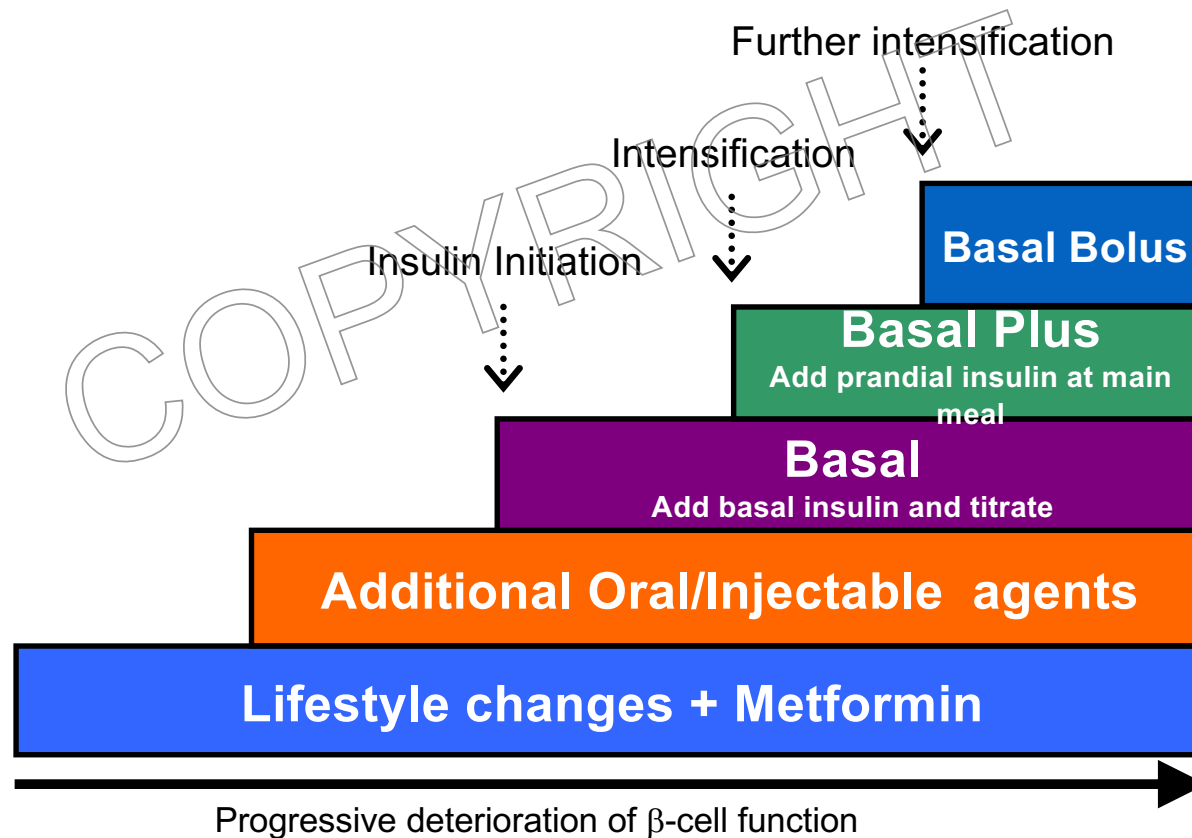


# A Practical Approach to Initiation and intensification of Insulin in T2DM – for glycaemic control

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# Initiation and intensification of Insulin in T2DM



# Patient

- 40 year old woman
- Newly diagnosed T2DM
- HbA1c 8.5%
- No complications
- Set HbA1c target < 7.0%
- Rx:

**Lifestyle changes + Metformin**

# Patient

- Check HbA1c in 3/12 + move to Step 2 if HbA1c > 7.0%

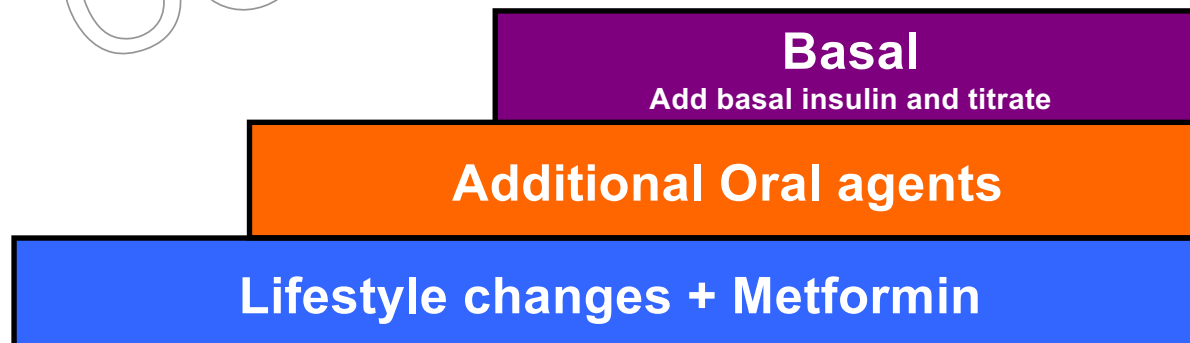
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**Additional Oral agents**

**Lifestyle changes + Metformin**

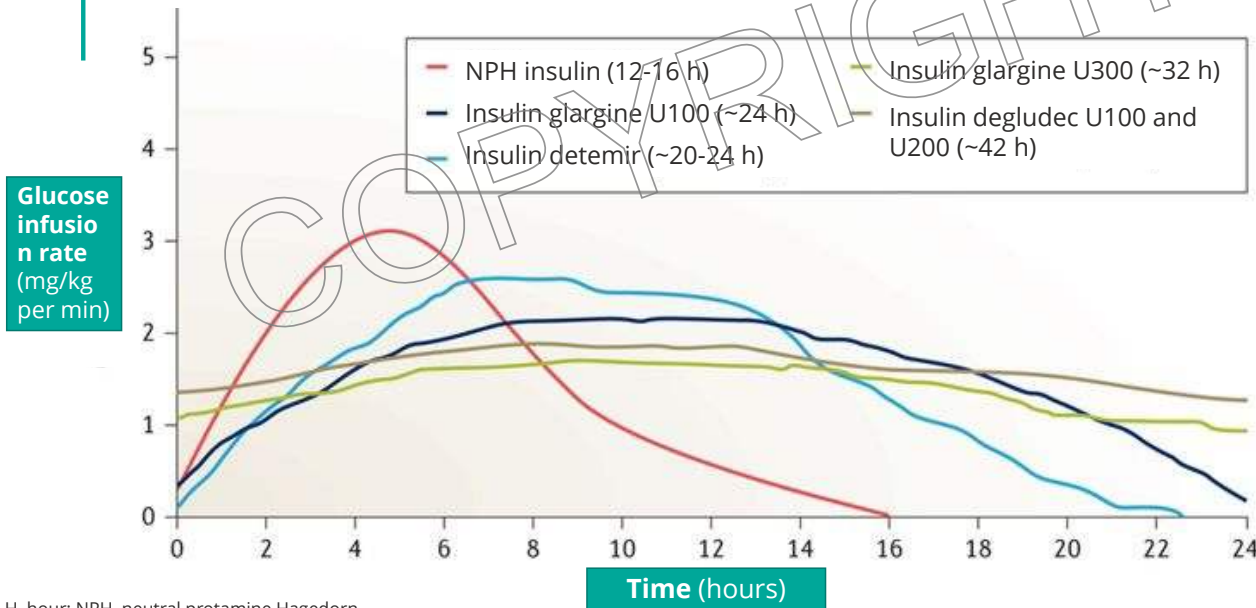
# Patient

- If HbA1c remains  $> 7.0\%$  or climbs to  $> 7.0\%$
- If drug intolerant
- If HbA1c  $> 10\%$



# Available basal insulins

## Basal Insulin Action Profiles

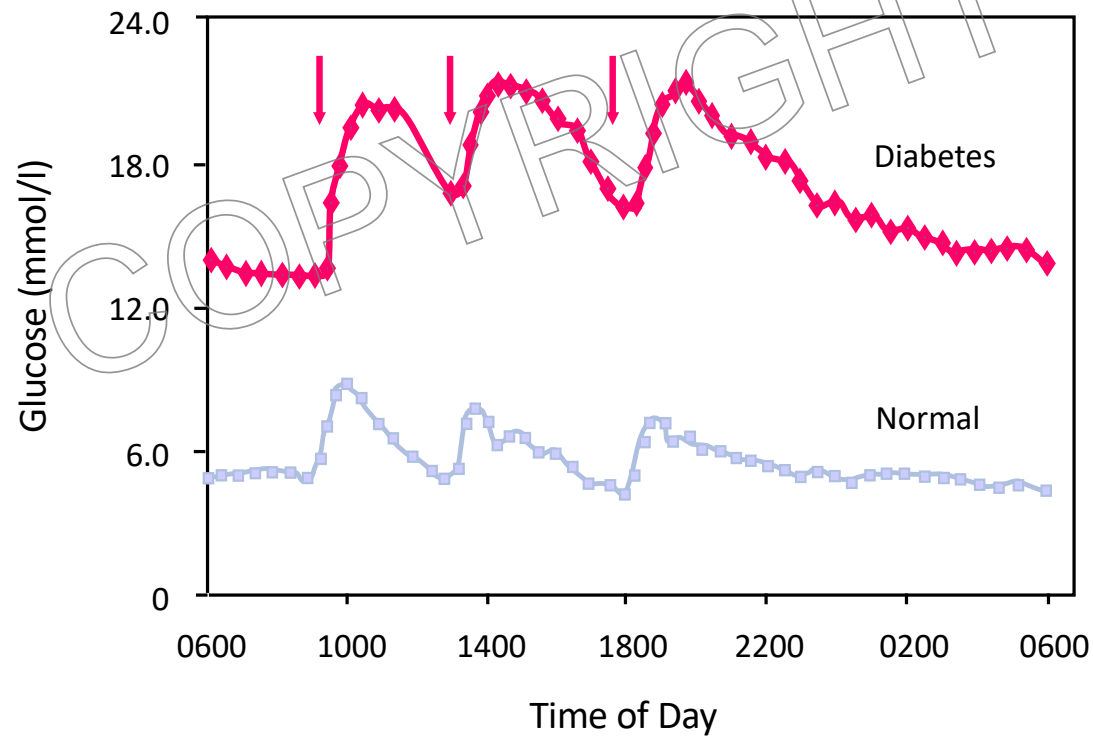


H, hour; NPH, neutral protamine Hagedorn.  
Mathieu C, et al. *Nat Rev Endocrinol*. 2017;13:385-399.



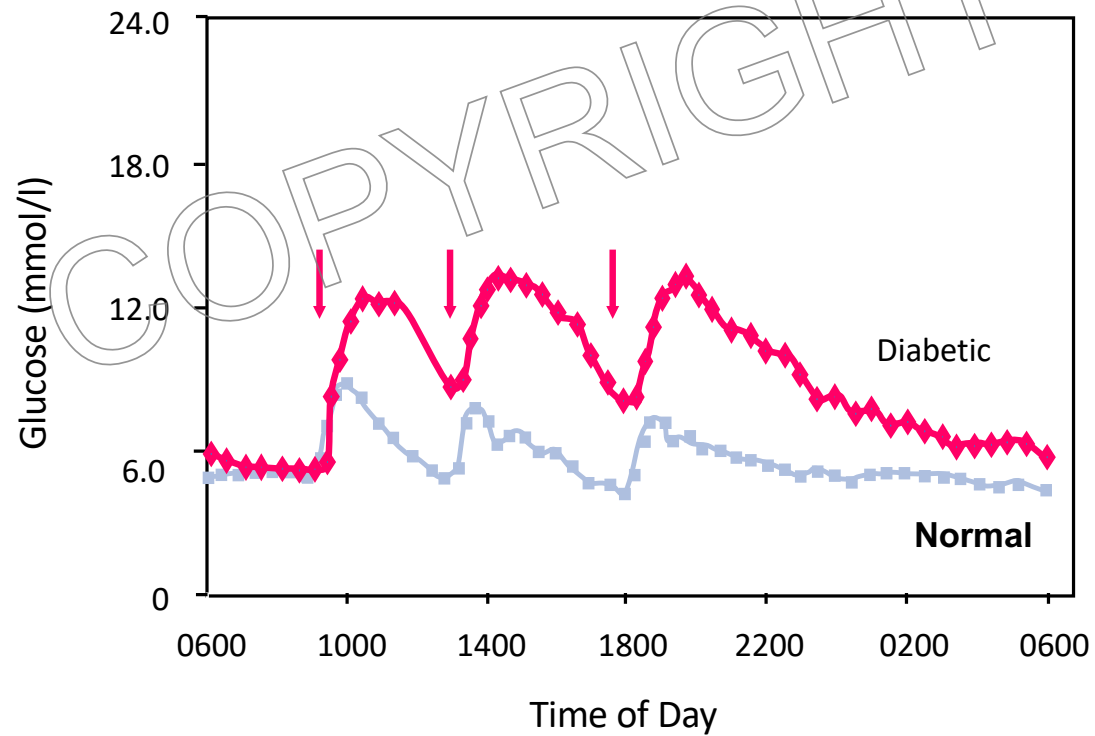
# Rationale for basal insulin

24-hour Plasma Glucose Curve:



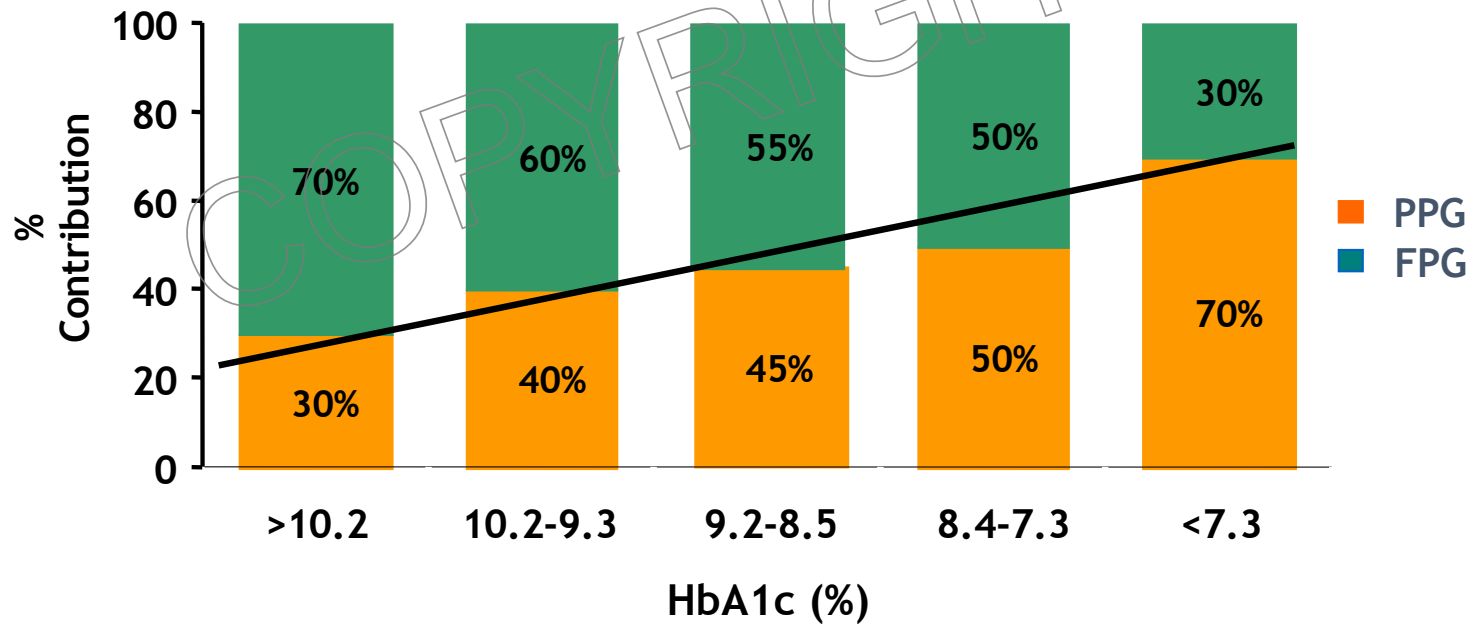
# Rationale for basal insulin

24-hour Plasma Glucose Curve:



Adapted from Polonsky KS et al. *N Engl J Med.* 1988;318:1231-1239.

# Rationale for basal insulin



Monnier L, et al. Diabetes Care. 2003;26:881-885.

# Initiation and adjustment of insulin

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# Initiation and adjustment of insulin

**START**

Start with bedtime NPH /  
long acting insulin; 6 - 10u

Start early,  
especially if  
HbA1c > 10%

Continue  
with OHAs

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# Initiation and adjustment of insulin

START

Start with bedtime NPH / long acting insulin; 6 - 10u

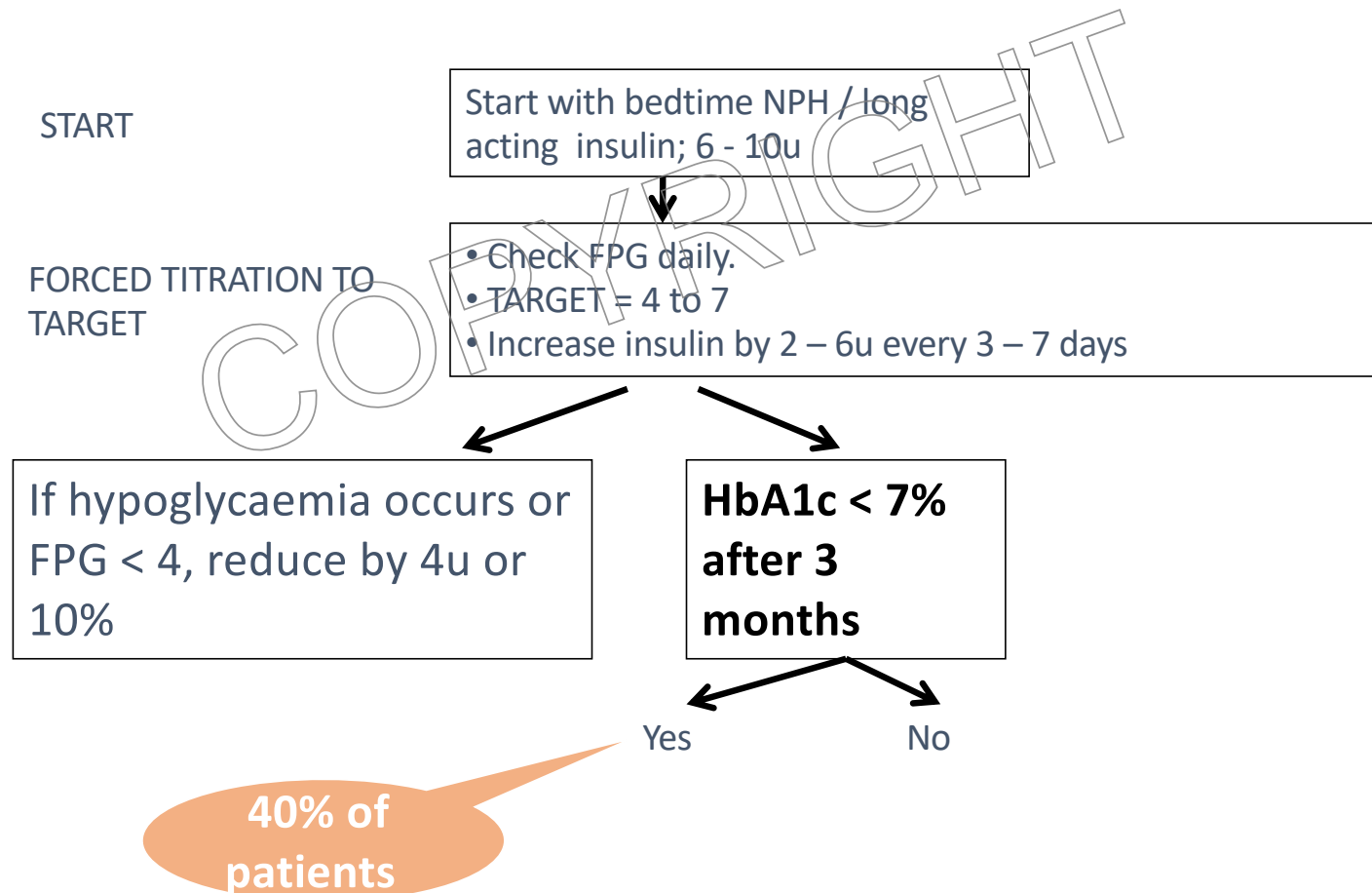


**FORCED  
TITRATION TO  
TARGET**

- Check FPG daily.
- TARGET = 4 to 7
- Increase insulin by 2u if > 3 readings > 7.0
- Increase insulin by 4u if > 3 readings > 8.0
- Increase insulin by 6u if > 3 readings > 9.0

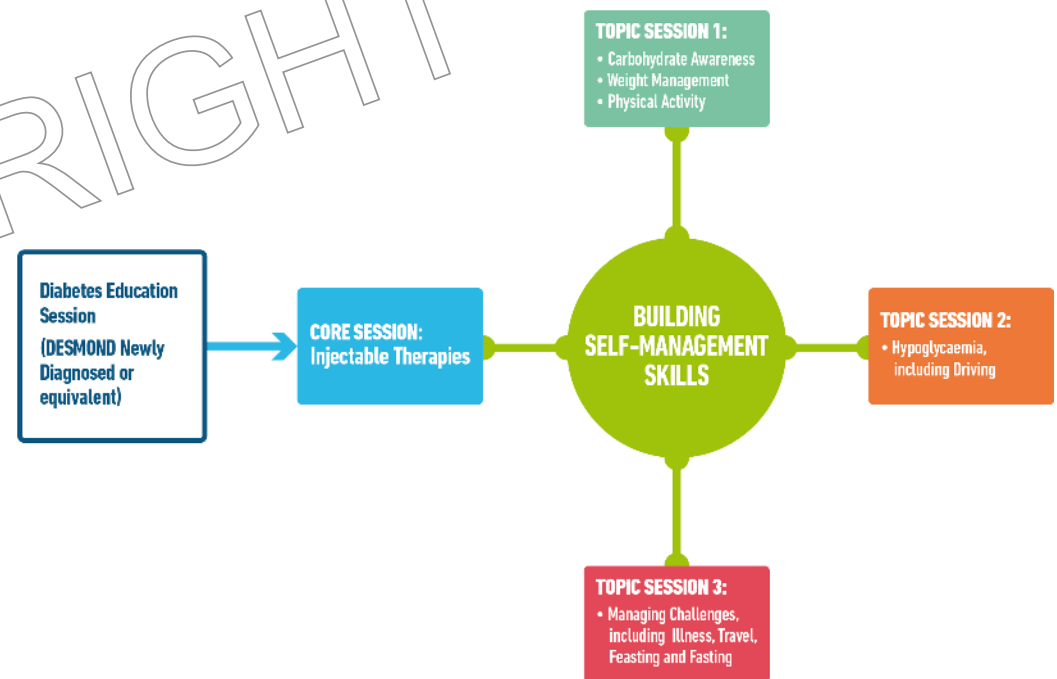
Review progress  
regularly: 1 – 3  
monthly

# Initiation and adjustment of insulin

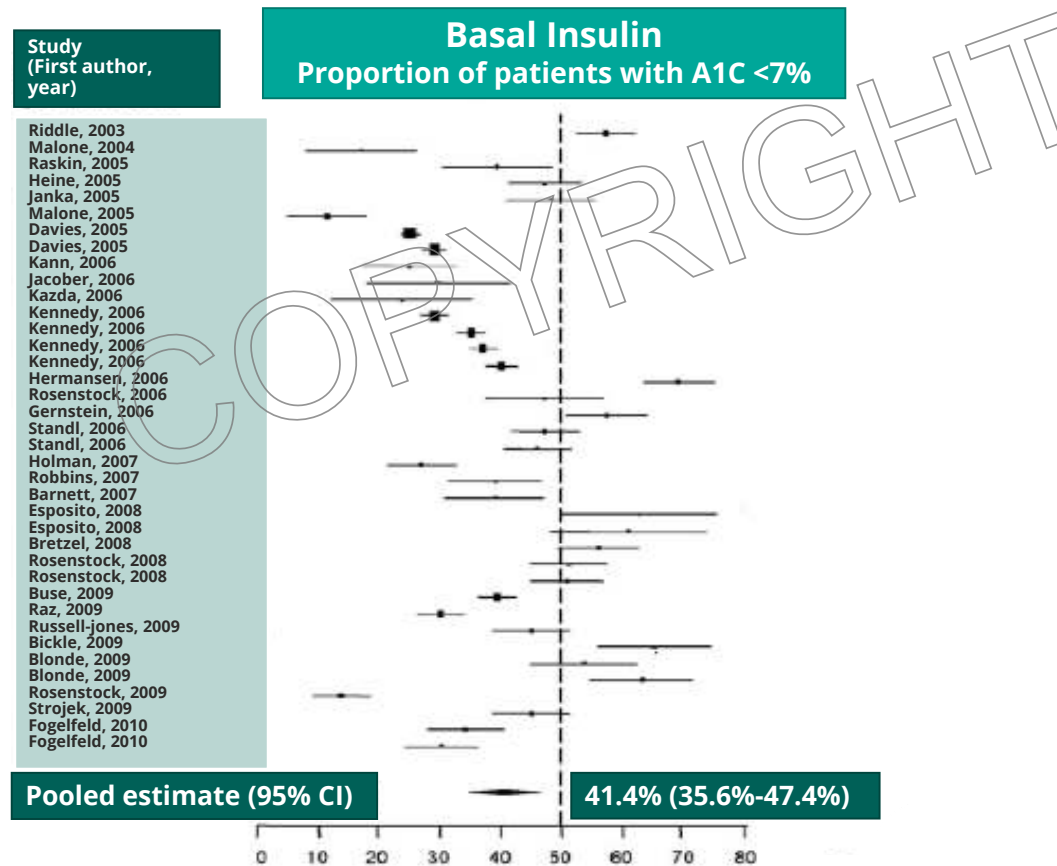


# 1. Minimum education when starting insulin

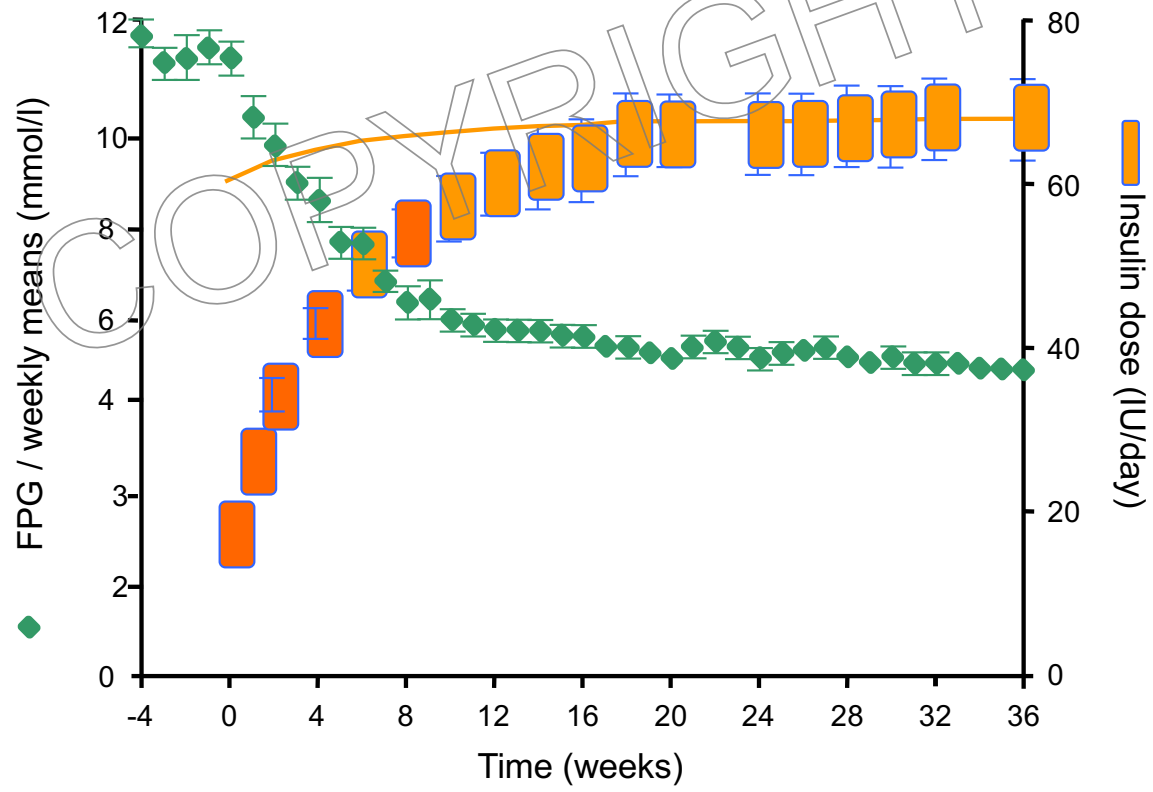
- All about insulin
- Home blood glucose monitoring
- When/who to call for help
- Hypo's
- Sick day rules, feasting and fasting



## 2. Achievement A1c < 7% with basal insulin regimen in T2DM

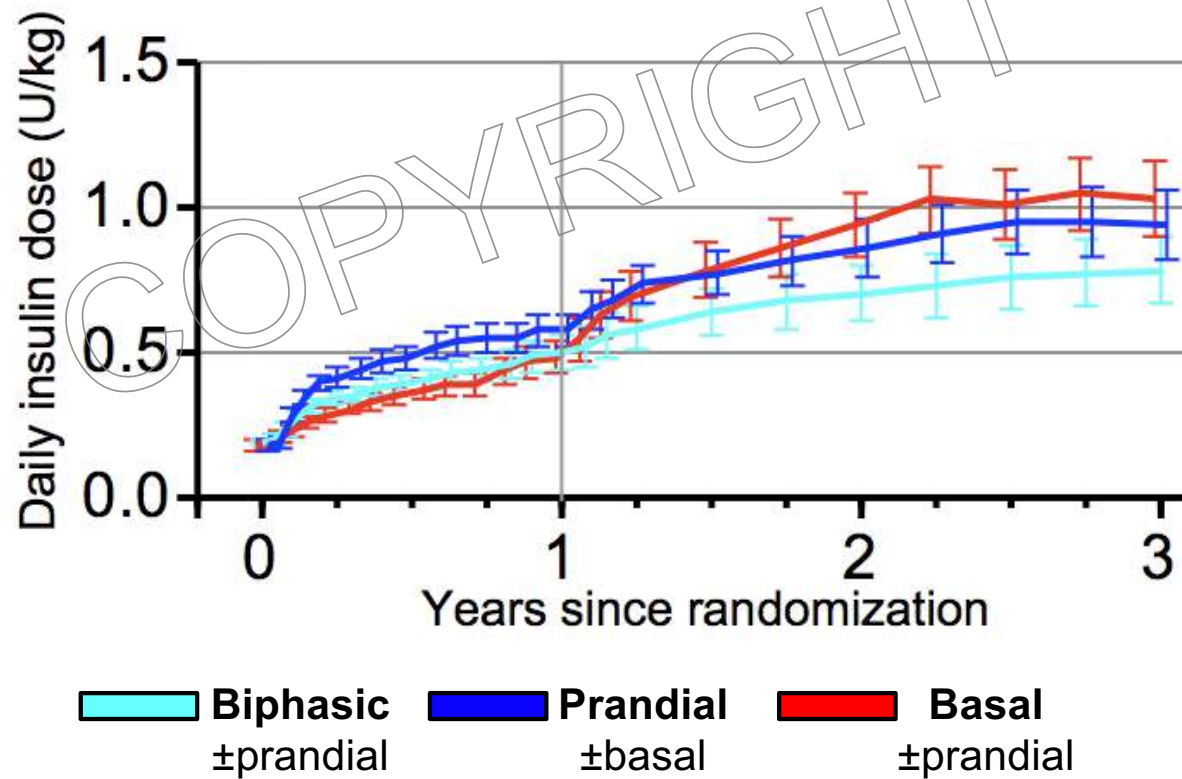


### 3. What is the expected dose? (LANMET study)

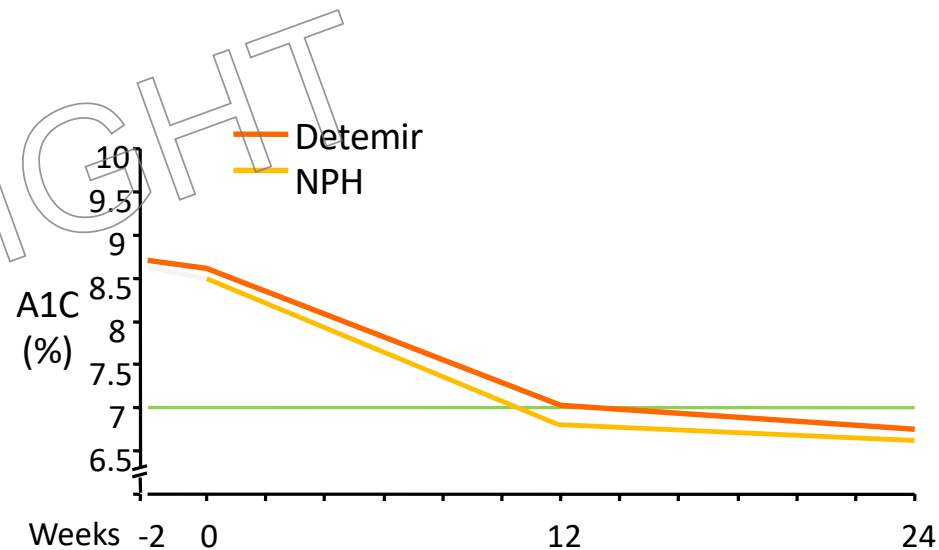
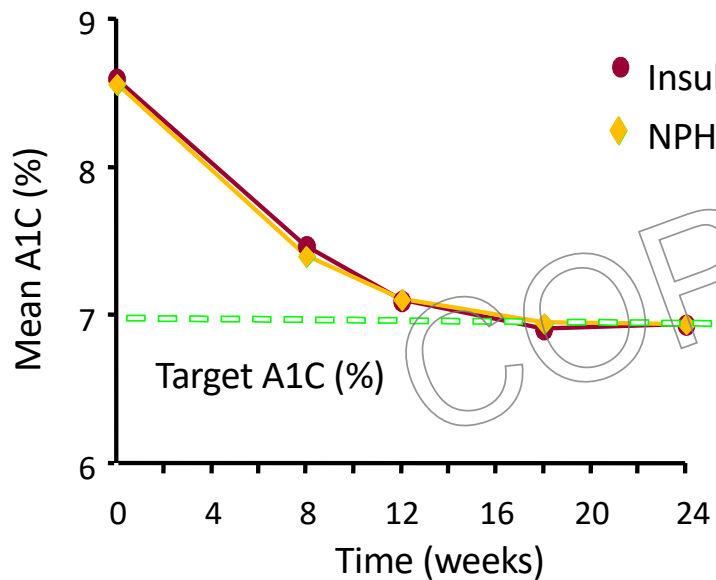


Adapted from Yki-Järvinen H, et al. Diabetologia 2006;49:442-51

### 3. 4-t Study: Insulin Doses Over 3 Years



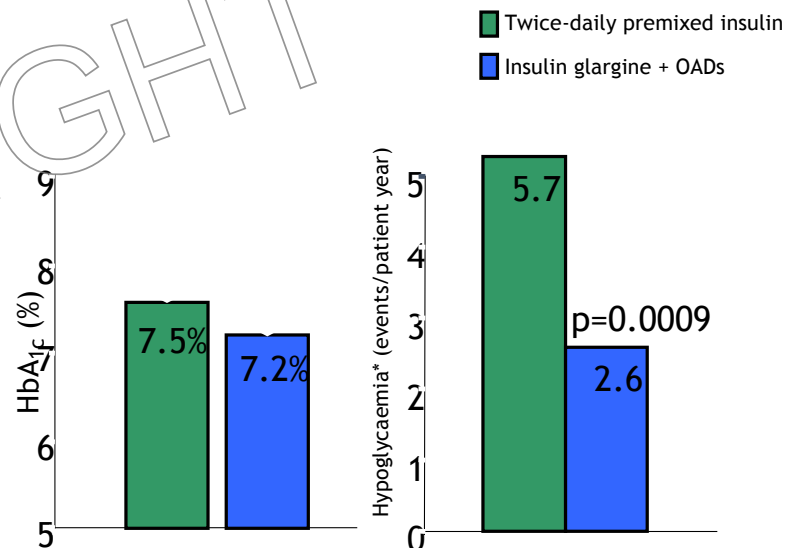
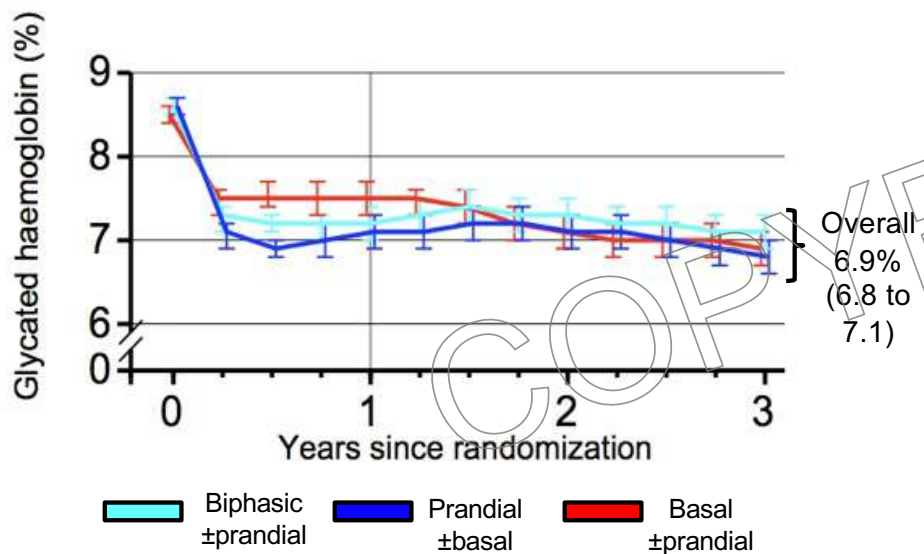
## 4. Analog vs. NPH Insulin Added to Oral Therapy



Riddle MC et al. *Diabetes Care*. 2003;26:3080-3086.

Hermansen, et al. *Diabetes Care*, 2006

## 5. Basal vs premix insulin Added to Oral Therapy



\*Confirmed symptomatic hypoglycaemia (blood glucose < 3.3 mmol/)

# 6. Alternatives to simple basal insulin

## Basal Insulin Plus SGLT2 Inhibitors in T2D

**CANA RCT (N=2072, 18 weeks); patients inadequately controlled on insulin ± OADs**

- A1C change with CANA 100 and 300 mg vs PBO: -0.6% and -0.7%; ( $P < 0.001$  for both)<sup>1</sup>

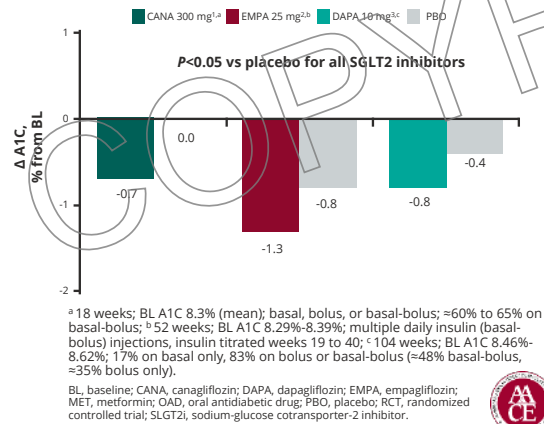
**EMPA RCT (N=563, 52 weeks); patients inadequately controlled on insulin ± MET**

- A1C change with EMPA 10 and 25 mg vs PBO: -0.4% and -0.5%; ( $P < 0.001$  for both)<sup>2</sup>

**DAPA RCT (N=808, 104 weeks); patients inadequately controlled on insulin ± OADs**

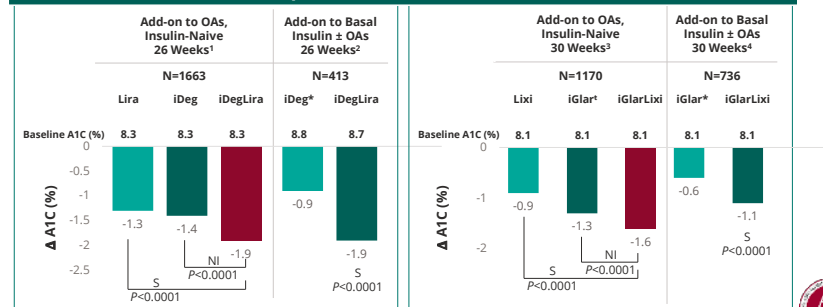
- A1C change with DAPA 5mg/10mg and 10 mg vs PBO: -0.4% and -0.5%; ( $P < 0.001$  for both)<sup>3</sup>

**In the CANA and EMPA studies, patients treated with SGLT2i had statistically significant weight loss vs PBO<sup>1,2</sup>**



## Glucose Control With Fixed-Ratio Combinations of Basal Insulin and GLP-1 RA

**Phase 3 RCTs in patients with T2D showed improved glycemic control with fixed-ratio basal insulin and GLP-1 RA combination compared with individual components administered alone**



1. Neal B, et al. *Diabetes Care*. 2015;38:403-411.  
 2. Rosenstock J, et al. *Diabetes Care*. 2014;37:1815-1823.  
 3. Wilding J, et al. *Diabetes Obes Metab*. 2014;16:124-136.

## Fixed-Ratio Combinations of Basal Insulin and GLP-1 RA



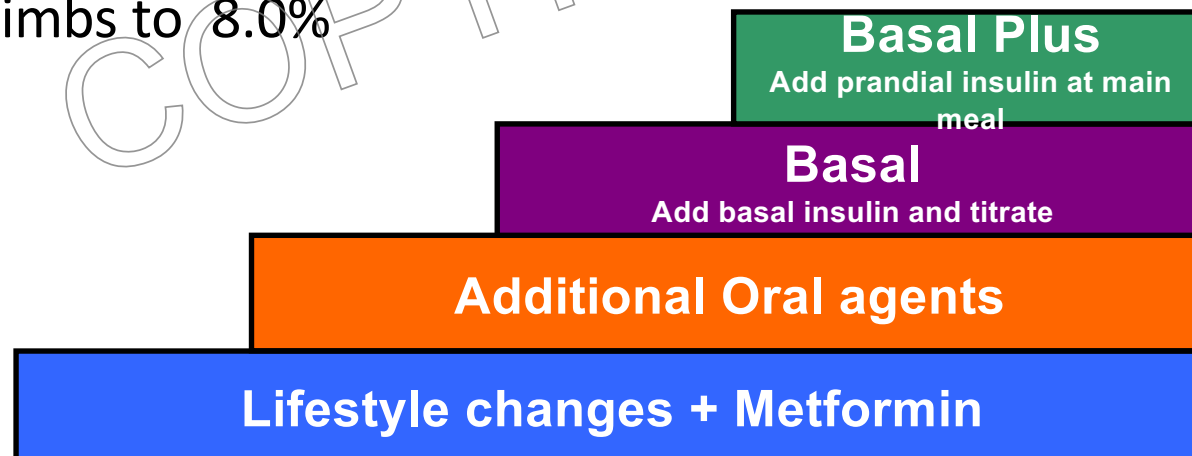
• iGlarLixi 100/33



• iDegLira 100/3.6

# Patient

- On NPH ( Protophane) 72u nocte
- FPG 5.5 mmol/l
- HbA1c climbs to 8.0%



# Intensification of insulin

START

Start with bedtime intermediate acting insulin; 6 - 10u

FORCED TITRATION TO TARGET

- Check FPG daily.
- TARGET = 4 to 7
- Increase insulin by 4 u if > 3 readings > 10.0

If hypoglycaemia occurs or FPG < 4, reduce by 4u or 10%

HbA1c  $\geq$  7% after 3 months

No

Yes

**Monitor pre meals; add 2<sup>nd</sup> injection**

# Intensification of insulin

HbA1c > 7.0 %;  
FPG < 5.5 mmol/l

Monitor pre meals;  
add 2<sup>nd</sup> injection

STOP Sulfonylurea  
CONTINUE Metformin  
CONSIDER BD  
Levemir/protophane

HbA1c > 7.0 %;  
FPG < 5.5 mmol/l;  
Monitor pre meals

BD pre-mix

**Basal PLUS**

Testing to ID how to  
intervene

COPYRIGHT

# Intensification of insulin

HbA1c > 7.0 %;  
FPG < 5.5 mmol/l;  
Monitor pre meals

Testing to ID  
how to  
intervene

**Pre-lunch** out of  
range: add rapid  
acting insulin at  
breakfast

**Pre-dinner** out of  
range: add rapid  
acting insulin at  
lunch

**Pre-bed** out of  
range: add rapid  
acting insulin at  
dinner

**Start 4u and increase by 2 u  
every 3 days according to  
pre or post meal glucose**

# Intensification of insulin

Basal



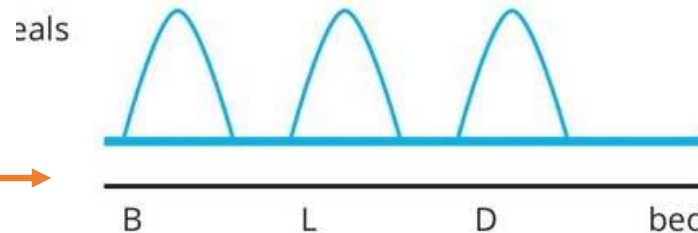
If glycaemic targets not met

Basal-Plus



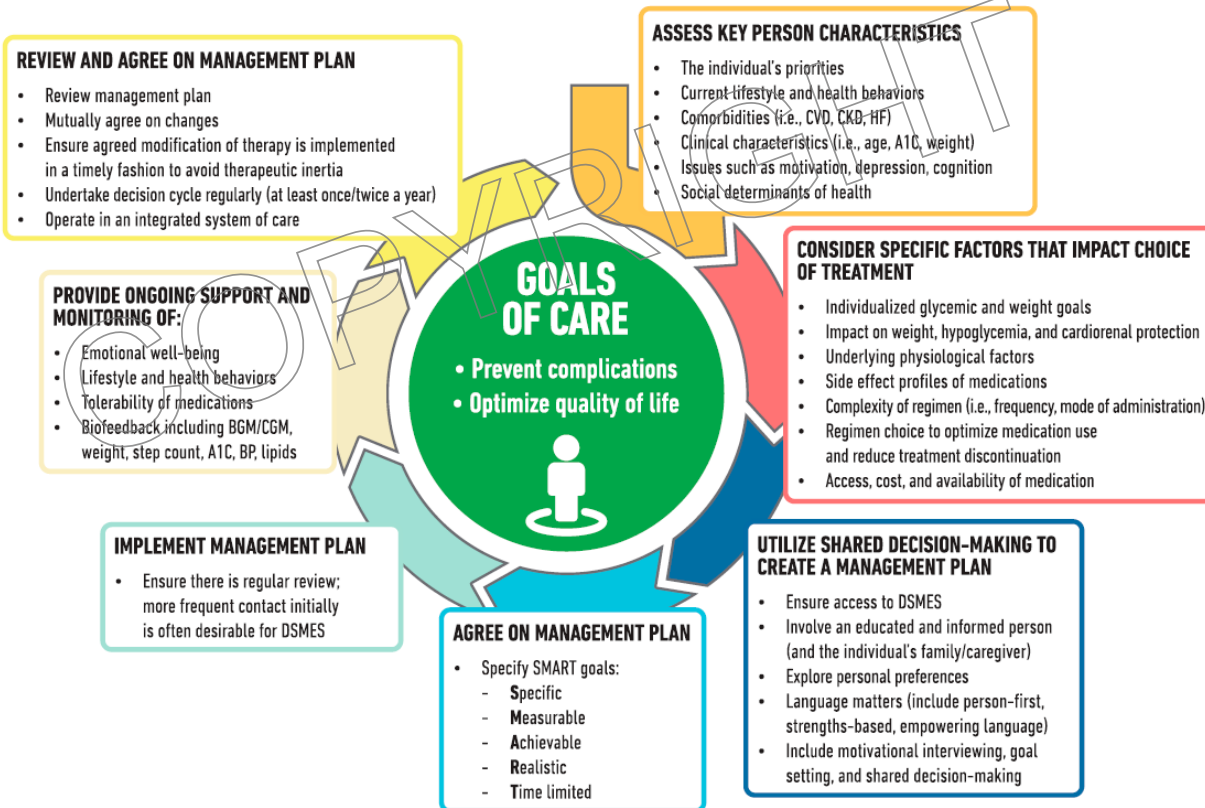
If glycaemic targets not met

Basal-Bolus or Multiple Daily Injections



# Insulin just a small part of comprehensive person-centered care

## DECISION CYCLE FOR PERSON-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



# Initiating insulin in T2DM

- Easy, safe
- Start now, this week
- Start low, titrate fast
- Expect doses of between 0.5 – 1u/kg at 3 months

