Wat u moet weten van de nieuwe ADA / EASD richtlijnen voor de behandeling van type 2 diabetes ...

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Blog: www.gmed.nl
Twitter: @bhrw

Duality of interest

- Research grants, advisory boards and clinical trial participation in the field of endocrine diseases and diabetes mellitus:
  - Alteon Inc
  - Astra Zeneca
  - Eli Lilly
  - Novartis
  - Pfizer
  - Roche
  - Amylin / BMS
  - AMGEN
  - Becton Dickinson
  - Glaxo Smith Kline
  - Novo Nordisk
  - Merck
  - Sanofi Aventis
  - Boehringer Ingelheim
- BMI 24,3 kg/m^2, waist circumference 98 cm
- Positive family history for T2DM

What's it all about ?

Reviews/Consensus Reports/ADA Statements

POSITION STATEMENT

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Silvio E. Inzucchi, MD[1]
Richard M. Bergenstal, MD[2]
John B. Buse, MD, PhD[3]
Michaela Diamant, MD, PhD[4]
Ele Ferrannini, MD[5]
Michael Nauck, MD[6]
Anne L. Peters, MD[7]
Apostolos Tsapas, MD, PhD[8]
Richard Wender, MD[9]
David R. Matthews, MD, DPhil[10,11,12]

treatment, and smoking cessation) is likely to have even greater benefits.

These recommendations should be considered within the context of the needs, preferences, and tolerances of each patient. individualization of treatment is the cor-

Inzucchi S E et al. Diabetes Care 2012;35:1364-79

The blurry world of guidelines

Guidelines do not replace incompettence ...

Probleem	Slecht gereguleerde diabeet type 2 en obesitas
Anamn	Geen informatie
L.O.	Geen informatie
Lab	Geen informatie
Indicatie	Graag instellen op Dpp-4 remmer
	Geen informatie
Medicatie	metfromine 1000 mg 3 dd1 tabl en glimepiride 6 mg 1 dd1 tabl
Advies	- Overname behandeling
	- Advies en terugverwijzing

Groningen, 2012

0
HOW IT WAS ?

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1975

- G.C.
- Ik zag uw patiënt op de polikliniek
- Alles was goed, de bloeddruk was 165/95
- Urine gluc: 0-6: 24; 6-12: 124; 12-18: 62; 18-24: 0
- De willekeurige glucose bedroeg 12.3 mmol/l
- Doorgaan met 88 E Lente 's ochtends
- Controle over 3 maanden werd afgesproken

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Progress since 1975 ….

- Self-monitoring of blood glucose
- HbA1c
- Association between blood glucose & complications
- New oral agents & insulins
- 'Metabolic control matters'
- DCCT
- UKPDS
- many other studies

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Are treatment algorithms really helpful in caring for individuals with T2DM ?

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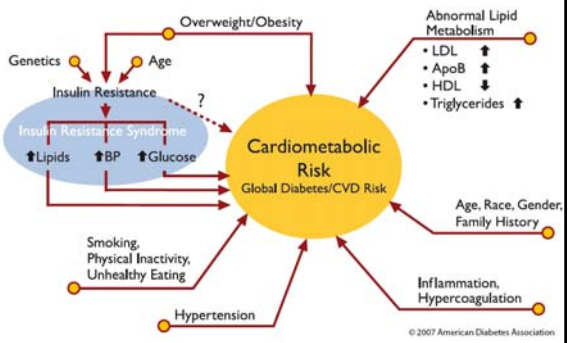
Type 2 diabetes: a complicated way to get cardiovascular disease and die young



Don't forget depression

www.diabetes.org/CMR

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Type 2 diabetes: the challenge

glucose
lipids
blood pressure
obesity

diet
normal living
quality of life

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1
GLYCAEMIC TARGETS

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Statement 1

There are very few really good clinical trials that can help us to decide which treatment to advise when and in which patients with type 2 diabetes mellitus

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Current dilemmas

Metformin only helps in obese

Higher insulin dose is associated with higher CVD risk

New drugs may have unexpected side-effects

Intensified diabetes treatment may kill you

New drugs are expensive and yet have to prove their benefit

Sulfonylurea are cheap

TZD's may break your bones

Doctors have too little time and do not care

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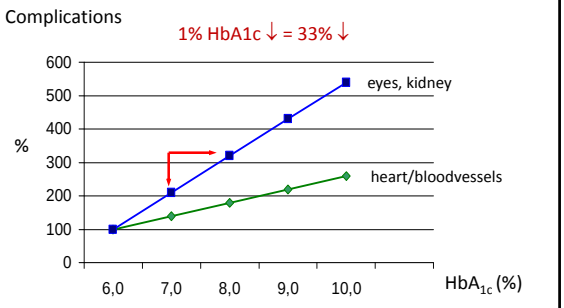
UKPDS epidemiologic study:

better glycaemic control means fewer complications in type 2 diabetes



UKPDS 1998

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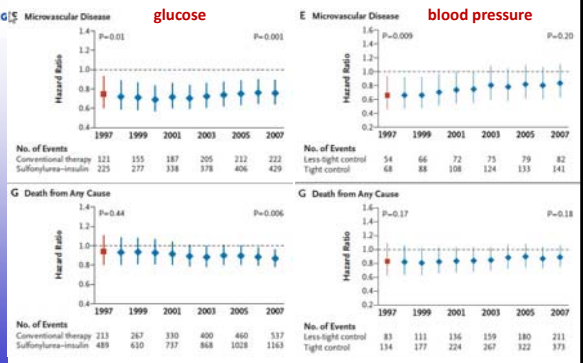
UKPDS 10 year follow- up



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

Holman et al. NEJM 2009

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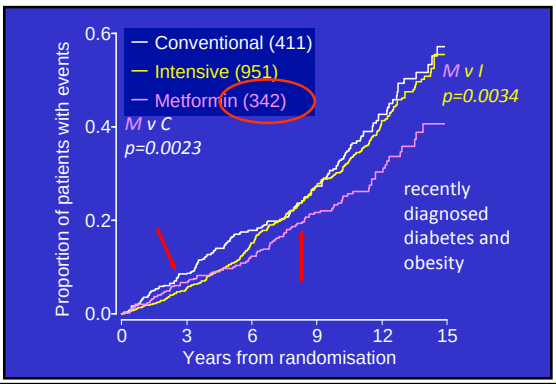
UKPDS longest study, but still controversial



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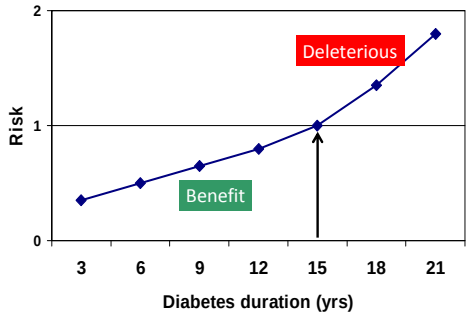
Diabetes duration determines the risk of c.v. events during intensive (insulin) therapy (VADT)



adapted from: Duckworth. ADA presentation VADT, June 2008

Coronary Artery Calcium Score (CAC) with CT-scan

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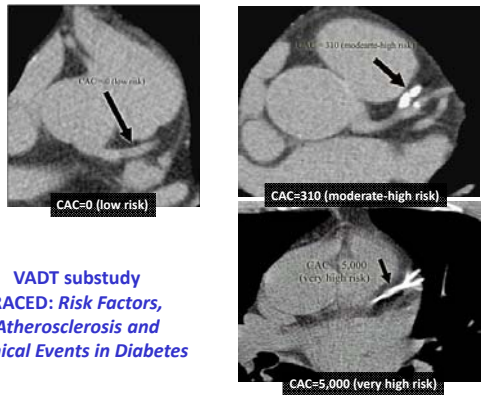

VADT substudy
RACED: *Risk Factors, Atherosclerosis and Clinical Events in Diabetes*

Primary endpoint in VADT substudy

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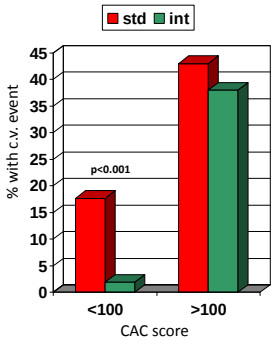
- CAC score measured in 301 VADT participants
- 40% had CAC score > 400
- CAC predicted new events
- Intensive therapy is especially effective in low CAC score



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

ACCORD showed high incidence of severe hypo

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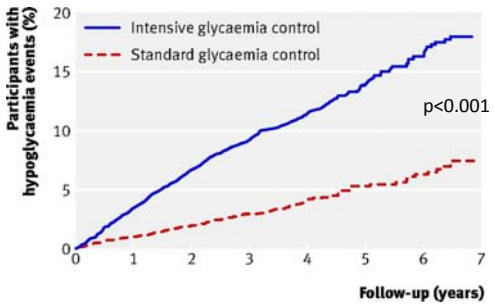

intensive control arm stopped prematurely because of increased C.V. events

ACCORD

Hypoglycaemia predicts c.v. events

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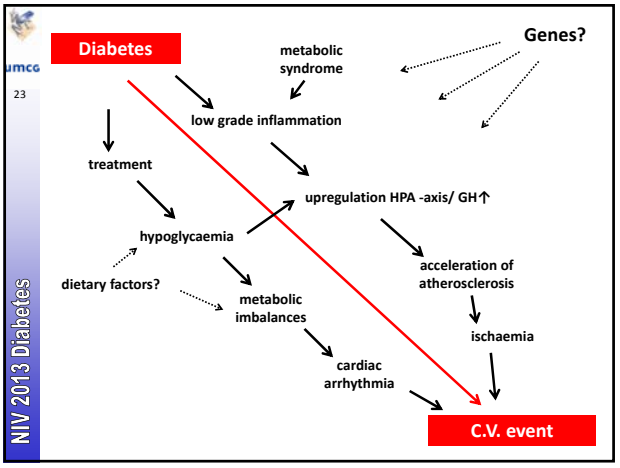
- Hypoglycaemia provokes physiological changes that affect the cardiovascular system
- Hypoglycaemia can have adverse effect on vasculature which is already damaged in diabetes
- This gives an increased risk of localized tissue ischaemia and major vascular events, e.g.:
  - Myocardial infarction
  - Cerebral ischaemia

Wright RJ and Frier BM. *Diab Metab Res Rev.* 2008;24:353-63



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Hazard ratios for all-cause mortality by HbA1c deciles

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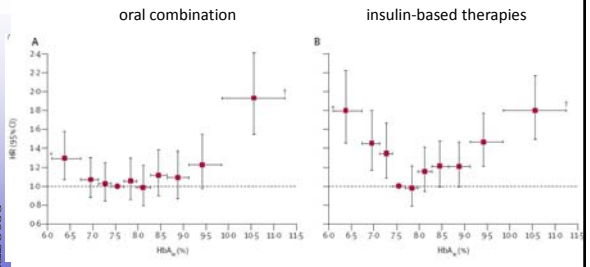

Primary care database on diabetes treatment in England:
1. Those on insulin had more c.v. disease & renal insufficiency
2. With very low HbA1c, we observe an *increase* in mortality

Currie CJ, et al. Lancet 2010; 375: 481–89

Same HbA1c, different numbers of hypoglycaemia

25

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!!

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HbA1c is NOT, I repeat NOT, the gold standard

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- Age
- gender
- BMI
- Hb, MCH, MCHC
- Current smoking
- Alcohol consumption
- Nutrition
- Certain genetic variants

All influence HbA1c levels

Low Hb → low HbA1c →
= having a serious disease → more likely to die

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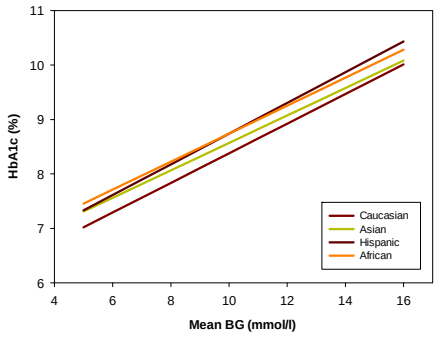
People from different ethnicities have a 0.2 – 0.5% higher HbA1c than western europeans for a given blood glucose



Wolffenbuttel et al. Diabetes Care 2013 (in press)

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New guideline: decision making to determine appropriate efforts to achieve glycaemic targets

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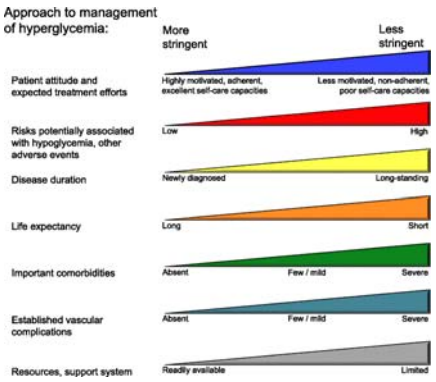

Inzucchi S E et al. Diabetes Care 2012;35:1364-79

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Statement 2

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Choose an individual target for glycaemic control depending on a patient's age, comorbidities, and ability to cope with all aspects of the disease

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HbA1c target depending on risk evaluation - 2012

30

Young < 40 years		Middle-aged 40-70 years		Elderly > 70 years	
Complications					
No	Yes	No	Yes	No	Yes
<6.0		<6.5		<7.0	
	<6.5		6.5-7.0		7.0-8.0

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

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TREATMENT ALGORITHM

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New drugs, new choices

Lifestyle intervention
(healthy food, weight reduction, physical activity)

Metformin
(metabolic control, less c.v. events, no hypoglycaemia, no weight increase

second line drug	features
Sulphonylurea	hypo, weight gain
Glinides	hypo, safe in renal insuff.
Thiazolidines	edema, c.v.d., bladder
α-Glucosidase inh.	pp. BG, GI side-effects
DPP-4 inhibitors	no hypo, neutral weight
GLP1 agonists	injections, weight loss
Insulin	injections, weight gain, BG measurements

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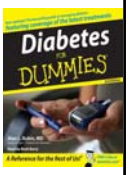
Progression of type 2 diabetes makes treatment choices / regimens more complicated



Lifestyle → Metformin → Combi tablets → GLP1 → Simple insulin → Complex insulin

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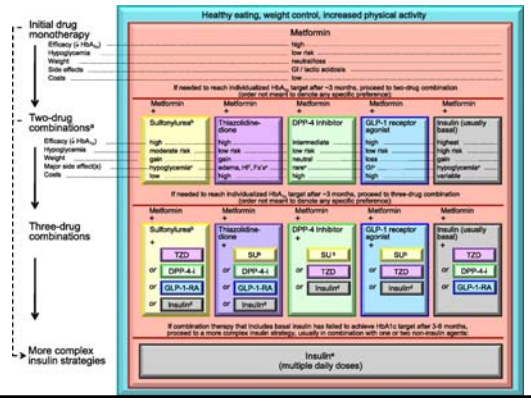
Recommendations for antihyperglycaemic therapy



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Possible choices based on 5 determinants

	Metformin + Sulfonylurea[b]	Metformin + Thiazolidine-dione
Two-drug combinations[a]		
Efficacy (↓ HbA_{1c})	high	high
Hypoglycemia	moderate risk	low risk
Weight	gain	gain
Major side effect(s)	hypoglycemia[c]	edema, HF, Fx's[c]
Costs	low	high

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	DPP-4i	GLP-1 RA	TZD	AGI	SU / GLN	INSULIN	SGLT-2
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Neutral	Loss	Gain	Neutral	Gain	Gain	Loss
RENAL/ GU	Contra-indicated Stage 3B,4,5	Dose Adjustment May be Necessary (Except Linagliptin)	Exenatide Contra-indicated CrCl < 30	May Worsen Fluid Retention	Neutral	More Hypo Risk	More Hypo Risk & Fluid Retention	Infections
GI Sx	Moderate	Neutral	Moderate	Neutral	Moderate	Neutral	Neutral	Neutral
CHF	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
CVD	Benefit			Neutral		?		
BONE	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	? Bone Loss

Few adverse events or possible benefits · Use with caution · Likelihood of adverse effects

Basic principles

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- Choice is based on patient and drug characteristics, with the over-riding goal of improving glycaemic control while minimizing side effects
- Shared decision making with the patient may help in the selection of therapeutic options
- Insulin is likely to be more effective than most other agents as a third-line therapy, especially when HbA1c is very high (e.g., ≥ 9.0%).

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Statement 3

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Choice of therapy has never been so complicated, as we have no single clue what is the best drug for the best patient

Pharmacogenomics ?

Metformin !

SU & Insulin !

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Basic principles

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- Choice is based on patient and drug characteristics, with the over-riding goal of improving glycaemic control while minimizing side effects.
- Shared decision making with the patient may help in the selection of therapeutic options
- Insulin is likely to be more effective than most other agents as a third-line therapy, especially when HbA1c is very high (e.g., ≥ 9.0%).

- **How do you want to that that when you have 5-10 minutes per patient ?**

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Pharmacogenetics in diabetes treatment ?

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Kir6.2 mutations and sulphonylurea effects

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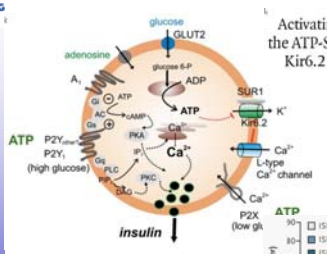
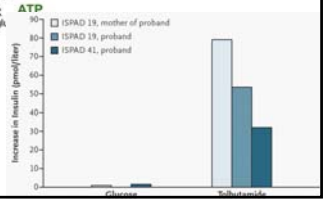


Activating Mutations in the Gene Encoding the ATP-Sensitive Potassium-Channel Subunit Kir6.2 and Permanent Neonatal Diabetes

N Engl J Med 2004; 350;1838-49



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Plasma metformine spiegels bij type 2 diabetes gebruikers van 2 dd 1 g

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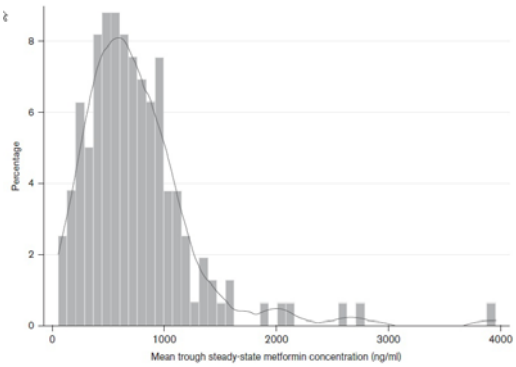

Christensen et al. Pharmacogen Genom 2011;21:837-50

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Organic cation transporter OCT/SLC22A and serum metformin levels / HbA1c decrease

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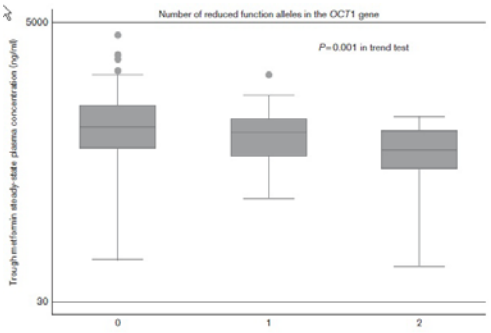

Organic cation transporter OCT/SLC22A and serum metformin levels / HbA1c decrease

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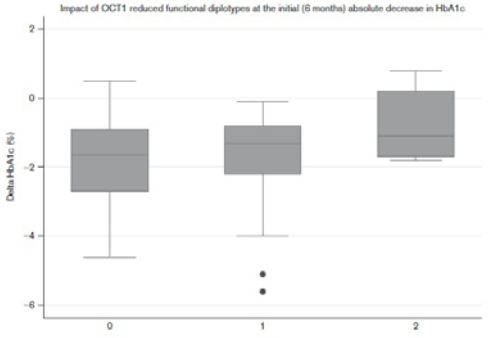

Pharmacogenetics still in its infancy

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3
INSULIN STRATEGIES

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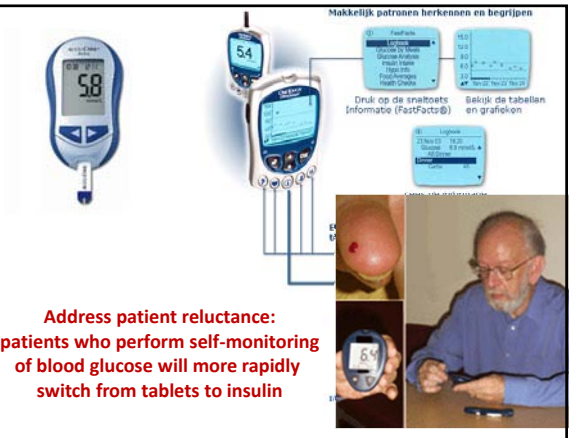

Address patient reluctance: patients who perform self-monitoring of blood glucose will more rapidly switch from tablets to insulin

Wolffenbuttel et al. Patient Educ Couns 1993;22:117-25

What do we want to achieve with insulin therapy ?

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- 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

Summary of factors for success in insulin therapy

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- **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 strategies

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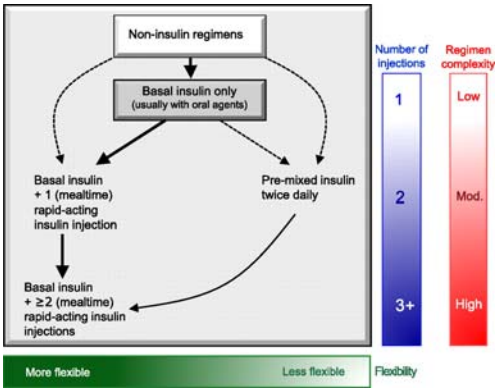

Inzucchi S E et al. Diab Care 2012;35:1364-79

Despite all guidelines, diabetes is treated differently all over Europe

Results from the INSTIGATE study

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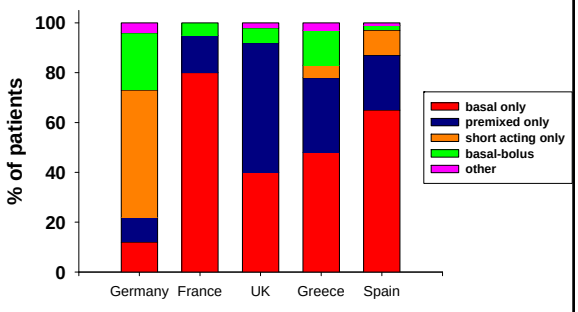

Smith H, et al. Diabetologia 2008; 51 (suppl. 1): S443

Evidence of effects of insulin regimens

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	Prandial / Intensified (basal-bolus) 3+	Conventional (premixed) 2	Basal (NPH / long-acting) 1
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	↓?	?	?

Multiple published papers 1995-2012

4T: three year effects of 3 treatment regimens

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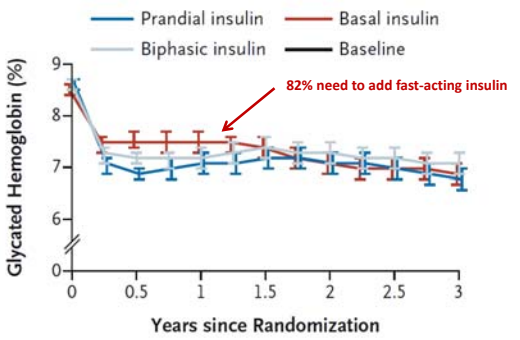

Holman R, et al. NEJM 2009

More intensive insulin treatment associated with higher body weight, insulin dose and hypoglycaemia

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	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

Insulin strategies

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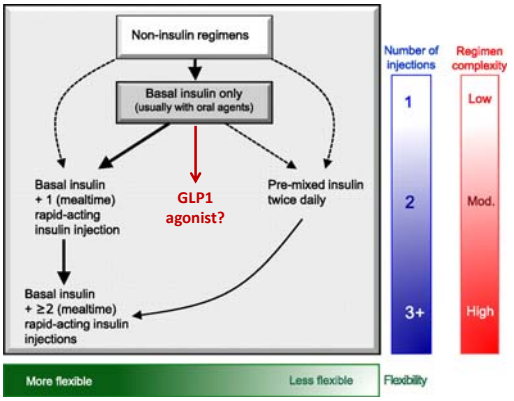

Inzucchi S E et al. Diab Care 2012;35:1364-79

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The Journal of Medicine

REVIEW

The combination of insulin and GLP-1 analogues in the treatment of type 2 diabetes

M.M. van der Klauw*, B.H.R. Wolffenbuttel

Department of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, *corresponding author: tel. +31 (0)50 3613962, fax +31 (0)50 3619392, e-mail m.m.van.der.klauw@umcg.nl. Both authors contributed equally to this review

Adding GLP-1 analogues to insulin has the benefit of reducing HbA1c as well as weight, while we know that the major problem with uptitrating insulin is weight gain. Further randomised trials will be needed to confirm what was found in these (mostly observational) studies.

Neth J Med 2012; 70: 436-443

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Statement 4

90% of the clinical studies are of limited values, since they do not compare NEW with CURRENT treatments so that we can change our algorithms

Active, not recruiting

The Effect of Liraglutide Versus Placebo When Added to Basal Insulin Analogues With or Without Metformin in Subjects With Type 2 Diabetes

Conditions: Diabetes; Diabetes Mellitus, Type 2

Interventions: Drug: liraglutide; Drug: placebo

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4
SOME ADDITIONAL THOUGHTS

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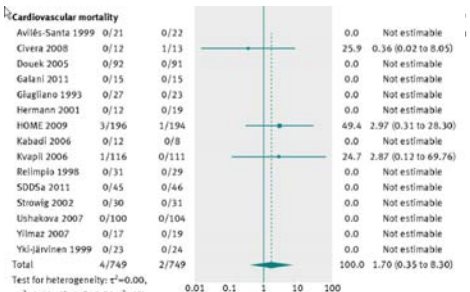
Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses

OPEN ACCESS



BMJ 2012;344:e1771 doi: 10.1136/bmj.e1771 (Published 19 April 2012)

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Recent arousal ?

Mortality and Other Important Diabetes-Related Outcomes With Insulin vs Other Antihyperglycemic Therapies in Type 2 Diabetes

Craig J. Currie, Chris D. Poole, Marc Evans, John R. Peters, and Christopher LI. Morgan

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"In T2DM, exogenous insulin associated with increased risk of diabetes-related complications"

JCEM 2013; 98:668-77.

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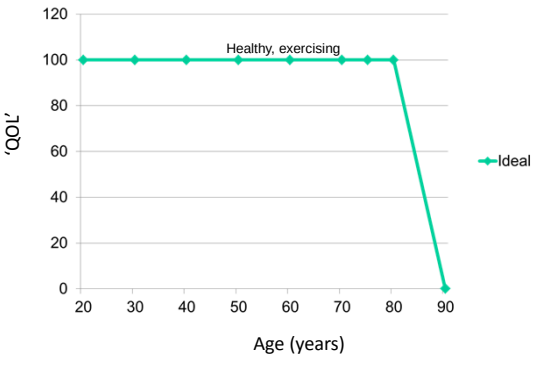
Health career paths in type 2 diabetes



Health career paths in type 2 diabetes

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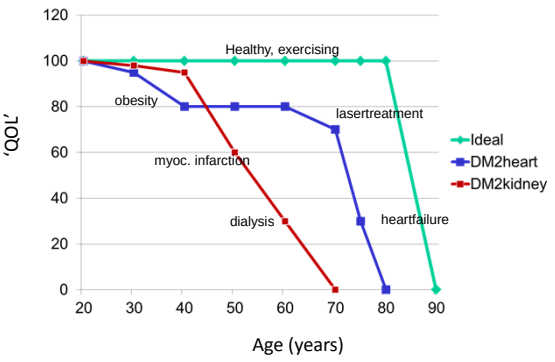

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Health career paths in type 2 diabetes

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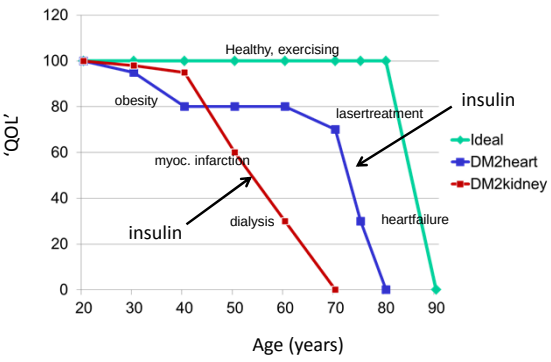

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Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

This article (10.1056/NEJMoa072761) was published at www.nejm.org on May 21, 2007.

N Engl J Med 2007;356:2457-71.

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DPP-4 inhibitors & cardiovascular risk

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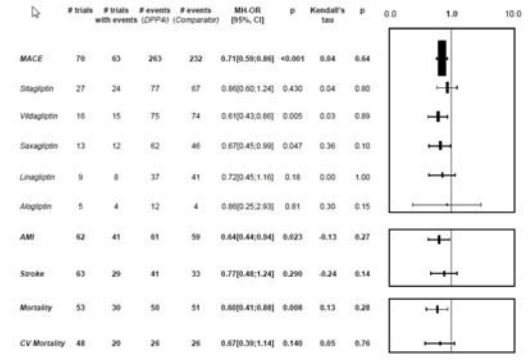

Monami M, et al. Diab Obes Metabol 2012 (online)

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Glucagon immunoreactivity associated with incretin therapy

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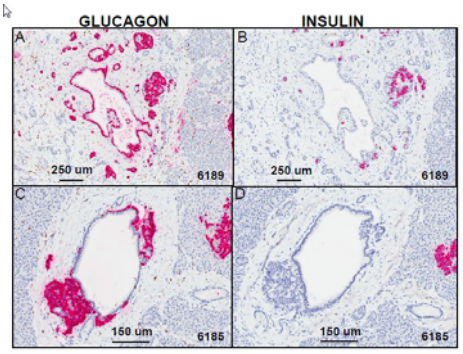

Butler EA, et al. Diabetes. 2013 Mar 22. [Epub ahead of print]

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SGLT2 inhibitors

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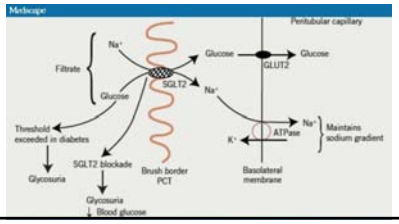
dapagliflozin
canagliflozin
empagliflozin



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Prospective evaluation of new drugs very needed

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RICHTLIJNEN VOOR POST AUTHORISATIE STUDIES

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'Proeftuinconcept' krijgt vorm in BIDON

November 2011

Op 6 oktober werd de stichting Innovatief Diabetes Onderzoek Nederland, ofwel BIDON, opgericht. Een mijlpaal in het realiseren van het 'proeftuinconcept', waar de NDF al lang naar streeft. Kenmerkend voor een proeftuin is dat gedurende een afgebakende periode, vergoeding mogelijk is van een nieuw geneesmiddel of behandelstrategie, onder vooraf vastgestelde voorwaarden en in combinatie met aanvullende dataverzameling. Kennis over effectiviteit komt sneller beschikbaar juist door bij nieuwe behandelvormen op gestructureerde wijze gegevens en ervaringen uit de klinische praktijk te bundelen in nationaal samenwerkingsverband. Deze kennis ondersteunt een versnelde en effectieve toepassing van nieuwe behandelwijzen en daarmee de kwaliteit van diabeteszorg.

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SGLT2-inh

Type 2 diabetes treatment is getting more difficult

Conclusions - 1

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- Targets for optimal glycaemic goals take a patient's age and comorbidity into consideration
- Beware of hypoglycaemia !!
- Choice of specific drug treatment is based on patient and drug characteristics, with the over-riding goal of *improving glycaemic control while minimizing side effects*
- A variety of drugs are available, none of them is the ideal drug, all have side-effects, some are cheap

Conclusions - 2

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- Only few drugs -if any- really address the pathophysiologic disturbances in type 2 diabetes
- Shared decision taking with a patient takes time, and also a well-informed patient
- Treatment of type 2 diabetes has become increasingly difficult, but also flexible

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Diabetes therapy → personalized medicine ???

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