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Landmark Studies

Landmark studies in diabetes

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Landmark Studies

Presentation outline

- glycaemic targets in guidelines
- postprandial blood glucose
- treatment algorithm
- what is successful diabetes treatment, and for whom?
- results of recent trials
- hypoglycaemia predicts CV events
- hypoglycaemia limits optimized control
- tailored therapy is necessary

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Landmark Studies

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 …

IDF

- Advise people with diabetes that maintaining a DCCT-aligned HbA1c below 6.5 % should minimize their risk of developing complications

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

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Landmark Studies

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), HbA_{1c} 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

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Landmark Studies

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

- A 72-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), HbA_{1c} 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

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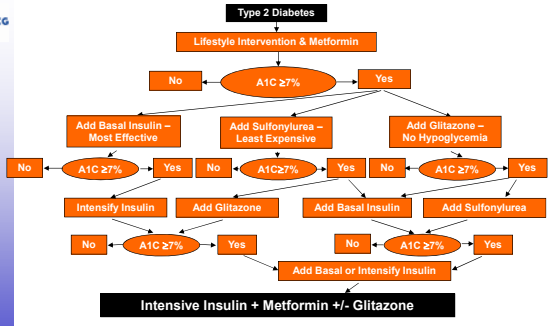
Landmark Studies

ADA/EASD Algorithm



Adapted from Nathan DM, et al. *Diabetes Care* 2006;29:1963-1972

Stapsgewijze behandeling type 2 diabetes

1. Lifestyle interventie
(gezonde voeding, afvallen, lich. inspanning)

2. Metformine
(metabole regulatie, minder CV events)
geen hypoglycemie, geen toename gewicht

3. Tweede (oraal) middel

SU	Glin	TZD	α-GI	DPP-4-Inh.	Ins.	Incretine mimetica
weinig gebruikt			weinig gebruikt	nieuw		nieuw

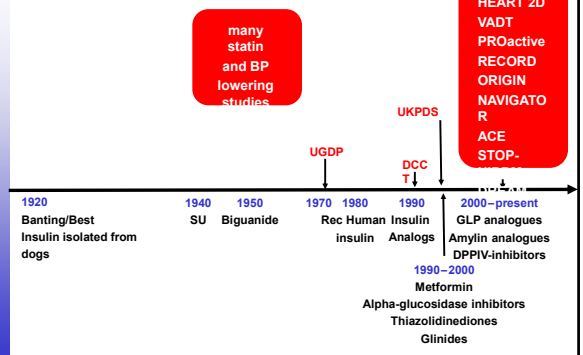
Landmark Studies

Additional goals of therapy ? Still many questions left !

- Evidence suggest to normalize glucose, blood pressure, lipids, body weight
- Should we strive for HbA1c below 7% ?
- If yes, what evidence that lower HbA1c will prevent CVD ?
- Special focus on postprandial blood glucose control?

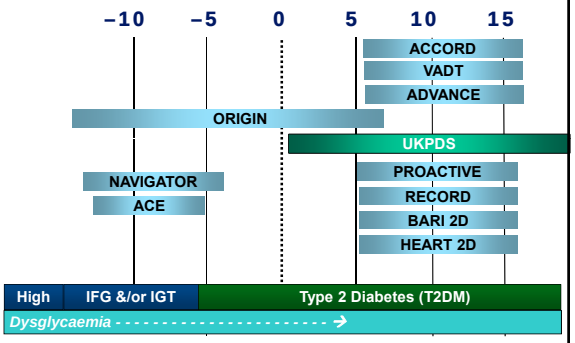
Landmark Studies

Timeline of development of diabetes therapies and landmark trials



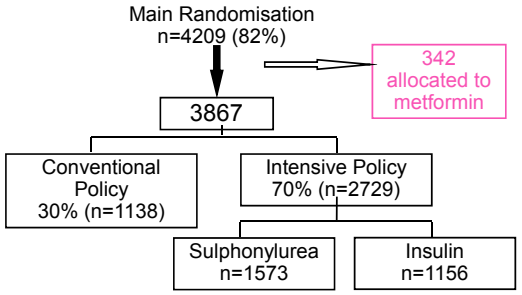
Landmark Studies

Glucose lowering to prevent CVD: Trials in people with dysglycaemia



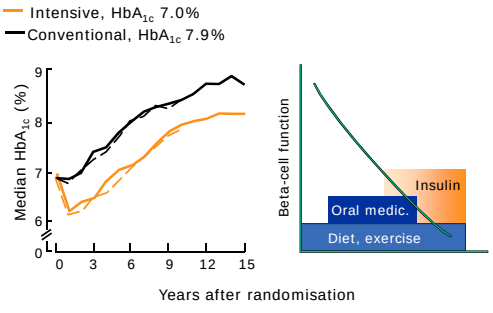
Landmark Studies

UKPDS glucose control study



Landmark Studies

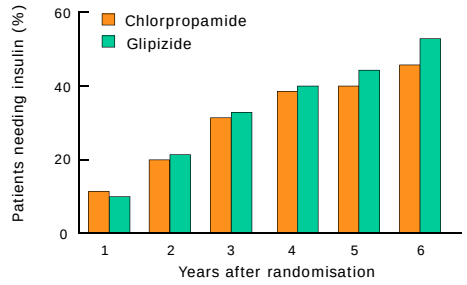
Diabetes is a progressive disease



Adapted from: UKPDS Study Group 1998

Landmark Studies

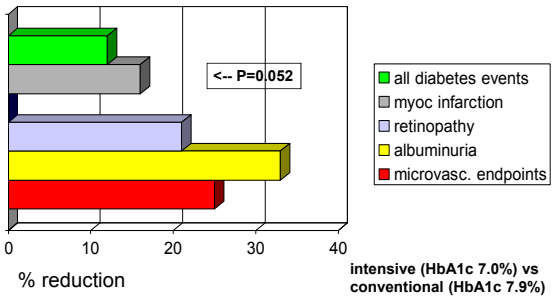
UKPDS: with advancement of time more insulin



Adapted from: Diabetes Care 2002;25:330–6

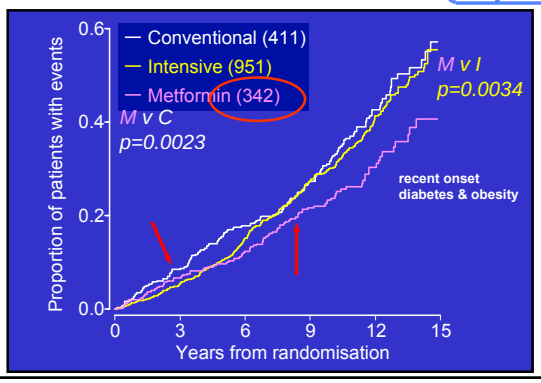
Strict glycaemic control with sulphonylurea* or insulin saves lives or limbs !

* chlorpropamide, glibenclamide !!



Metformin reduces complications, but please be patient (and obese)

ukpds



Non–UKPDS Trials: Metformin vs. other interventions

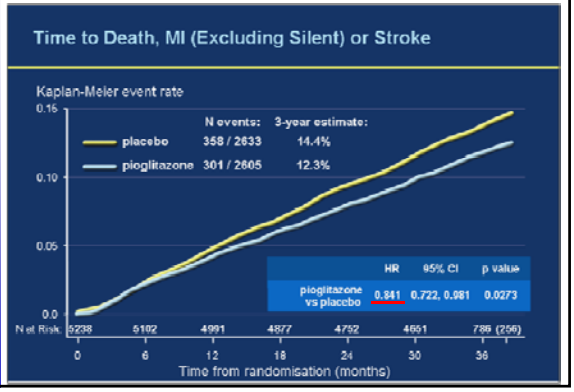
Study	MET n/N	Comparison	RR (Fixed) 95% CI Favours Metformin	RR (Fixed) 95% CI Favours Comparison	Weight (%)	RR (fixed) 95% CI
All-cause mortality						
DeFronzo 1995	1/210	0/209			49.6	2.99 [0.12, 72.88]
Horton 2000	1/178	0/172			50.4	2.90 [0.12, 70.69]
Subtotal (95% CI)	388	381			100.0	2.94 [0.31, 28.16]
Ischemic heart disease						
DeFronzo 1995	1/210	0/209			25.2	2.99 [0.12, 72.88]
Hallsten 2002	1/13	0/14			24.2	3.21 [0.14, 72.55]
Horton 2000	1/178	0/172			25.5	2.90 [0.12, 70.69]
Teupe 1991	1/50	0/50			25.1	3.00 [0.13, 71.92]
Subtotal (95% CI)	451	445			100.0	3.02 [0.62, 14.75]

0.01 0.1 1 10 100

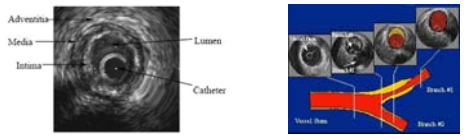
Saenz A, et al. *Cochrane Database Syst Rev.* 2005;(3):CD0

Pioglitazone reduces c.v. events in type 2 diabetics with existing CVD

PROactive

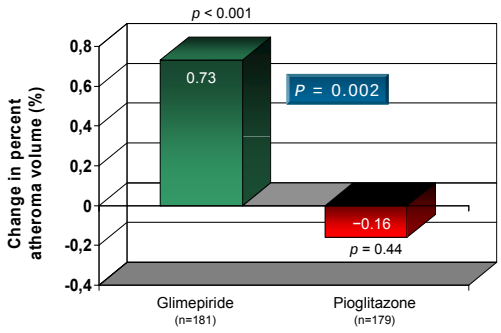


PERISCOPE: Study Design



Adapted from Nissen SE, et al. *JAMA.* 2008;299:1561-73

PERISCOPE primary efficacy parameter: *change in percent atheroma volume*



Adapted from Nissen SE, et al. *JAMA*. 2008;299:1561-73

2008: the results of three long-awaited studies are presented

ADVANCE

ACCORD

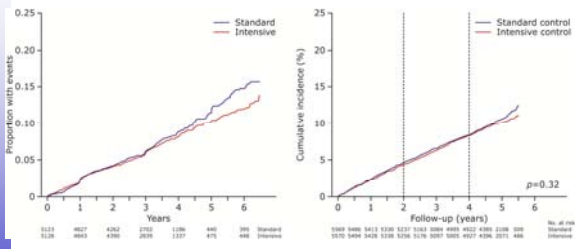
VADT

Which lessons can be learned from these clinical trials ?

AAV: heterogenic inclusion criteria

- *ADVANCE*: age > 54 yrs, and
  - earlier macrovascular or microvascular complication, or
  - at least one other risk factor for c.v. disease
- *ACCORD*: HbA1c ≥ 7.5%, and
  - a. 40-79 yrs and c.v. disease, or
  - b. 55-79 yrs and
    1. significant atherosclerosis, albuminuria, LVH, or
    2. at least 2 additional risk factors for c.v. disease
- *VADT*: veterans, age > 41 yrs, HbA1c > 7.5%, no major c.v. events in the previous 6 months

Macrovascular Outcomes



ACCORD ADVANCE

AAV overall results

- ADVANCE:
  - no cardiovascular benefit, but *reduction proteinuria*
- ACCORD:
  - no benefit primary endpoint
  - in pat's without baseline c.v. events reduction non-fatal MI
  - 3-fold increase severe hypoglycemia
  - *intensive arm stopped prematurely* because of side-effects
- VADT:
  - *no benefit primary endpoint*
  - 3-fold increase severe hypoglycaemia

adapted from: ADA presentations ADVANCE, ACCORD, VADT, June 2008

AAV: differences in baseline characteristics

	ACCORD	ADVANCE	VADT
Diabetes duration (yr)	Median 10	8.0±6.4	11.5±7.7
Age (yr)	62±7	66±6	60±10
BMI (kg/m²)	32.2±5.5	28±5	31.3±4.6
Baseline HbA1c (%)	8.3±1.1	7.5	9.4±1.5
On trial HbA1c	6.4 vs 7.5	6.5 vs 7.3	6.9 vs 8.4
Blood pressure	136 / 75	145 / 81	132 / 76
Hypertension (%)	?	> 75	72
Prior macrovasc events (%)	35	32	40

ACCORD vs. ADVANCE vs. PROactive in perspective

Landmark Studies

	ACCORD		ADVANCE		VADT	
	Std	Int	Std	Int	Std	Int
On trial HbA1c (%)	7.5	6.4	7.30	6.53	8.4	6.9
Insulin use (%) *	55	*77*	24	40	70	90
Metformin use (%)	87	*95*	67	74	57	61
All-cause mortality (/1000/yr)	11.3	*14.3* *HR 1.22*	19.1	17.9	18.9	20.4
Nonfatal MI (/1000/yr)	13.1	*10.4* *HR 0.76*	5.6	5.5	15.5	12.8
Nonfatal stroke (/1000/yr)	3.4	3.7	7.5	7.7	7.2	5.6

* at study end

Speculations on possible causes of increased mortality in ACCORD

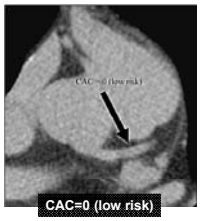
Landmark Studies

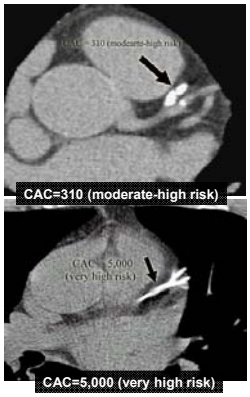
- Specific population characteristics
  - avg age 62 yrs, diabetes duration 10 yrs.
- Rapid reduction of HbA1c
- Hypoglycaemia and consequent c.v. event
- Drug interactions
- Statistical error
- Other …

Does VADT give an answer ??

Coronary Artery Calcium Score (CAC)

Landmark Studies



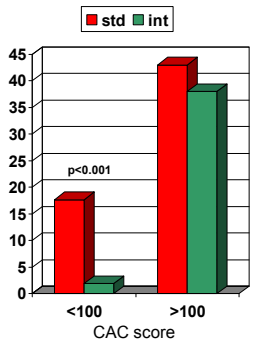


VADT substudy RACED: *Risk Factors, Atherosclerosis and Clinical Events in Diabetes*

Primary endpoint in VADT substudy

Landmark Studies

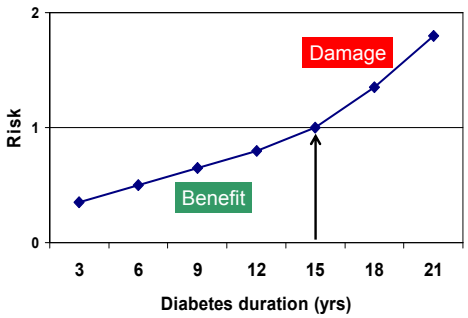
- CAC score in 301 VADT participants
- 40% had CAC score > 400
- CAC predicted new events
- Intensive therapy is especially effective in low CAC score



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

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

Landmark Studies



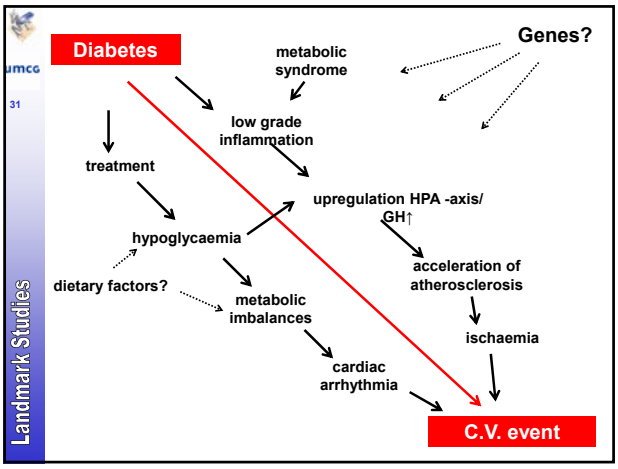
adapted from: Duckworth. ADA presentation VADT, June 2008

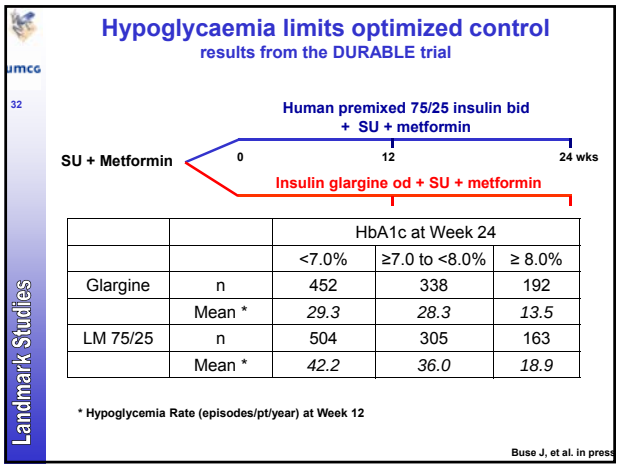
Hypoglycaemia predicts c.v. events

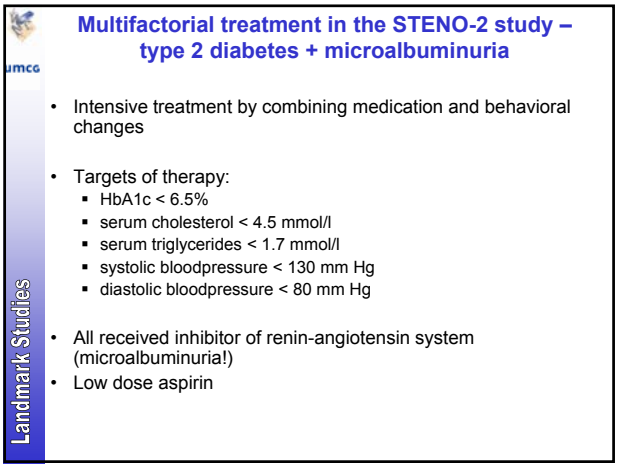
Landmark Studies

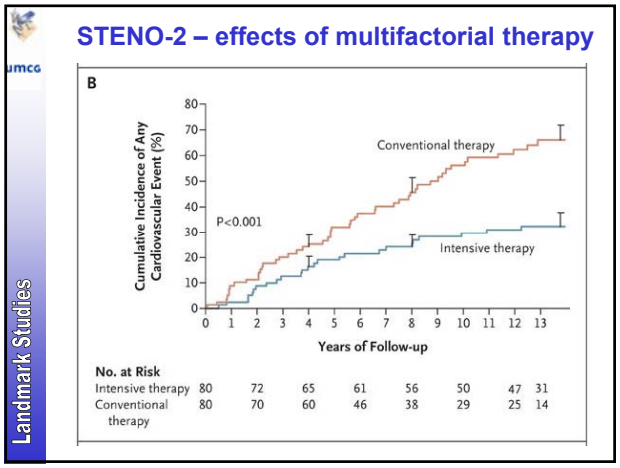
- Hypoglycaemia provokes physiological changes that affects cardiovascular system
- Can have adverse effect on vasculature already damaged in diabetes
- Increased risk of localized tissue ischaemia and major vascular events
  - Myocardial infarction
  - Cerebral ischaemia

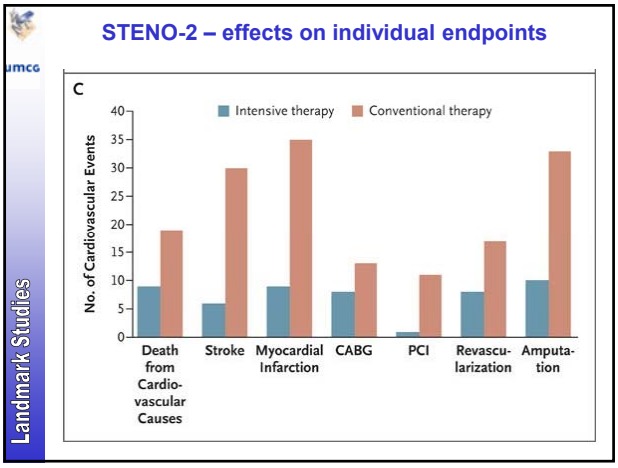
Wright RJ and Frier BM. *Diab Metab Res Rev.*

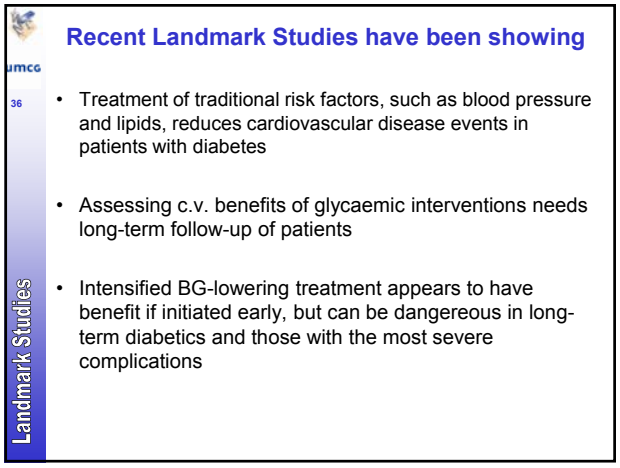

Diabetes
metabolic syndrome
Genes?
low grade inflammation
treatment
upregulation HPA -axis/ GH↑
hypoglycaemia
acceleration of atherosclerosis
dietary factors?
metabolic imbalances
ischaemia
cardiac arrhythmia
C.V. event
Landmark Studies


Hypoglycaemia limits optimized control
results from the DURABLE trial
Human premixed 75/25 insulin bid + SU + metformin
SU + Metformin
0
12
24 wks
Insulin glargine od + SU + metformin
HbA1c at Week 24
<7.0%
≥7.0 to <8.0%
≥ 8.0%
Glargine
n
452
338
192
Mean *
29.3
28.3
13.5
LM 75/25
n
504
305
163
Mean *
42.2
36.0
18.9
* Hypoglycemia Rate (episodes/pt/year) at Week 12
Buse J, et al. in press
Landmark Studies


Multifactorial treatment in the STENO-2 study – type 2 diabetes + microalbuminuria
• Intensive treatment by combining medication and behavioral changes
• Targets of therapy:
▪ HbA1c < 6.5%
▪ serum cholesterol < 4.5 mmol/l
▪ serum triglycerides < 1.7 mmol/l
▪ systolic bloodpressure < 130 mm Hg
▪ diastolic bloodpressure < 80 mm Hg
• All received inhibitor of renin-angiotensin system (microalbuminuria!)
• Low dose aspirin
Landmark Studies


STENO-2 – effects of multifactorial therapy
B
Cumulative Incidence of Any Cardiovascular Event (%)
Conventional therapy
P<0.001
Intensive therapy
Years of Follow-up
No. at Risk
Intensive therapy 80 72 65 61 56 50 47 31
Conventional therapy 80 70 60 46 38 29 25 14
Landmark Studies


STENO-2 – effects on individual endpoints
C
Intensive therapy
Conventional therapy
No. of Cardiovascular Events
Death from Cardio-vascular Causes
Stroke
Myocardial Infarction
CABG
PCI
Revascu-larization
Amputa-tion
Landmark Studies


Recent Landmark Studies have been showing
• Treatment of traditional risk factors, such as blood pressure and lipids, reduces cardiovascular disease events in patients with diabetes
• Assessing c.v. benefits of glycaemic interventions needs long-term follow-up of patients
• Intensified BG-lowering treatment appears to have benefit if initiated early, but can be dangereous in long-term diabetics and those with the most severe complications
Landmark Studies

Recent Landmark Studies have been showing

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- Hypoglycaemia predicts c.v. events
- For some patients and/or physicians, hypoglycaemia limits their willingness to increase insulin doses.

Landmark Studies

Postprandial BG as a target ?

a little dessert

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Landmark Studies

HEART2D: prandial vs. basal strategy in type 2 diabetic patients post-MI

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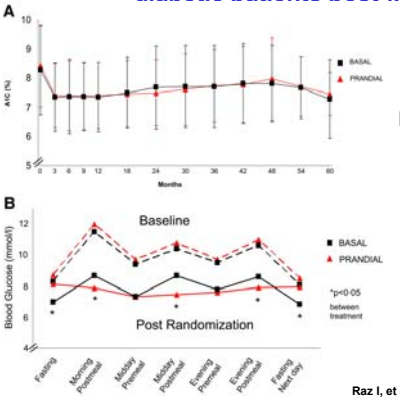

Age 61±10 yrs
BMI 29.1±4.6
Diabetes duration 9.2± 7 yrs

Raz I, et al. Diabetes Care 2009; 32: 38

Landmark Studies

HEART2D: no effect of prandial strategy in type 2 diabetic patients post-MI

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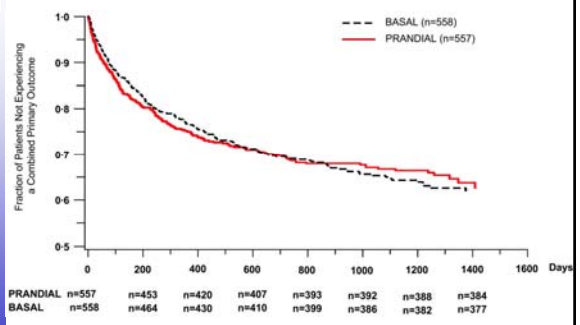

Raz I, et al. Diabetes Care 2009; 32: 38

Landmark Studies

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

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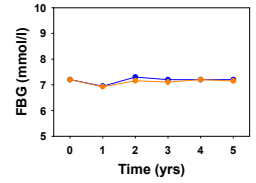

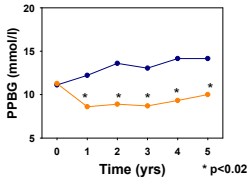

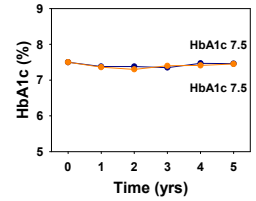

374 Japanese pat's w. T2DM
3 injections fast-acting insulin,
NPH if needed

Regular (Actrapid) vs Insulin aspart (NovoRapid)

Nippon ultrapid Insulin & diabetic Complications Evaluation (NICE)

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

Landmark Studies

. . . reduces cumulative c.v. events

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

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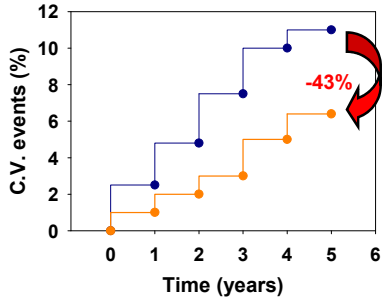

HR 0.57
CI: 0.34-0.95
(p<0.02)

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

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

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Landmark Studies

- These data on postprandial BG control support the concept of intensified BG-lowering treatment early in the course of diabetes
- This concept is comparable with data in type 1 diabetes (DCCT)

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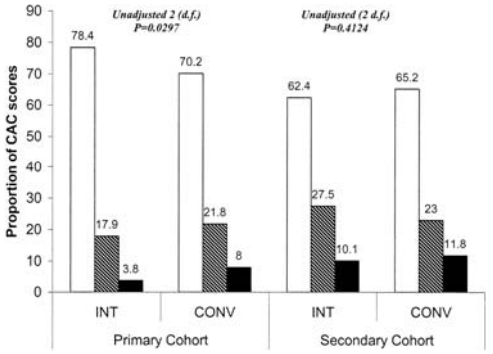
Landmark Studies

Distribution of CAC scores (Agatston units) by cohort and treatment group 8 years after DCCT



Cleary et al. Diabetes 2006; 55: 3556-65

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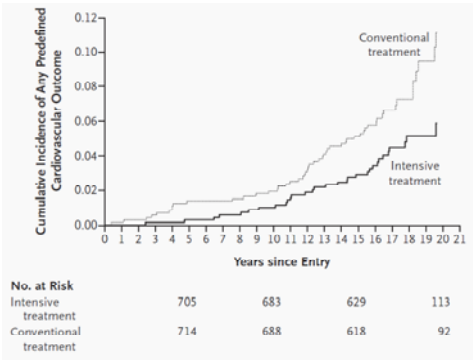
Landmark Studies

Incidence of CVD in type 1 diabetes during follow-up after DCCT



DCCT/EDIC Study Research group. NEJM 2005; 353:2643

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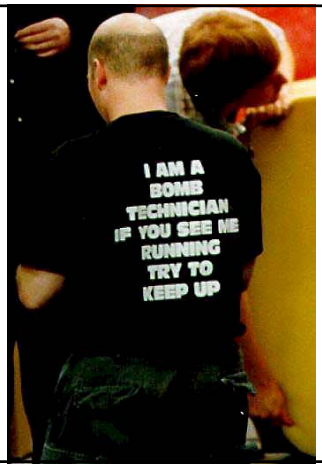
Landmark Studies



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