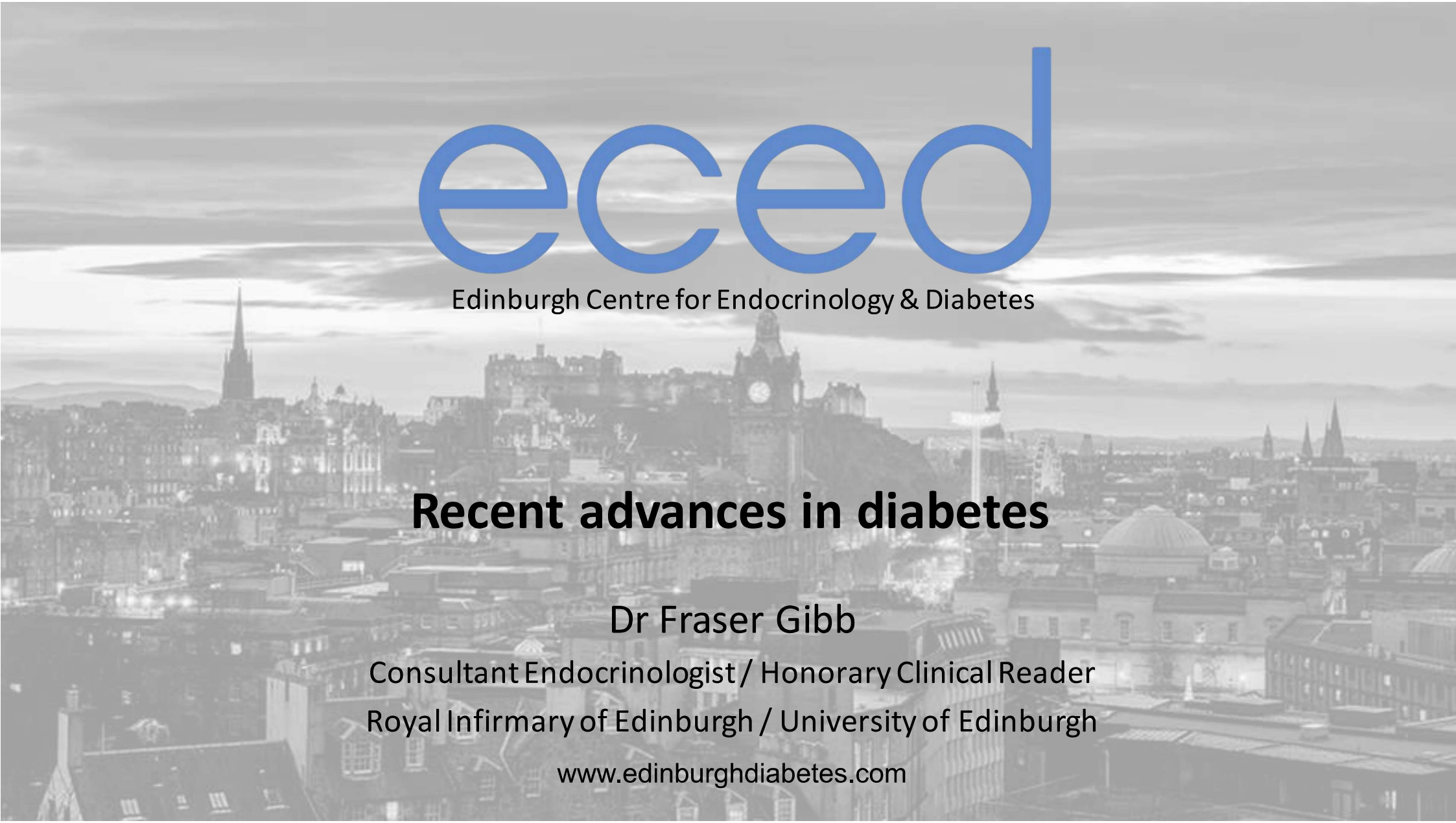


Edinburgh Centre for Endocrinology & Diabetes

Recent advances in diabetes

Dr Fraser Gibb

Consultant Endocrinologist / Honorary Clinical Reader

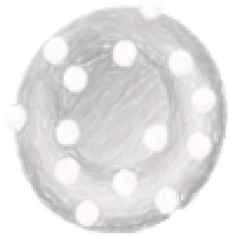
Royal Infirmary of Edinburgh / University of Edinburgh

www.edinburghdiabetes.com

Types of diabetes

Why it matters

HbA1c



Blood test in clinic

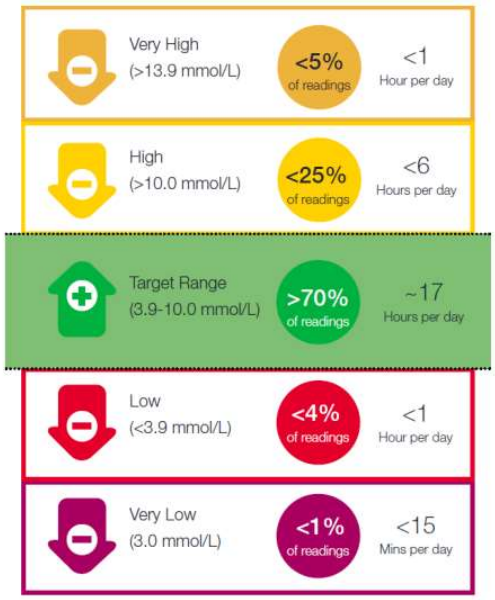
Amount of glucose attached to haemoglobin

Gives a measure of glucose control over the past 2 – 3 months

HbA1c <53 mmol/mol (7%) as a typical target

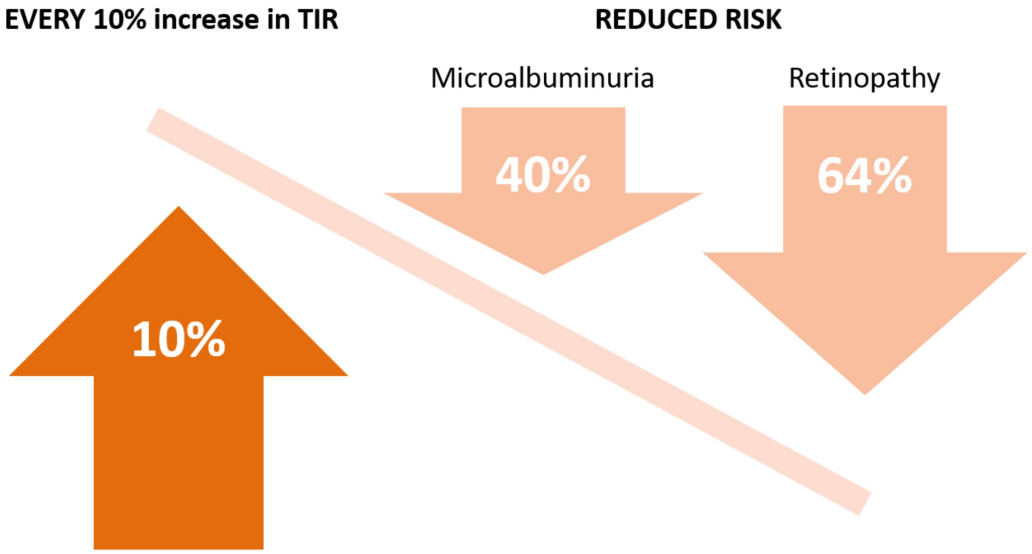
Doesn't take into account low glucose or variability

CGM metrics

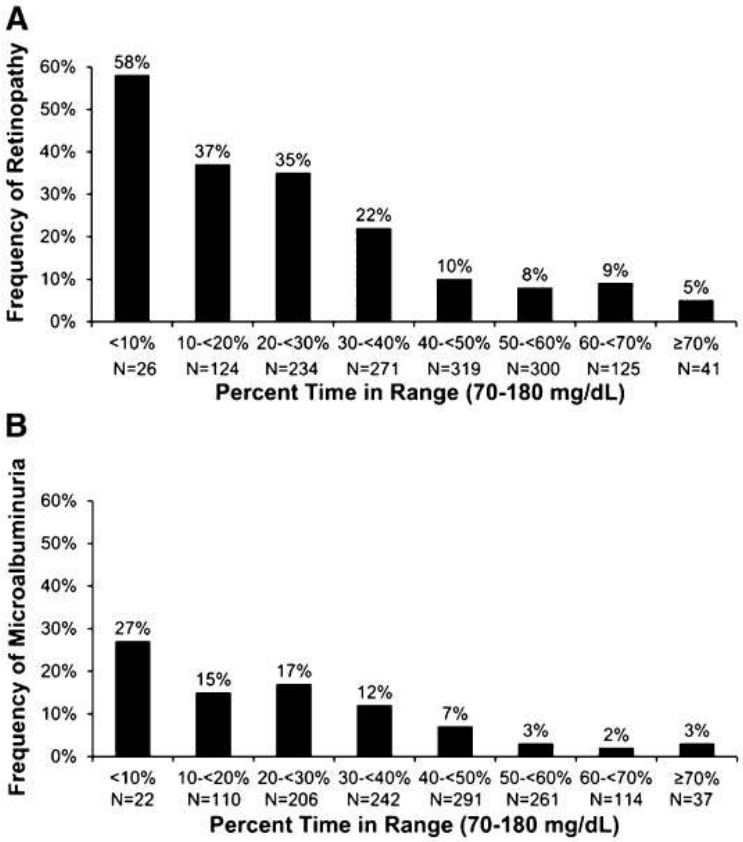


Time in range

Relationship to microvascular complications



Adapted from: Beck RW et al. *Diabetes Care* 2018;42:400–405; Lu J et al. *Diabetes Care* 2018;41:2370–2376.



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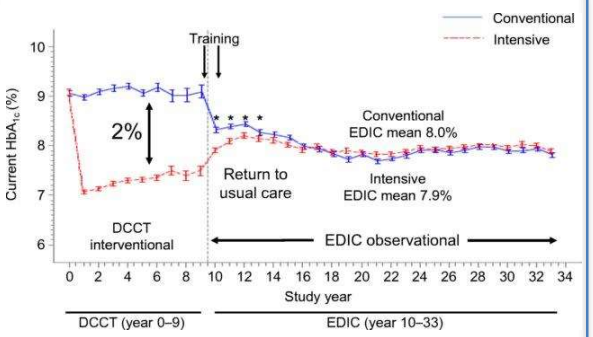
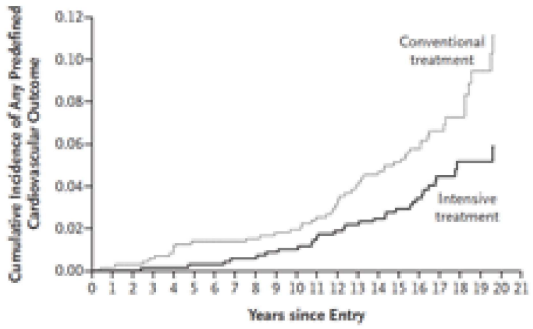
The importance of effective treatment

2020s diabetes – 1980s outcomes?



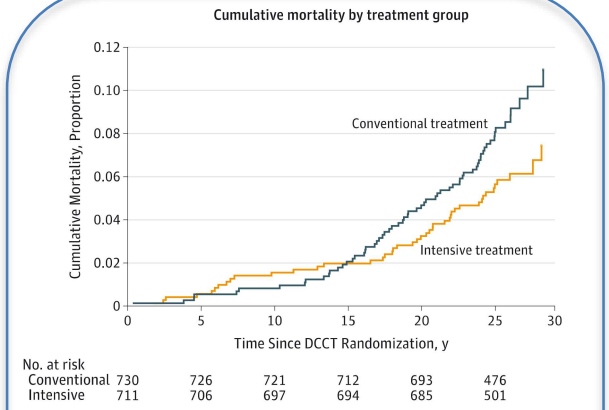
2% (22mmol/mol) HbA1c difference for 6.5 years

Diabetologia (2021) 64:1049–1058
https://doi.org/10.1007/s00125-021-05397-4



Cardiovascular disease risk reduced by 42%

N Engl J Med 2005; 353: 2643-53.

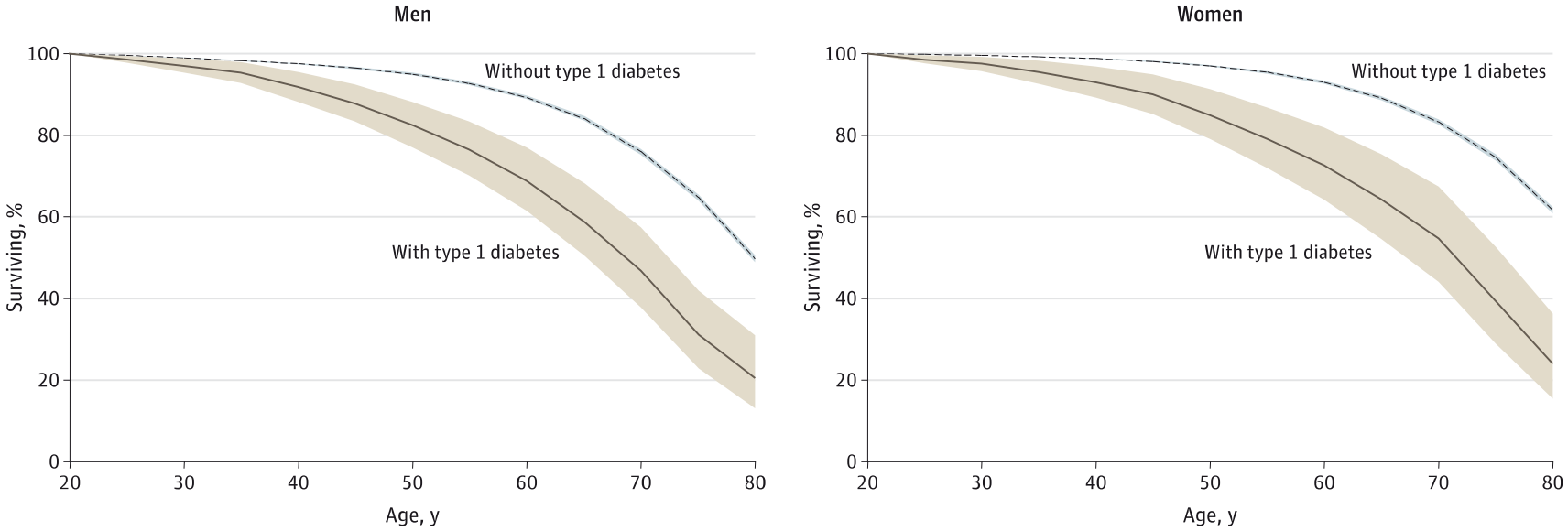


Risk of death reduced by 33%

JAMA 2015; 313(1): 45-53.

Type 1 diabetes excess mortality

Significant loss of life – an average of 12 years in Scotland



Estimated Life Expectancy in a Scottish Cohort With Type 1 Diabetes, 2008-2010

Shona J. Livingstone, MSc; Daniel Levin, MSc; Helen C. Looker, MBBS; Robert S. Lindsay, FRCP; Sarah H. Wild, FRCP; Nicola Joss, MD; Graham Leese, MD; Peter Leslie, MD; Rory J. McCrimmon, FRCP; Wendy Metcalfe, MD; John A. McKnight, FRCP; Andrew D. Morris, FRCP; Donald W. M. Pearson, FRCP; John R. Petrie, MD; Sam Philip, MD; Naveed A. Sattar, FRCP; Jamie P. Traynor, MD; Helen M. Colhoun, MD; for the Scottish Diabetes Research Network epidemiology group and the Scottish Renal Registry

JAMA. 2015;313(1):37-44. doi:10.1001/jama.2014.16425

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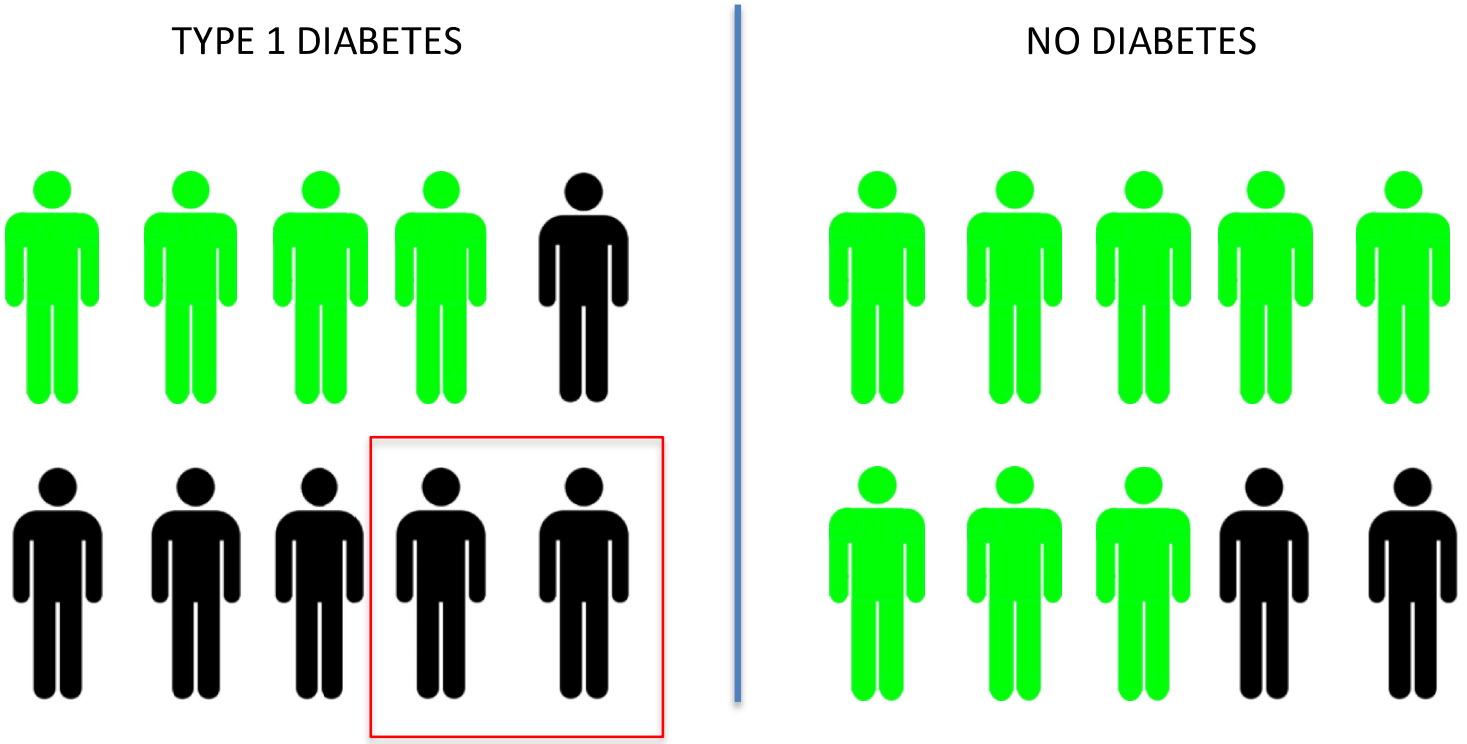
Expected loss of life at age 70

The effect of type 1 diabetes



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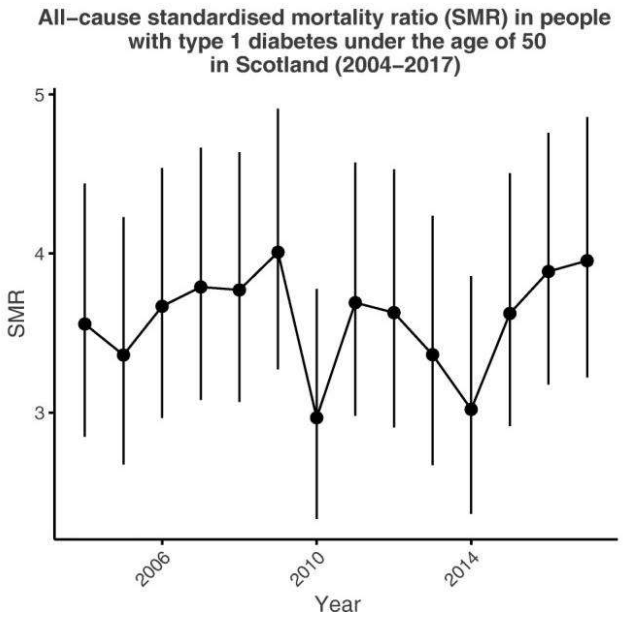
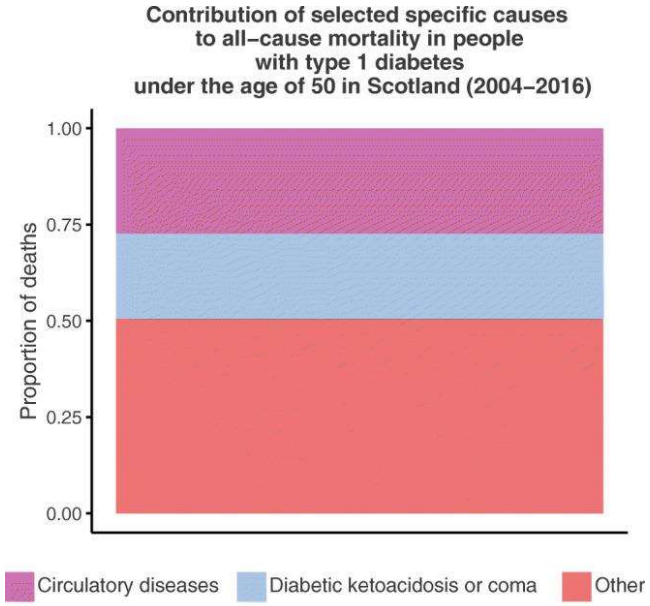
Mortality in T1 diabetes

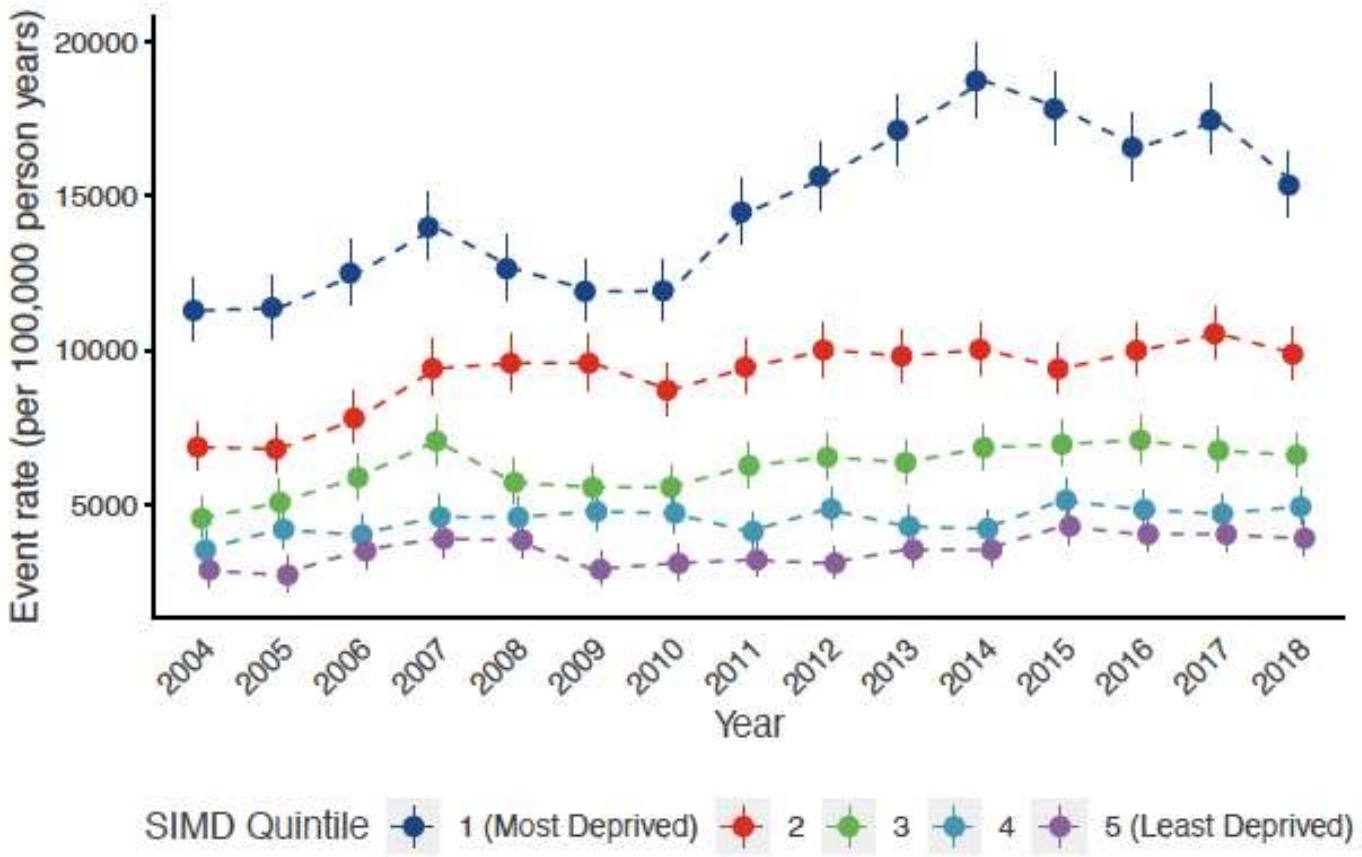
In people under 50 years of age





DKA trends in Scotland

Widening socioeconomic disparity



Diabetes Care 2021;44(9):2010–2017
https://doi.org/10.2337/dc21-0689

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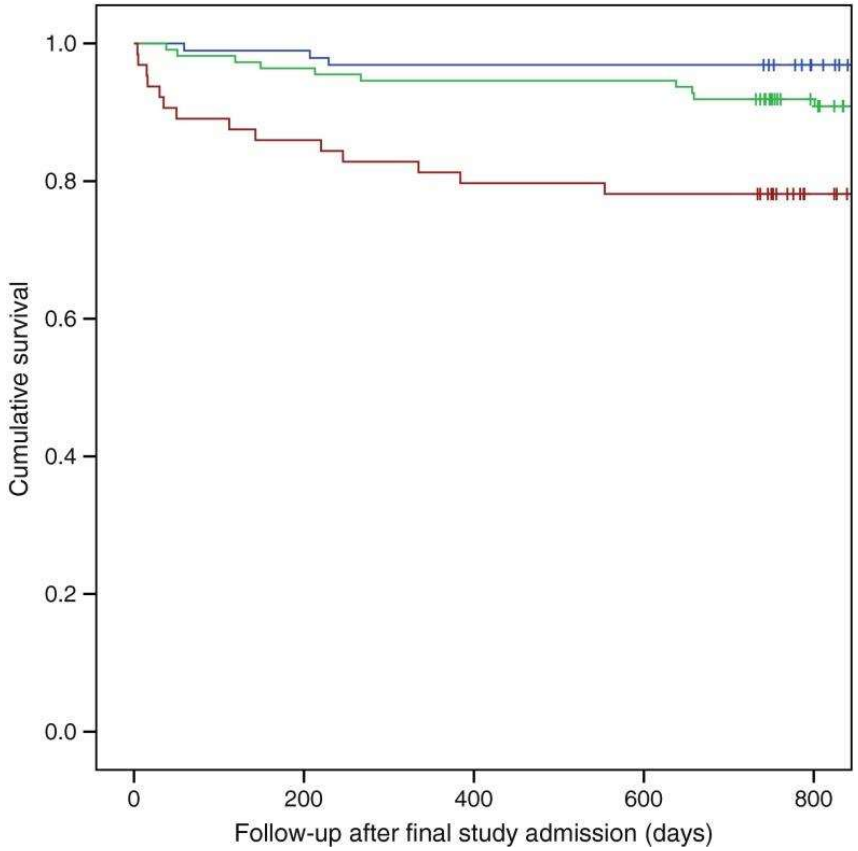
Diabetic Ketoacidosis

Association with subsequent mortality



Diabetes timeline

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for Endocrinology &
Diabetes

1920s

Frederick Grant Banting
1891-1941

Banting developed the research idea and in collaboration with Banting made most of the experiments and surgeries.

Charles Herbert Best
1899-1978

Best collaborated with Banting on most of the experiments and surgeries that led to the discovery of insulin.

John James Rickard MacLeod
1876-1935

MacLeod provided the laboratry and scientific guidance through all research steps. He had an active role in the final steps of isolating and purifying of insulin.

James Bertram Collip
1892-1965

Collip played a central role isolating and purifying insulin.

1940s


CLINITEST
2132
6 TEST TUBES
ames
CLINITEST
REAGENT TABLETS FOR URINALYSIS
TEST FOR URINE SUGAR
FOR IN VITRO DIAGNOSTIC USE
POISON:
ames
36 REAGENT TABLETS


Standard Procedure
TESTING:
1/4%
1/2%
3/4%
1%
2% or more

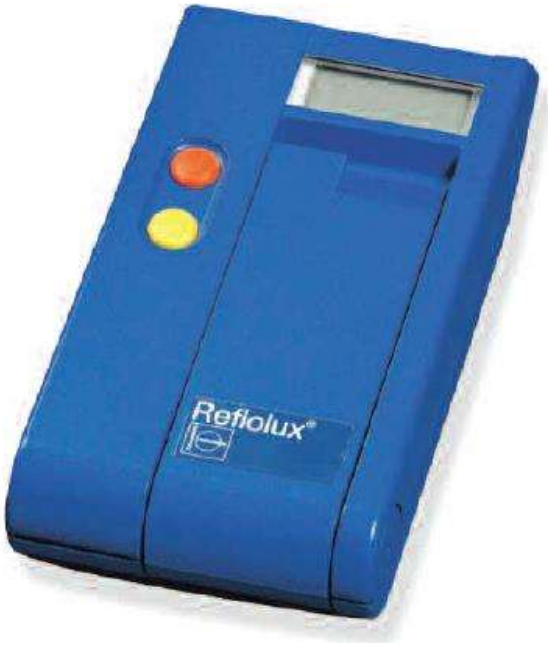
1960s

1970s


Reflomat


Dextrostix
Ames
REFLECTANCE METER
Dextrostix
Ames

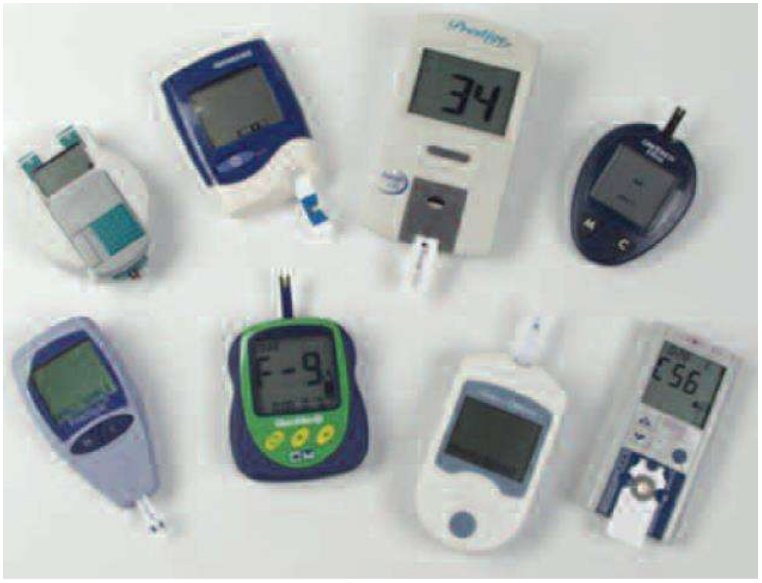
1980s


Reflolux®

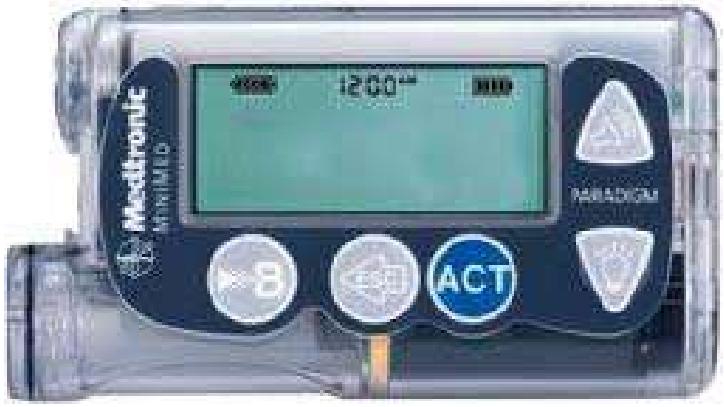

AUTO SYRINGE®
EUGLY Infusion Pump
BOLUS
TIME
T of RC
BASAL
B
A
P/R
BOLUS
AUDIO
PRG/RN
1
2
3
4
5
6
7
8
9
C
0
E
CLEAR
ENTER


NovoPen

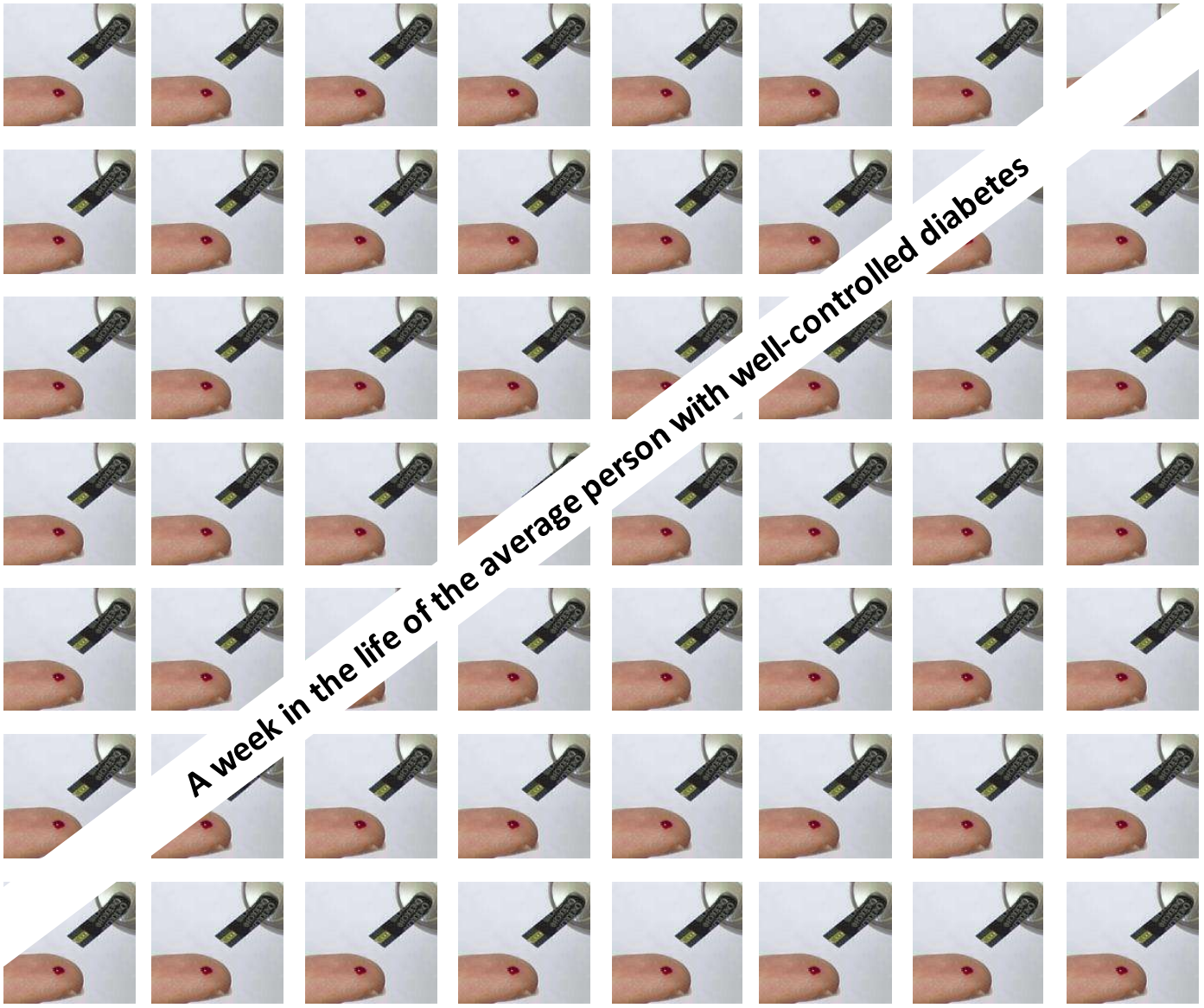
1990s



2000s


Medtronic
MiniMED
ACT
PARADIGM


FreeStyle
Navigator
85
mg/dL
Acknowledge
Main

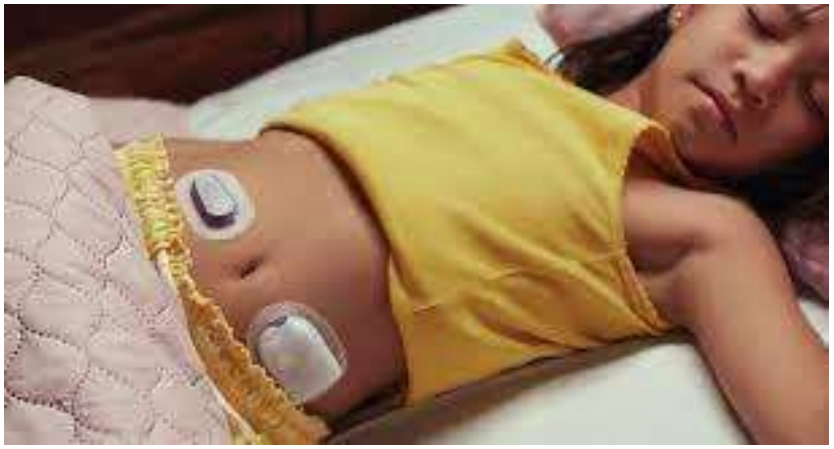

A week in the life of the average person with well-controlled diabetes

2010s


Android APS...
8.0
0min ago
Δ 0.2 mmol
CANCEL: E 1.30U/H @23:08 0/30MIN
BOLUS
CALCULATOR
CALIBRATION


10:00
120
0.5 U

2020s




3:41 pm
mg/dL 127
Carbs
BG
G-Burst
Target


7:35 AM
14 Nov
162
mg/dL
3
HRS
INSULIN ON BOARD
3.4 u
BOLUS
Control-IQ: 0.80 u
DexcomG6

Optimising glycaemic control

Three key components

Glucose data	Action	Insulin delivery
rtCGM	CL Algorithms	CSII
isCGM	Carb counting	MDI
HBGM	Fixed doses	BD insulin

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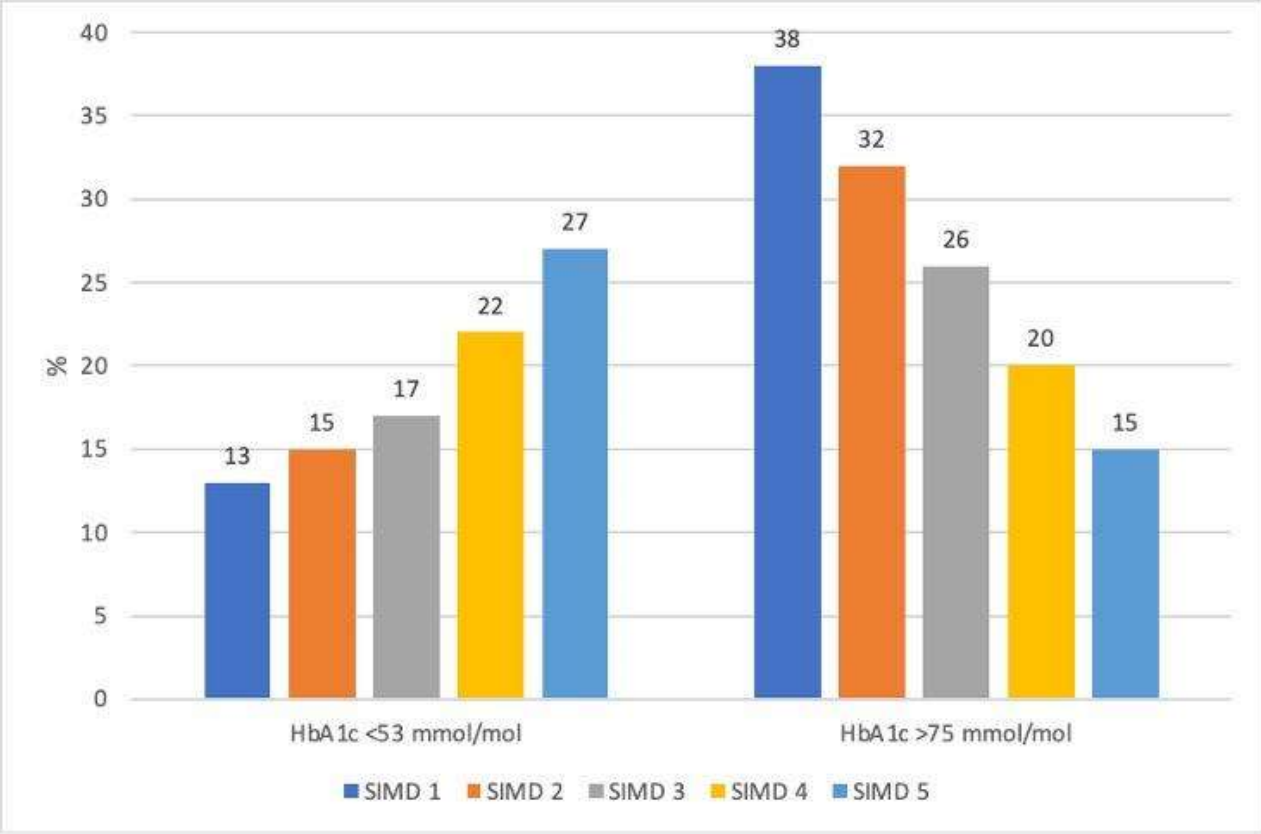
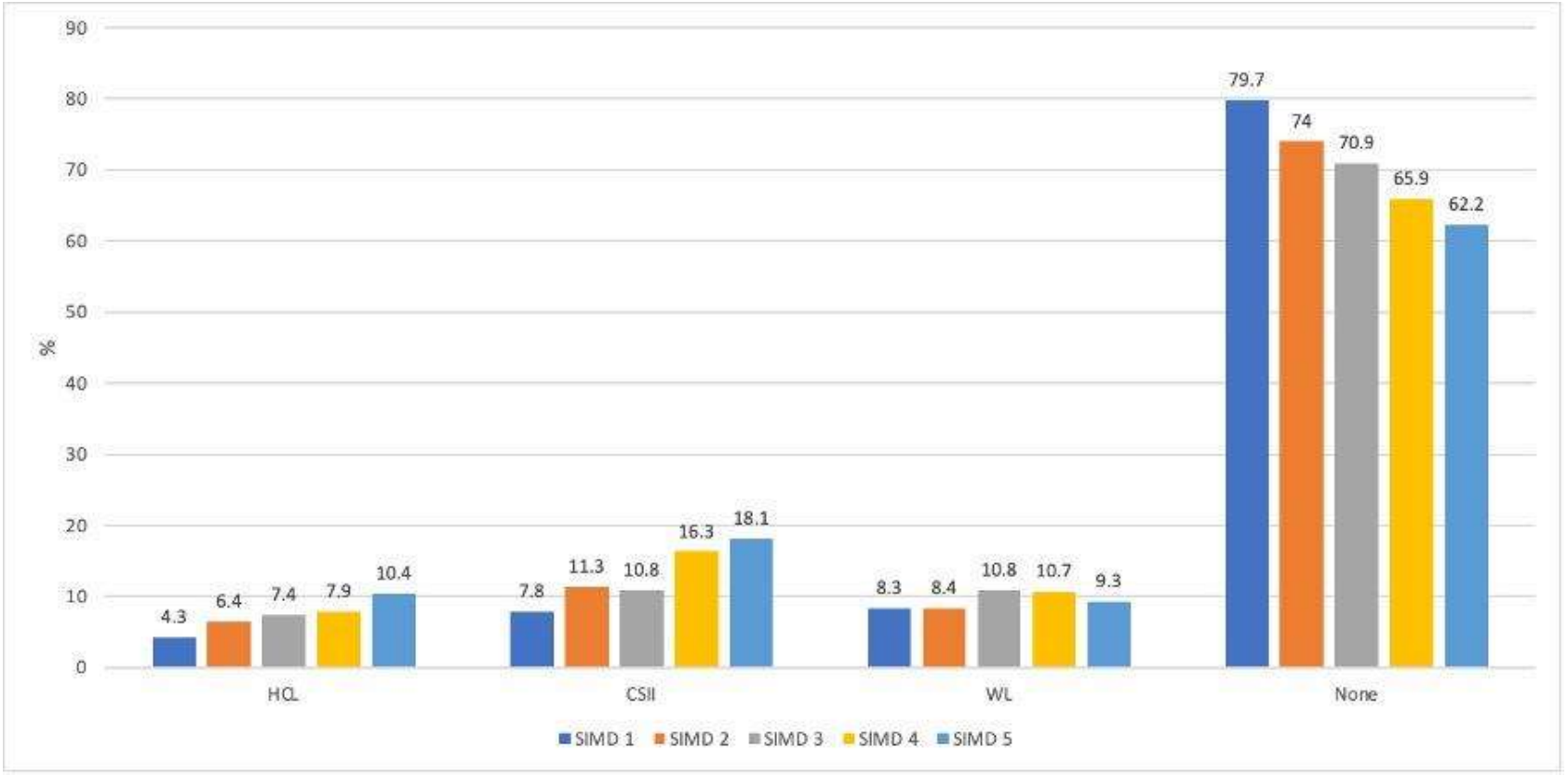
Deprivation and HbA1c

Clear socioeconomic gradient



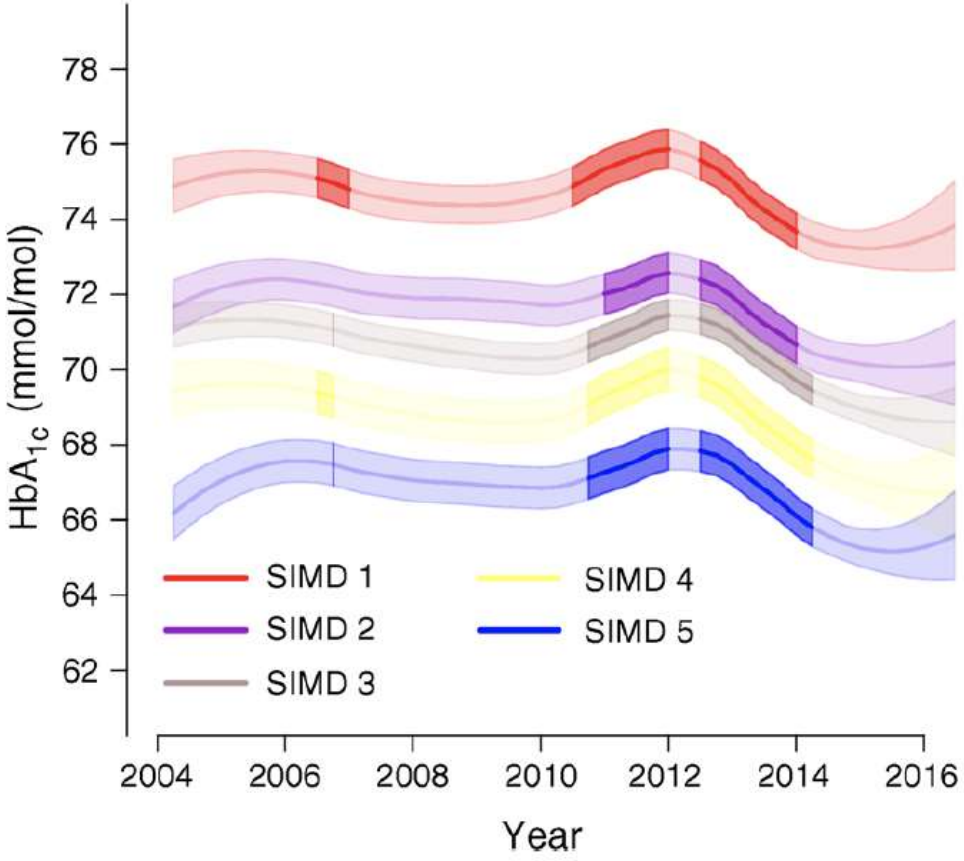
Deprivation and technology use

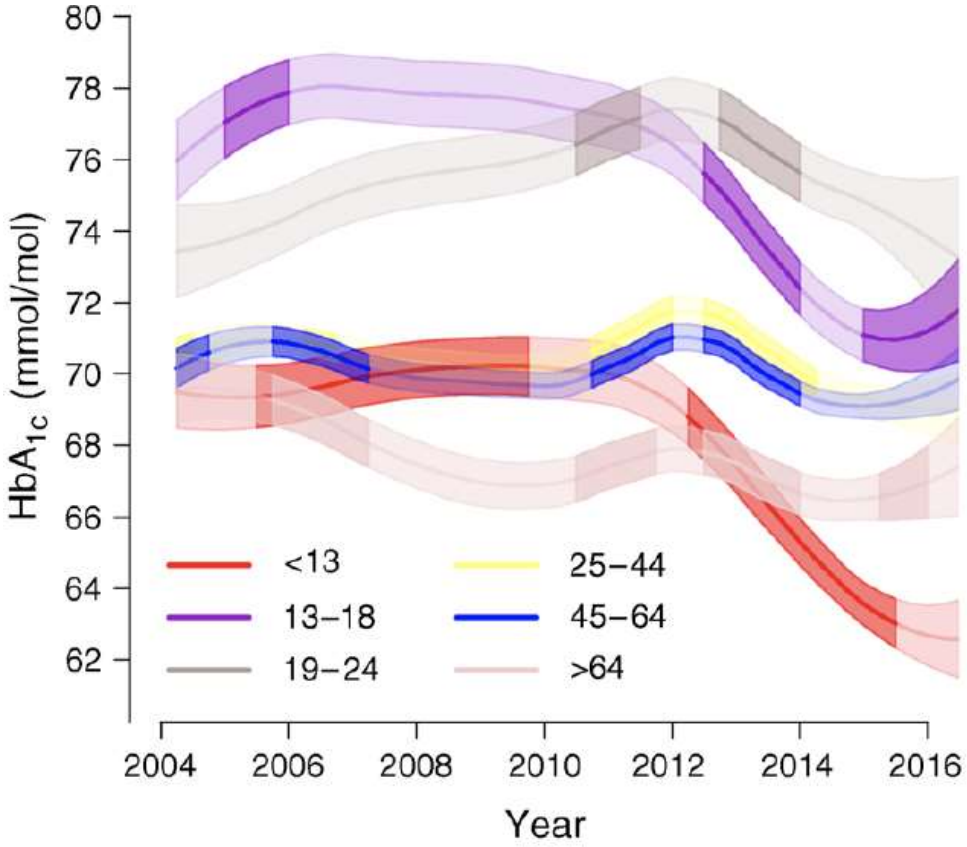
Clear socioeconomic gradient



Trends in HbA1c in Scotland

By SIMD quintile and age





Diabetologia (2019) 62:1375–1384
https://doi.org/10.1007/s00125-019-4900-7

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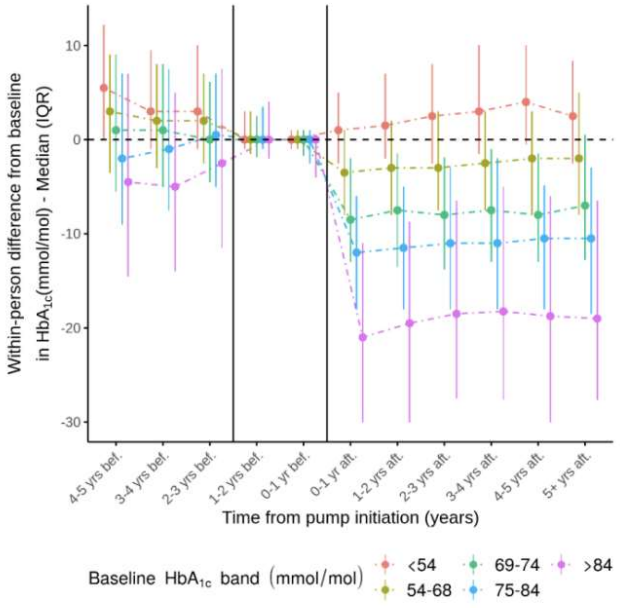
Diabetes

Insulin pump data from Scotland

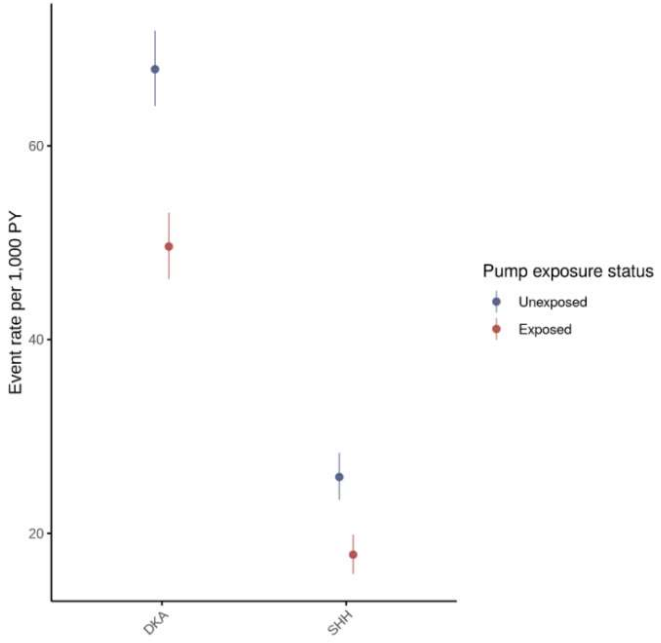
Large HbA1c benefit and reduced DKA & severe hypo

Nationwide Scottish study – N=4,684 pump-users (2004-2019)

Substantial drop in HbA_{1c} among those with high starting HbA_{1c}



Marked decrease overall in DKA and SHH rates post-pump initiation



SDRN epidemiology group – submitted for publication

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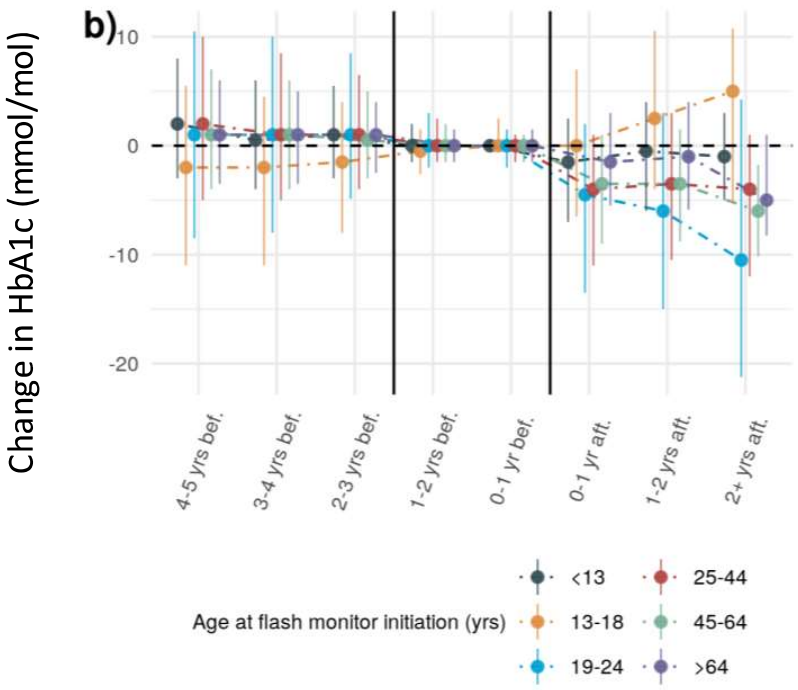
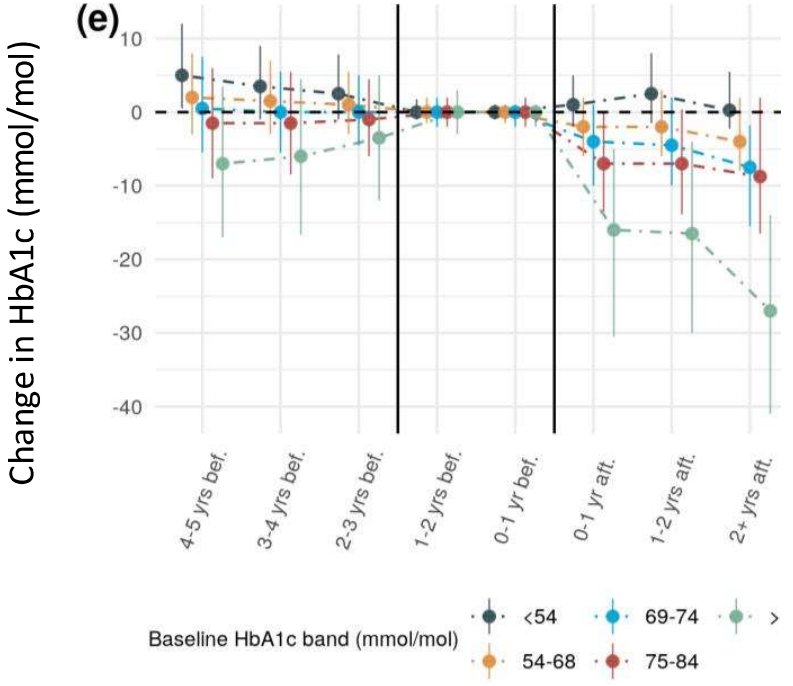
Flash monitoring in Scotland

Data from 9,500 flash monitoring users





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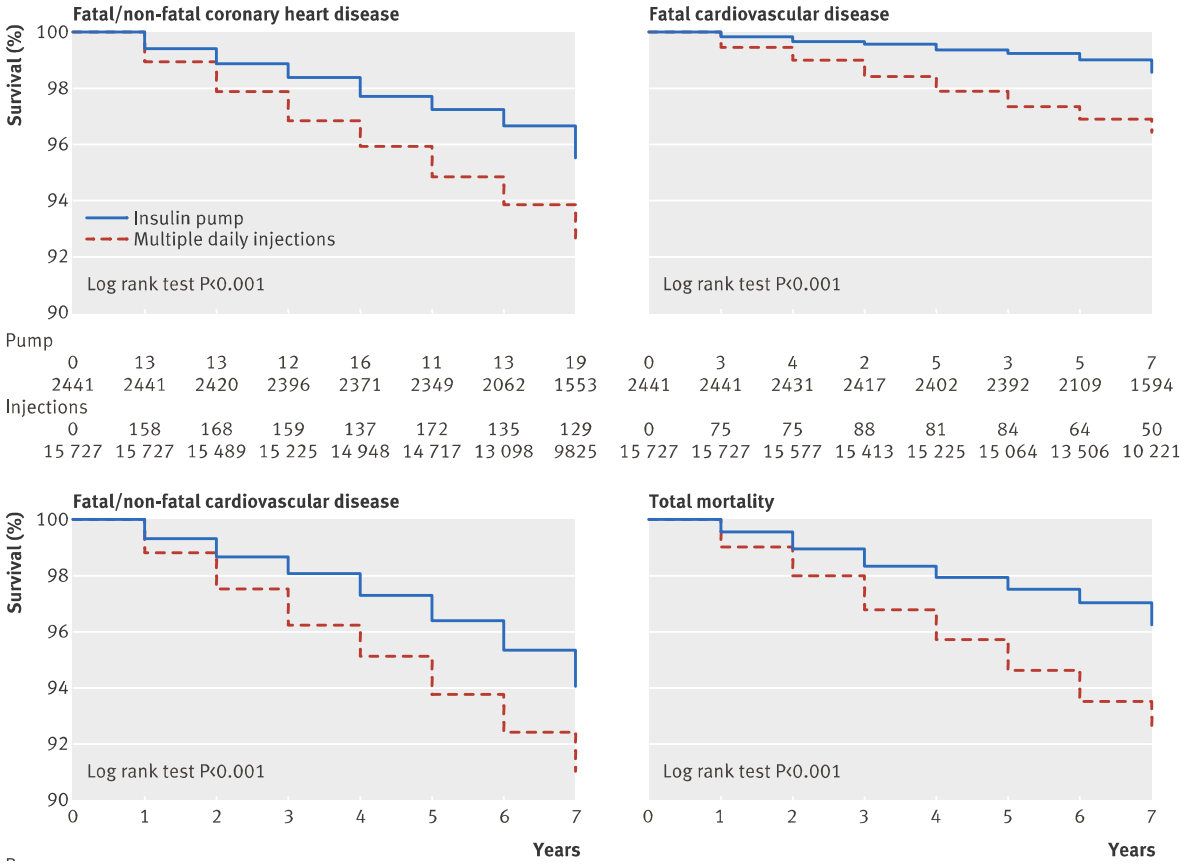
Possible mortality benefit

Swedish database observational study



Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18 168 people with type 1 diabetes: observational study

BMJ 2015;350:h3234

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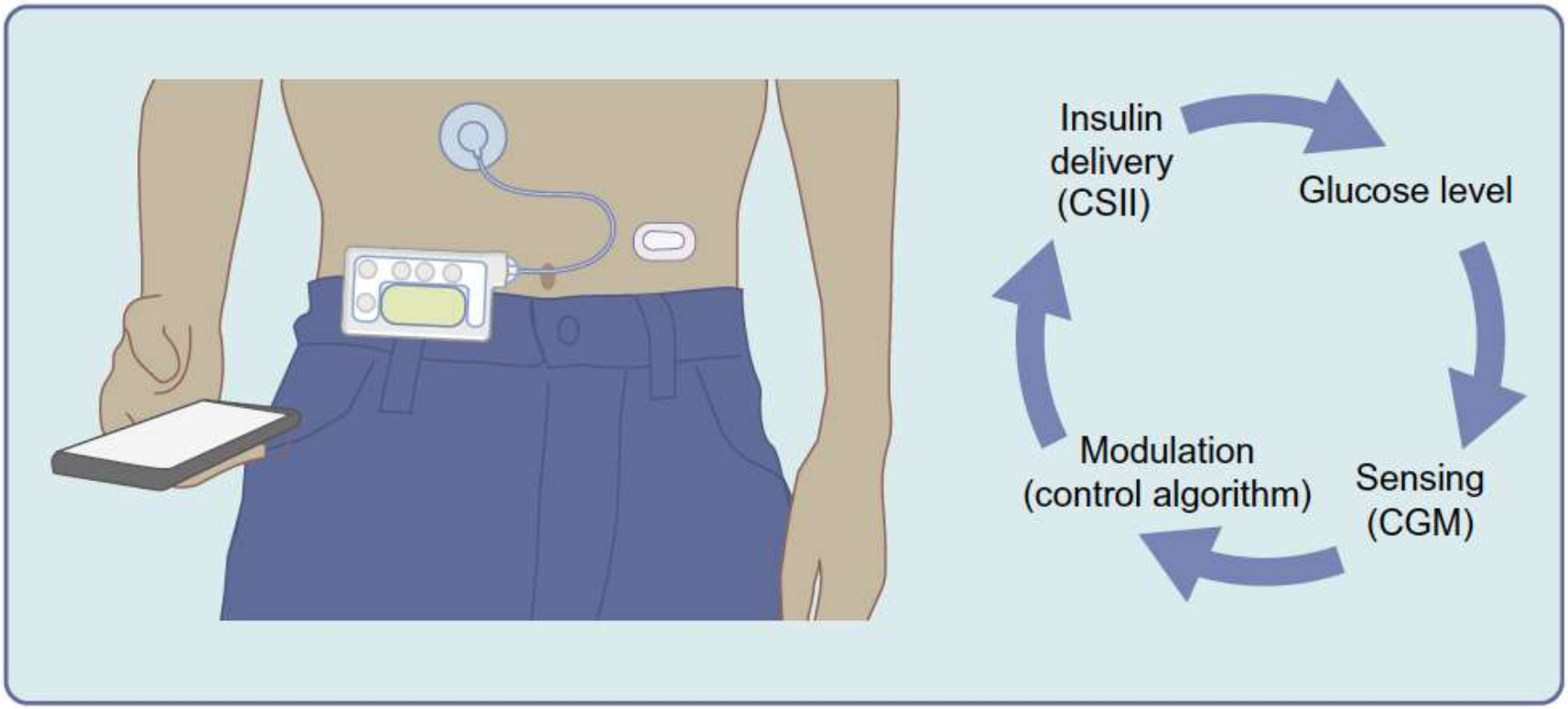
Closed loop systems

The basics



Diabetologia. 2021; 64: 1007 - 1015

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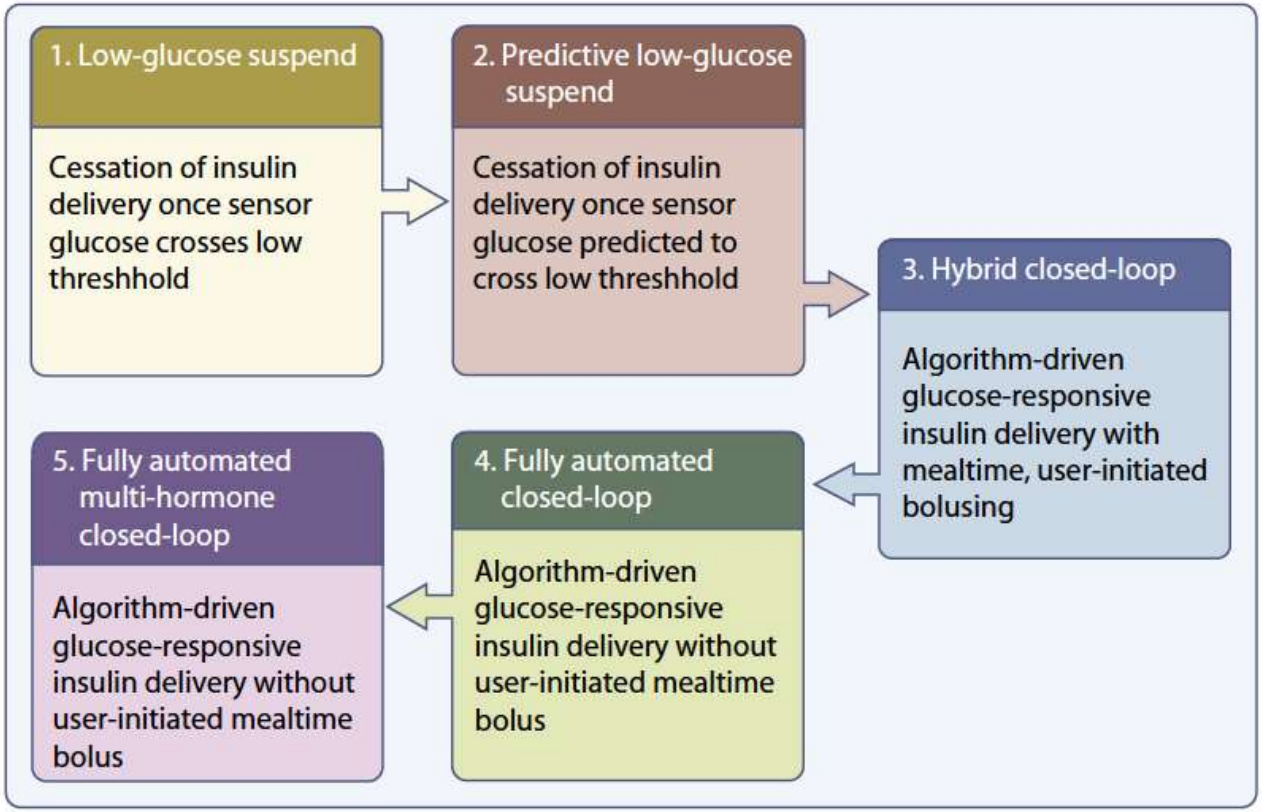
Closed loop systems

The basics



Diabetologia. 2021; 64: 1007 - 1015

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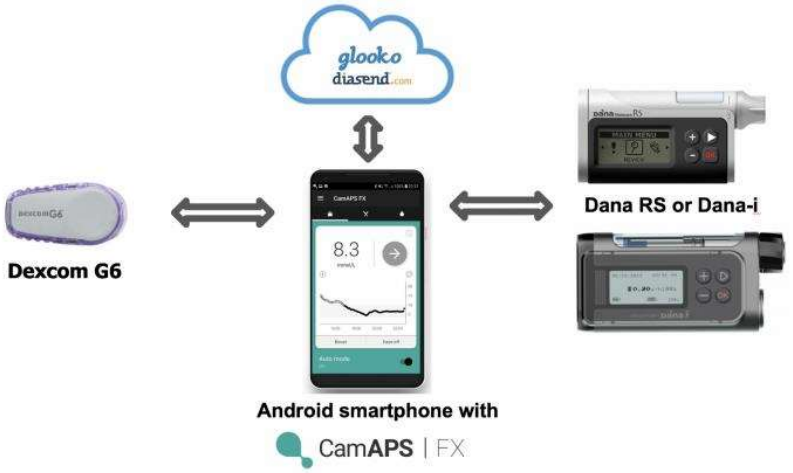
Hybrid closed-loop systems

Evidence from the key clinical studies



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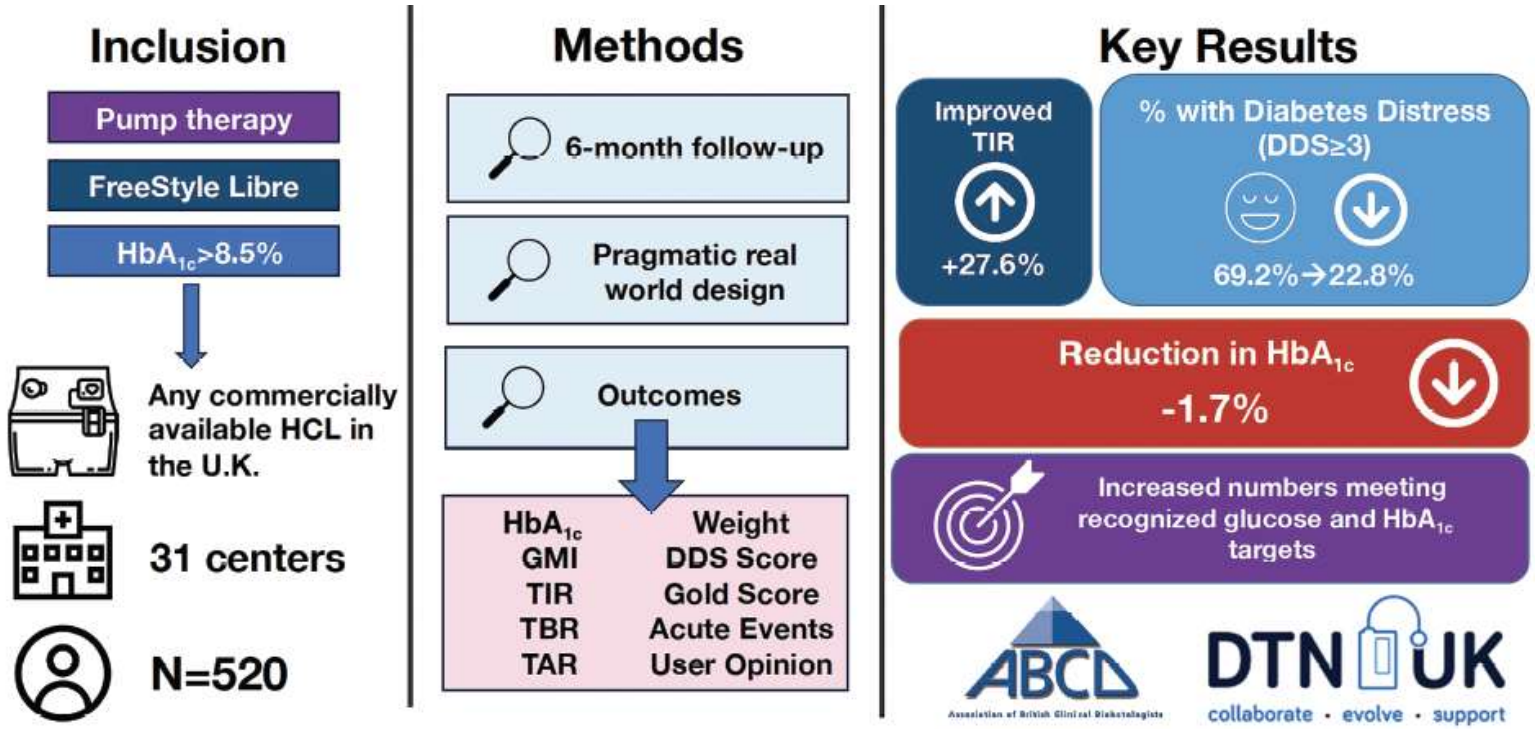
NHS England Adult Audit

521 adults (46% 780G / 37% CIQ)



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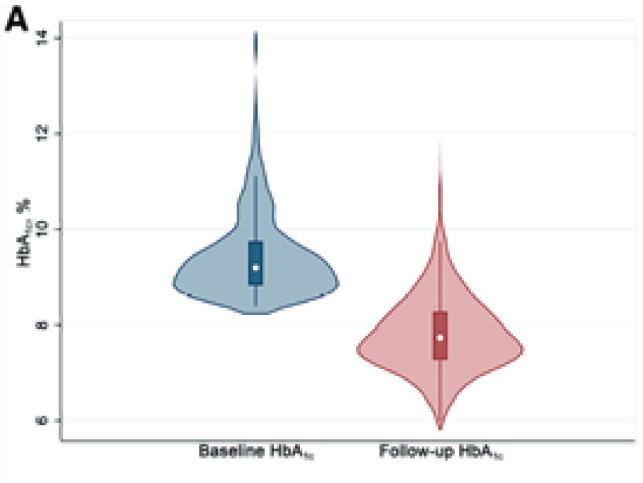
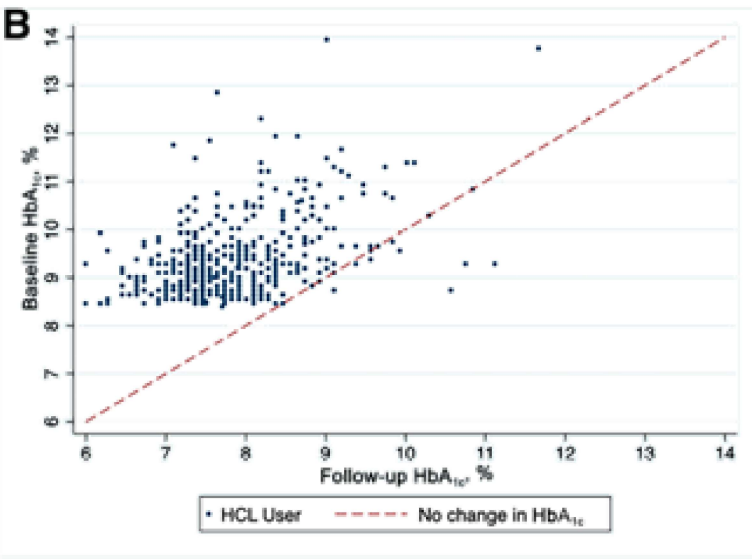
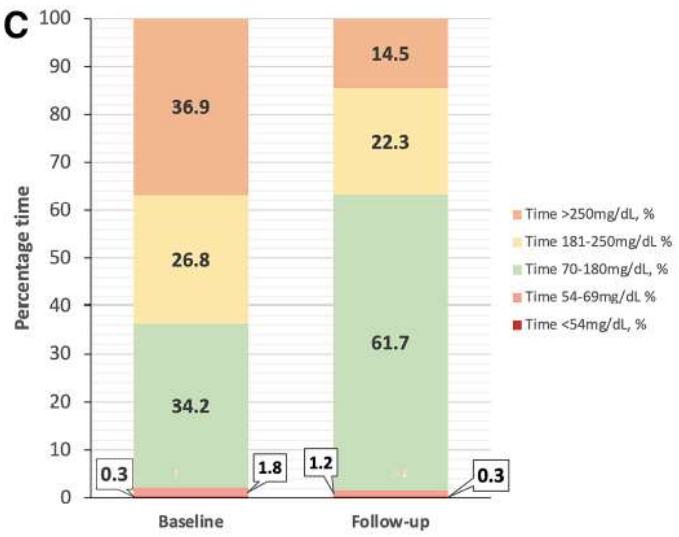
NHS England Adult Audit

HbA1c and CGM changes







NHS England Adult Audit

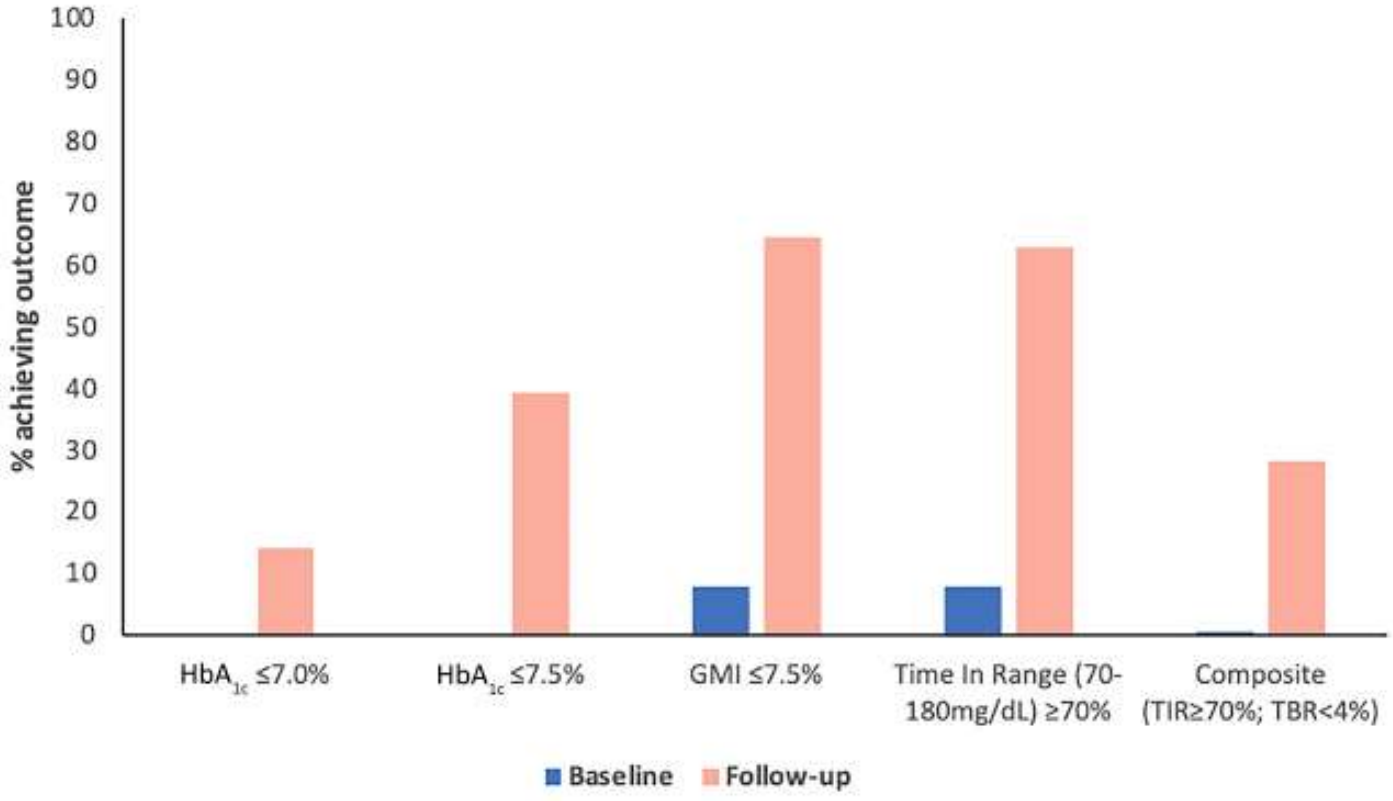
Summary of results

	n§	Baseline	Follow-up	Change (95% CI)	*P**
HbA_{1c}					
mmol/mol	436	78.9 ± 9.1	62.1 ± 9.1	−16.7 (−15.8, −17.6)	<0.001
%	436	9.4 ± 0.8	7.8 ± 0.8	−1.5 (−1.4, −1.6)	<0.001
Glucose data					
TAR, level 2 (>250 mg/dL), %	407	37.2 ± 19.1	14.9 ± 11.8	−22.4 (−20.5, −24.2)	<0.001
TAR, level 1 (181–250 mg/dL),# %	381	26.8 ± 10.3	22.3 ± 11.7	−4.5 (−3.0, −6.1)	<0.001
TIR (70–180 mg/dL),# %	417	34.2 ± 14.5	61.9 ± 13.1	27.8 (26.2, 29.4)	<0.001
TBR (54–69 mg/dL),# %	411	1.8 ± 2.4	1.3 ± 1.6	−0.5 (0.2, 0.8)	<0.001
TBR (<54 mg/dL),# %	397	0.37 ± 1.00	0.35 ± 0.57	−0.03 (−0.13, 0.18)	0.729
Coefficient of variation#	325	38.0 ± 6.9	35.2 ± 6.7	−2.8 (−1.9, −3.6)	<0.001
Patient-reported outcome measures					
Gold score	415	2.3 ± 1.4	1.9 ± 1.2	−0.4 (−0.2, −0.5)	<0.001
Diabetes distress score	412	3.3 ± 1.3	2.2 ± 1.0	−1.1 (−1.0, −1.3)	<0.001
Diabetes distress score (average ≥3),† % (*n*)	412	69.2 (285)	22.8 (94)	−46.4 (−191)	<0.001
Impaired awareness of hypoglycemia (Gold score ≥4), % (*n*)	415	16.9 (70)	9.4 (39)	−7.5 (−31)	<0.001

Data are mean ± SD unless otherwise indicated. TAR, time above range. *Statistical significance calculated using unpaired *t* tests for all covariates included in this table, following assessment for skew. †Statistical significance calculated using Chi-squared tests. §Number with available paired data at baseline and follow-up included in analysis for a given outcome; total cohort = 520. #Data derived from isCGM at baseline and real-time CGM at follow-up.

NHS England Adult Audit

Meeting targets



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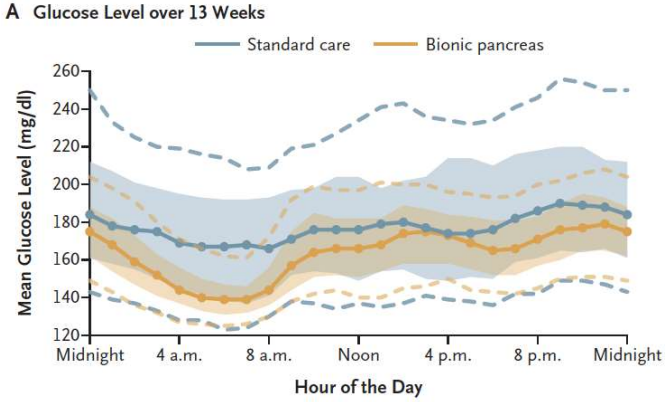
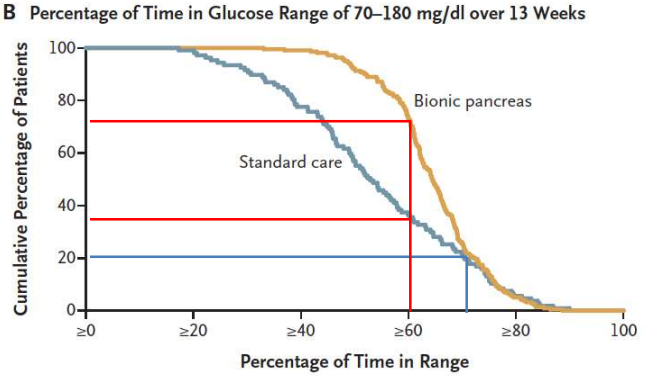
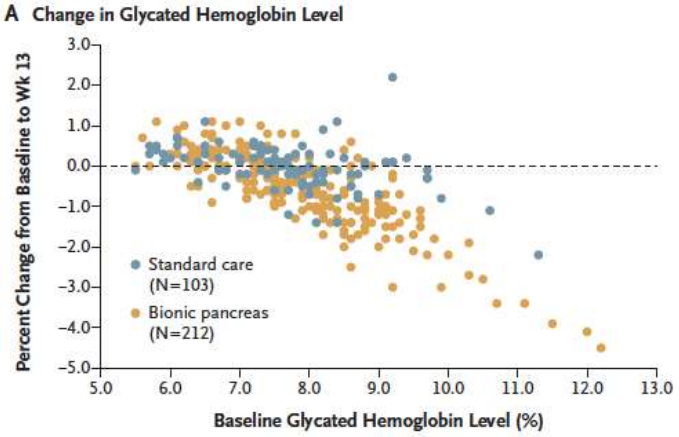
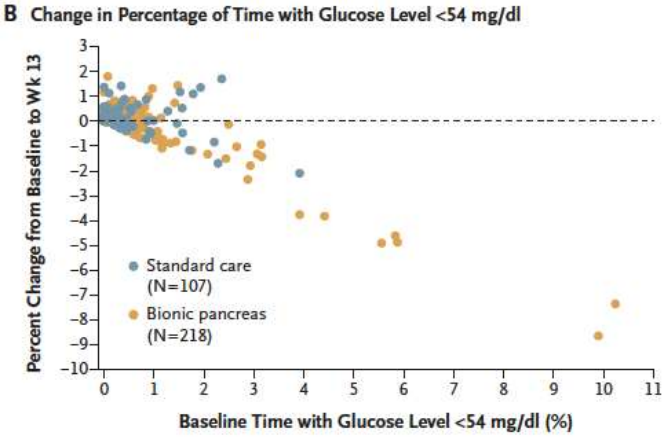
'Bionic' pancreas - iLet

13-week RCT in children and adults (6 to 79 years)









N Engl J Med 2022; 387: 1161 – 72

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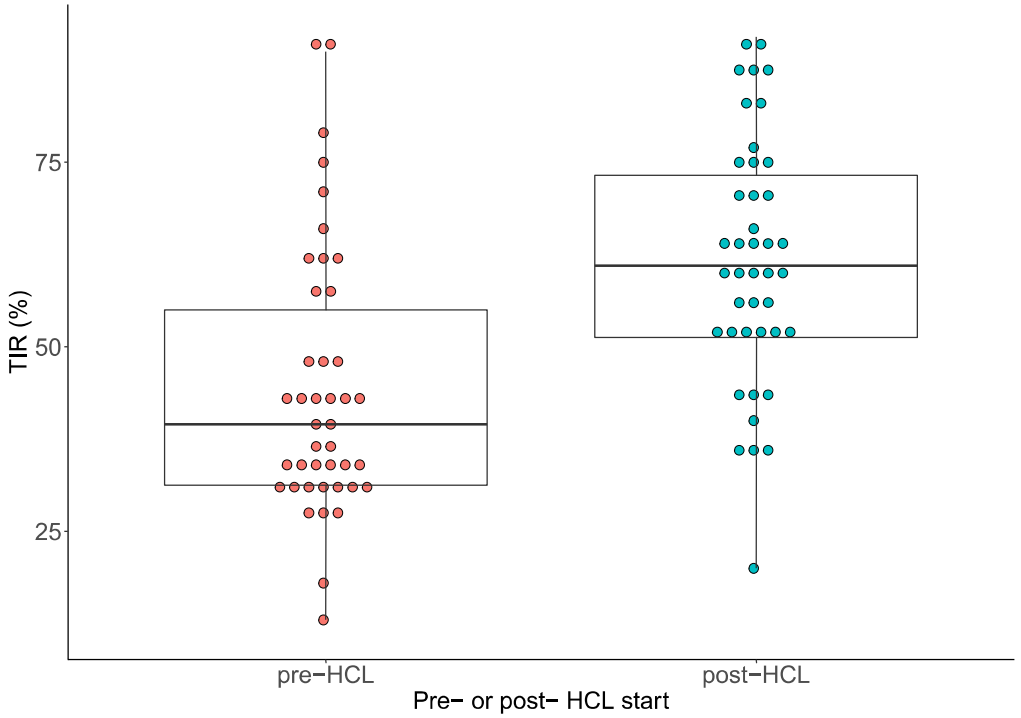
Effect upon CGM metrics

Edinburgh data from pump to closed loop

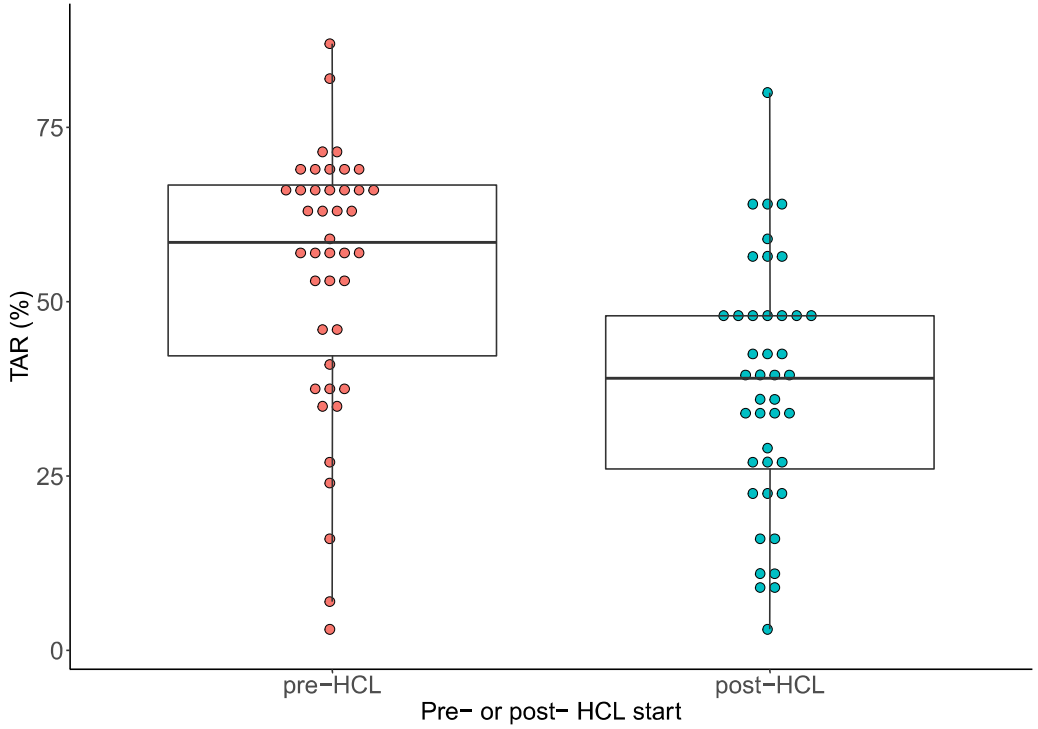
p < 0.001



40 (31 – 55) %

61 (51 – 73) %

p < 0.001



59 (42 – 67) %

39 (26 – 48) %

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How far does £1m go over 4 years?

Closed loop options

62 people

56 people

89 people*

*with L2

77 people*

* L3 as extra cost

118 people*

*if L3 on prescription

Immunotherapy

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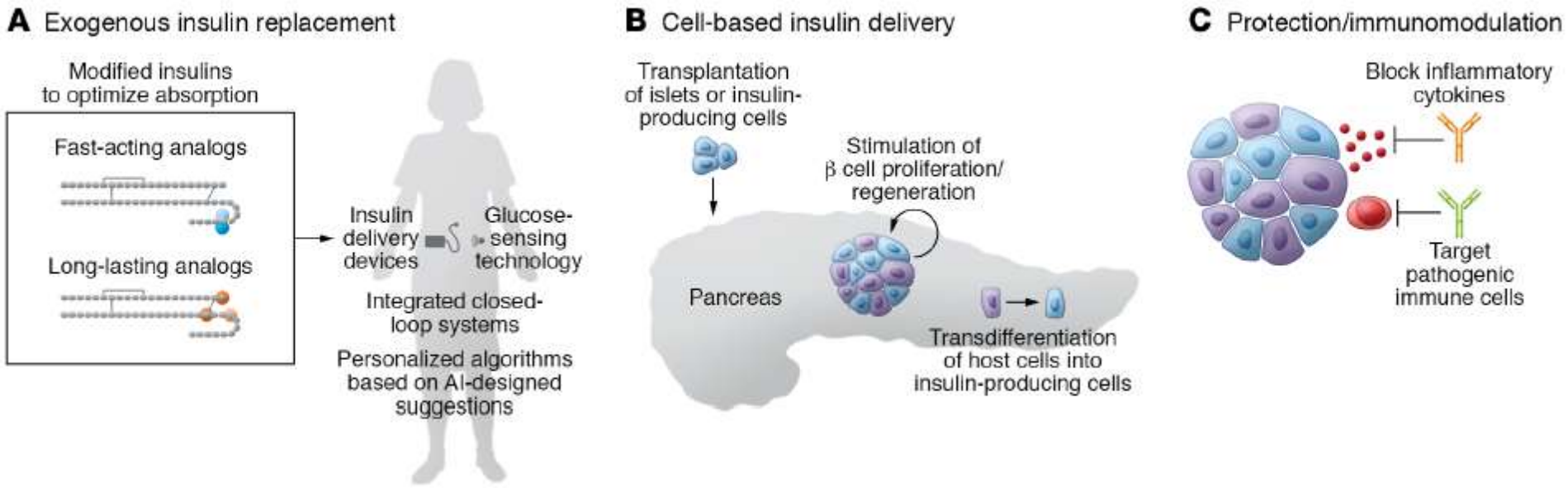
Strategies for treating T1 diabetes

Beyond exogenous insulin



J Clin Invest. 2021;131(8): e142242

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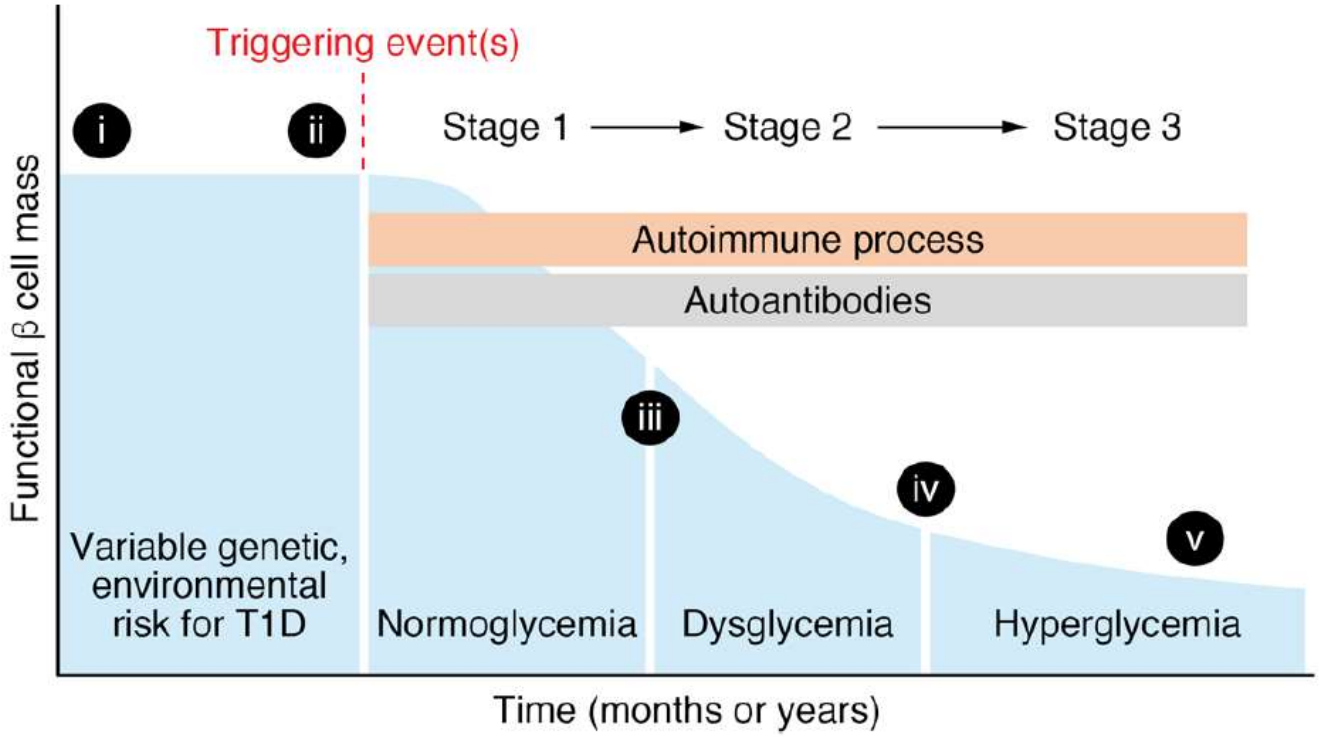
Stages of type 1 diabetes

Progression over time



J Clin Invest. 2021;131(8): e142242

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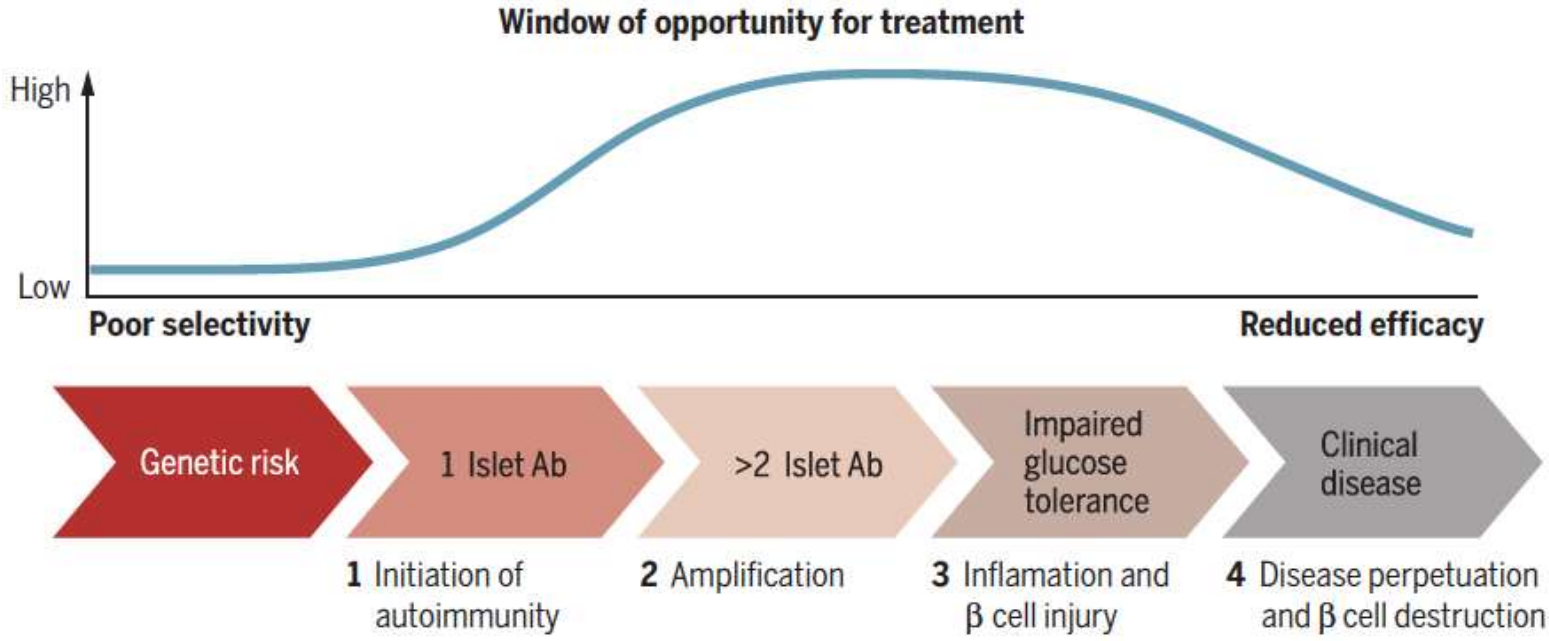
Immunotherapy

Window of opportunity



Science. 2021; 373: 510 – 516

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FDA NEWS RELEASE

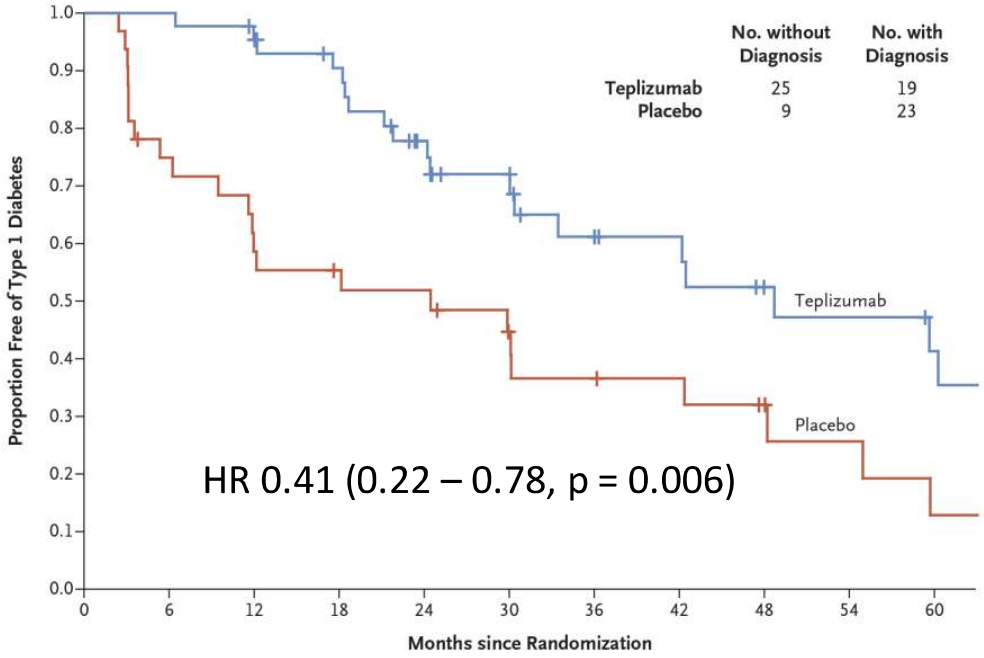
FDA Approves First Drug That Can Delay Onset of Type 1 Diabetes

For Immediate Release: November 17, 2022

Today, the U.S. Food and Drug Administration approved Tzield (teplizumab-mzwv) injection to delay the onset of stage 3 type 1 diabetes in adults and pediatric patients 8 years and older who currently have stage 2 type 1 diabetes.

Teplizumab

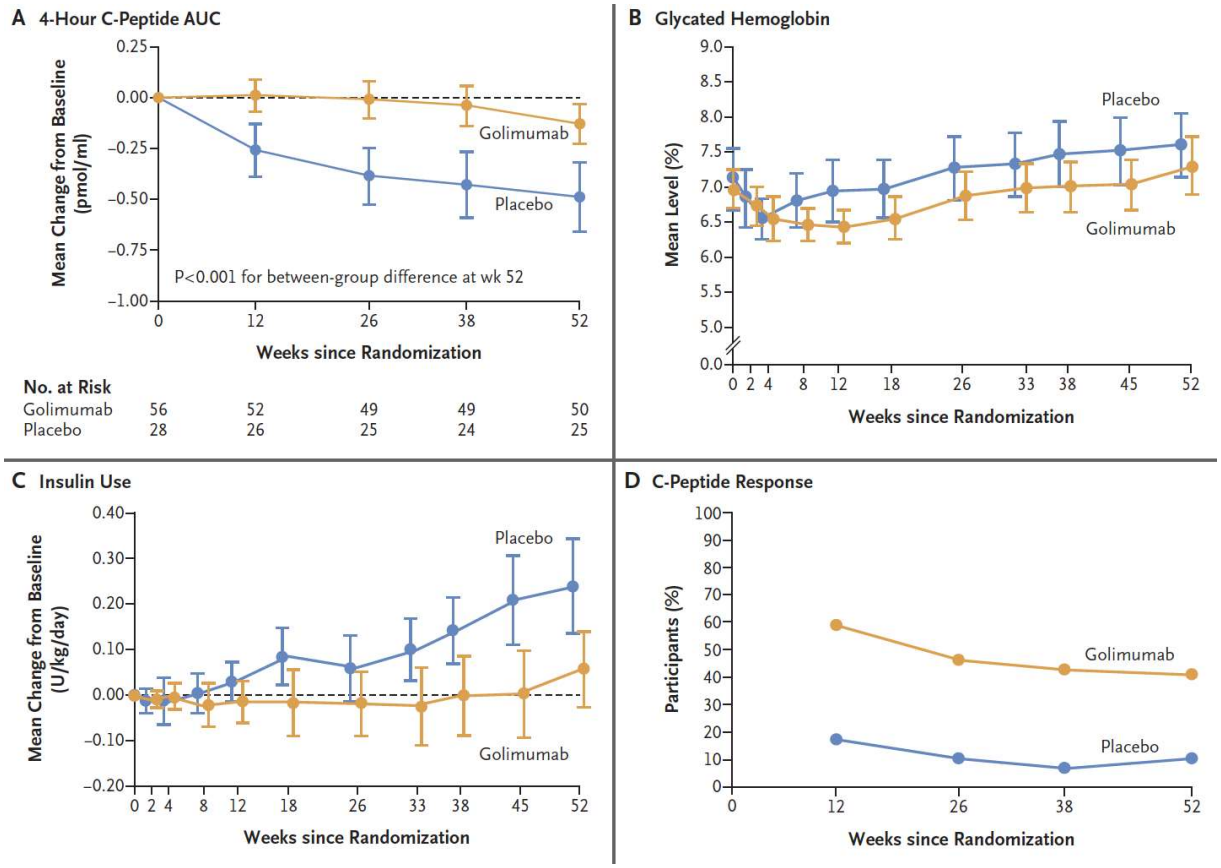
Key evidence



- 1st degree relative
- 2 or more diabetes Ab
- Dysglycaemia:
  - Fasting glucose 6.1 – 6.9mM *and/or*
  - 2hr PP glucose ⩾7.8mM and <11.1mM *and/or*
  - 30 / 60 / 90 minute OGTT glucose >11.1 mM

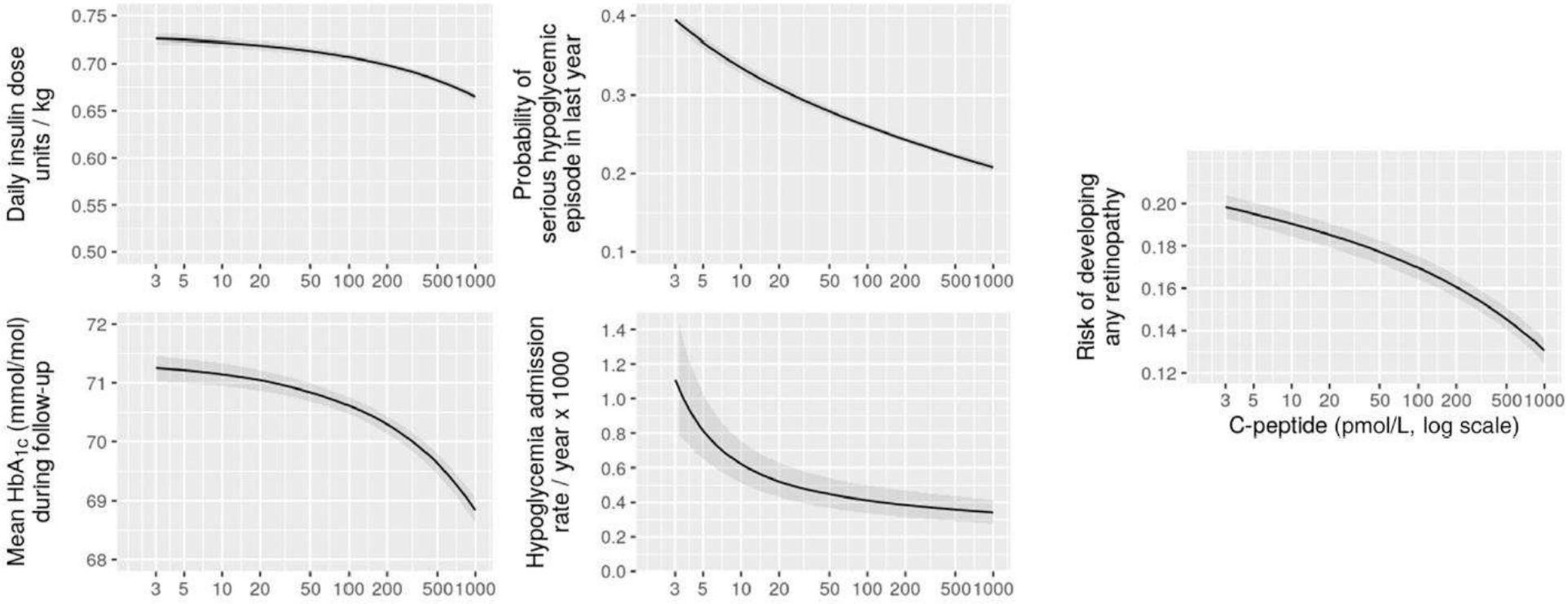
Golimumab (anti-TNFα Ab)

In newly diagnosed T1 diabetes in the young



C-peptide is important

Even in established type 1 diabetes



Diabetes Care 2021; 44:390-398

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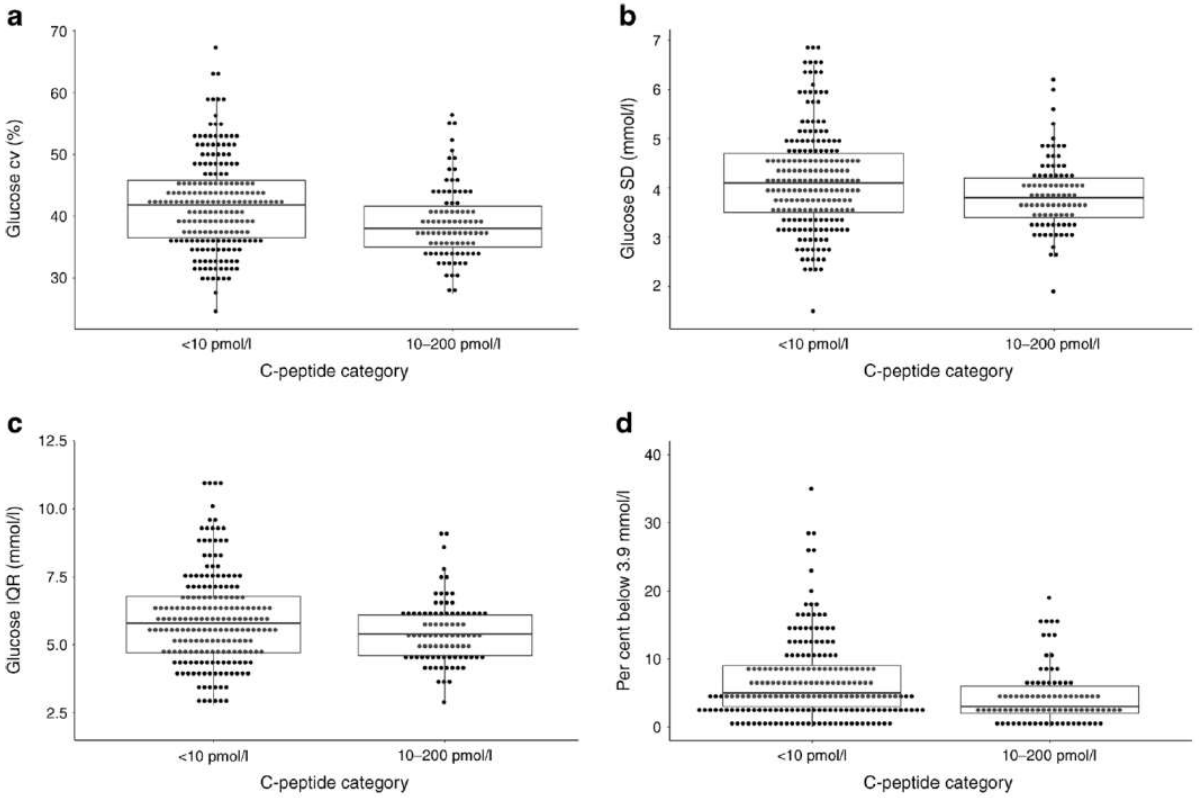
C-peptide is important

Even in established type 1 diabetes



Diabetologia 2020; 63:906-914

Immunotherapy

Multiple targets and studies

Target pathways	Examples	Strengths	Limitations	Clinical status	References, https://clinicaltrials.gov identifiers
Cytokine antagonists	Abs to IL-6, IL-1, IL-21, TNF, IL-12/23, IL-8	Some are approved therapies in other settings, specific to a given target	Target late stage of disease pathogenesis, not initiating nodes of disease; off-target effects; continuous treatment needed	Varies by target (e.g., TNF-α versus IL-1β), several being tested in phase 1, 2 studies of stage 3 T1D patients	(*57*, *58*), NCT02293837, NCT02443155, NCT02204397, NCT04628481
Cytokine agonists	IL-2, IL-10 cytokines	Induce dominant regulatory cells	Continuous therapy likely needed; off-target effects	Being tested in phase 1, 2 studies of stage 3 T1D patients	(*61*), NCT04279613, NCT01862120, NCT02772679
T_{eff} depletion and exhaustion (T_{ex})	Anti-CD3, ATG, anti-CD2	Target effector pathways, short course of therapy	Can be linked with adverse events and broad suppression	Being tested in phase 2, 3 studies in stage 2 and 3 T1D patients	(*43*–*53*), NCT00965458
Inhibition of T cell activation	CTLA-4/CD28, CD40/CD154, CD2 blockade	Both conditioning agents and tolerance promoting	Shown limited efficacy over time as single agents in new onset T1D	Testing in phase 2 studies in stage 2 and 3 T1D	(*10*, *55*) NCT01773707, NCT03929601
Checkpoint agonists	Abs to PD-1, CTLA-4, β cell expressing PD-L1	Early experimental successes in shutting down autoreactive cells	May suppress immunity to cancers and infectious diseases; limited to a subset of Ag-specific T cells	Preclinical	
Regulatory cell-based therapies	CAR/TCR-T_{regs}, Tr1, MDSC, B_{reg}, $FOXP3^+$ programmed cells, tolerogenic DCs	Dominant immune regulation across multiple T cell specificities and cell types	Difficult drug development process: living drug difficult to control function without means to regulate cells	Preclinical and early phase 1 trials underway	(*63*, *65*–*67*), NCT02772679, NCT01947569, NCT04061746

Science. 2021; 373: 510 – 516

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Immunotherapy

Multiple targets and studies

Target pathways	Examples	Strengths	Limitations	Clinical status	References, https://clinicaltrials.gov identifiers
B cell antagonists	Anti-CD20	Strong efficacy in autoimmune diseases	Mechanism of action still unclear	Approved in multiple autoimmune diseases	(56), NCT00279305, NCT03929601
Autoantigen therapies	Peptides, nanoparticles, tolerogenic mRNAs and DNAs	Specific and safe; may require continuous dosing	May not achieve tolerance if mechanism is directly targeting effector cells due to epitope spreading	Early clinical trials	(64), NCT04590872, NCT01536431
Tissue microenvironment	IDO, adenosine agonists, tyrosine kinase inhibitors	Adaptive immunity; multiple pathways targeted	Off-target activities	Early clinical trials	NCT01781975
β cell regeneration	Verapamil, glp-1 agonists	Adaptive immunity; multiple pathways targeted	Do not induce immune tolerance as monotherapies	Being tested in combination with immunotherapies	NCT02443155, NCT04233034, NCT02372253
Microbiome	BCG, probiotics, coxsackie B vaccine	Focused on gut to pancreas linkage, immune reprogramming	Early studies underway with complex mechanistic understanding	Being tested as both vaccine for prevention and treatment	NCT02081326, NCT03423589, NCT04141761

Science. 2021; 373: 510 – 516

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Weight loss

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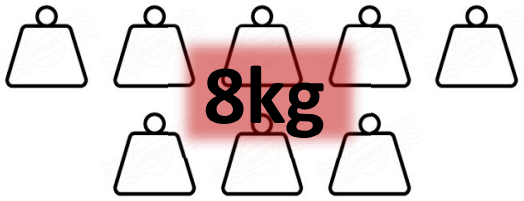
Semaglutide

50mg oral dose – PIONEER PLUS



N = 1606

68 week follow up

T2 on 1 to 3 OHAs

58% male – weight 96kg – age 58 yrs

HbA1c reduction 22 mmol/mol

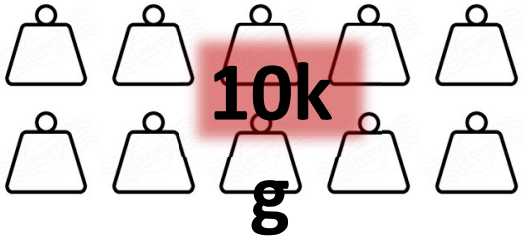
27% nausea / 18% vomiting

THE LANCET

10.1016/ S0140-6736(23)01127-3

Orforglipron

45mg oral dose



N = 383

26 week follow up

T2 +/- metformin

59% male – weight 100kg – age 59 yrs

HbA1c reduction 23 mmol/mol

25% nausea / 22% vomiting

THE LANCET

10.1016/ S0140-6736(23)01302-8

Orforglipron

45mg oral dose

N = 272

36 week follow up

Overweight and obesity

41% male – weight 109kg – age ~55 yrs

HbA1c reduction not assessed

37% nausea / 27% vomiting

The NEW ENGLAND JOURNAL of MEDICINE

10.1056/NEJMoa2302392

Tirzepatide

15mg weekly – SURMOUNT-2

N = 938

72 week follow up

T2 on OHAs

49% male – weight 101kg – age 54 yrs

HbA1c reduction 23 mmol/mol

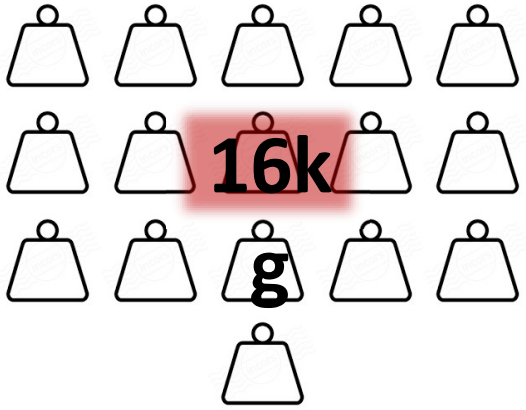
20% nausea / 11% vomiting

THE LANCET

10.1016/ S0140-6736(23)01292-8

Cagrilintide + Semaglutide

2.4mg weekly / 2.4 mg weekly



N = 92

32 week follow up

T2 on metformin +/- SGLTi

64% male – weight 106kg – age 58 yrs

HbA1c reduction 24 mmol/mol

29% nausea / 10% vomiting

THE LANCET

10.1016/ S0140-6736(23)01163-7

Semaglutide

Oral dose 50mg – OASIS 1

N = 667

68 week follow up

Overweight (8%) or obese

27% male – weight 105kg – age 50 yrs

HbA1c reduction 2 mmol/mol

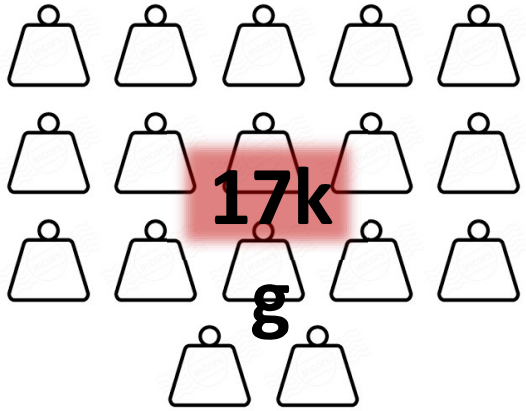
52% nausea / 24% vomiting

THE LANCET

10.1016/ S0140-6736(23)01185-6

Retatrutide

12mg weekly



N = 281

36 week follow up

T2 +/- metformin

44% male – weight 98 kg – age 56 yrs

HbA1c reduction 22 mmol/mol

20% nausea / 11% vomiting

THE LANCET

10.1016/S0140-6736(23)01053-X

Retatrutide

12mg weekly

N = 338

48 week follow up

Overweight or obese

52% male – weight 107 kg – age 48 yrs

HbA1c reduction not assessed

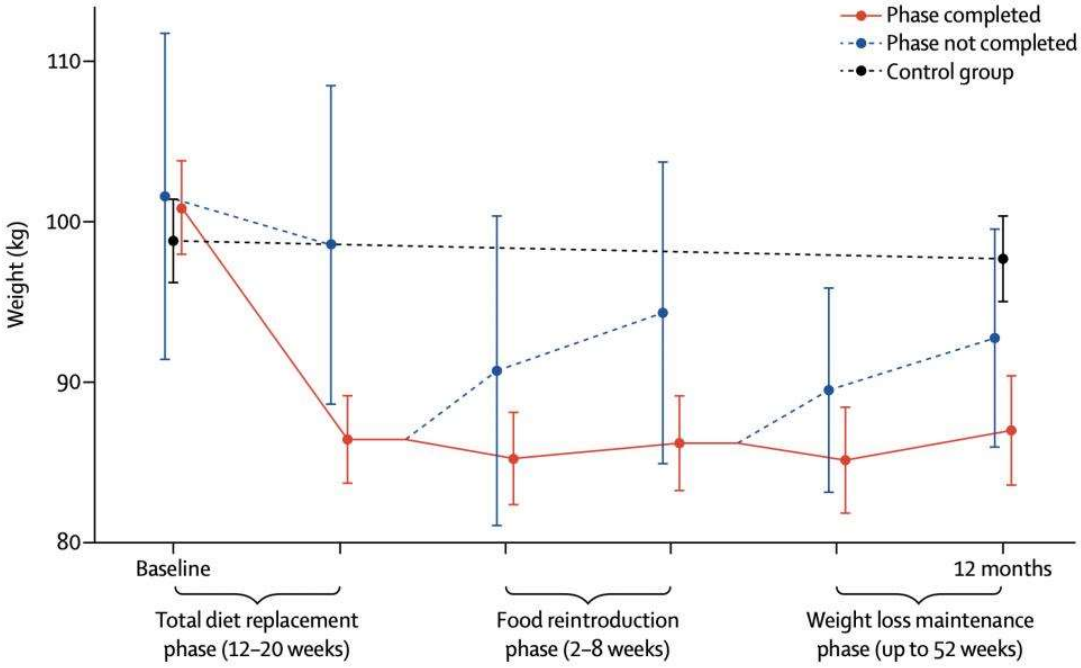
45% nausea / 19% vomiting

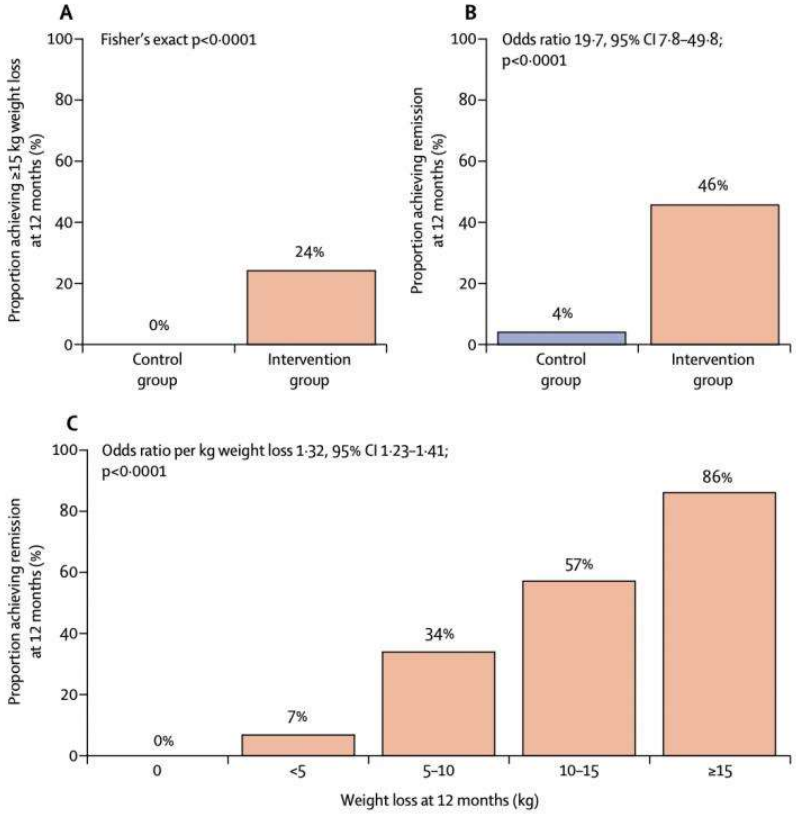
The NEW ENGLAND JOURNAL of MEDICINE

10.1056/NEJMoa2301972

Diabetes remission

800 calorie meal-replacement diet

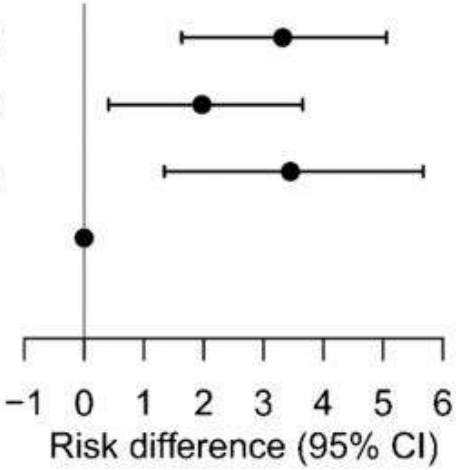


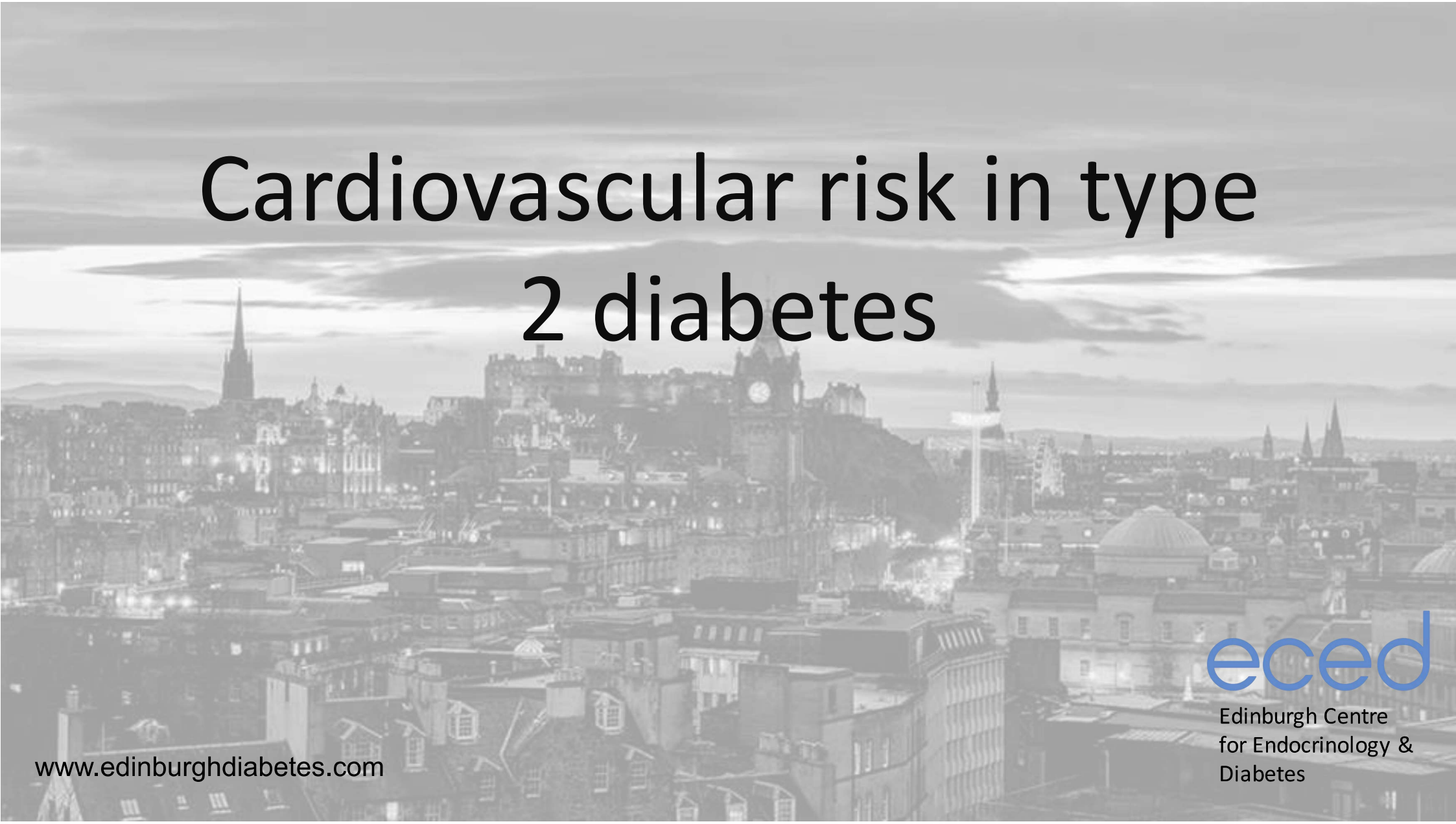


Diabetes remission

Note of caution

Glycaemic control & GLDT	Standardised 5 year risk (%) (95% CI)	Risk difference (%) (95% CI)
Persistent T2D not on GLDT	13.6 (12.3, 14.9)	3.3 (1.6, 5.1)
Remission not on GLDT	12.3 (11.2, 13.3)	2.0 (0.4, 3.7)
Poorly controlled on GLDT	13.7 (12.0, 15.6)	3.5 (1.3, 5.7)
Well−controlled on GLDT	10.3 (9.1, 11.6)	Reference





Cardiovascular risk in type 2 diabetes

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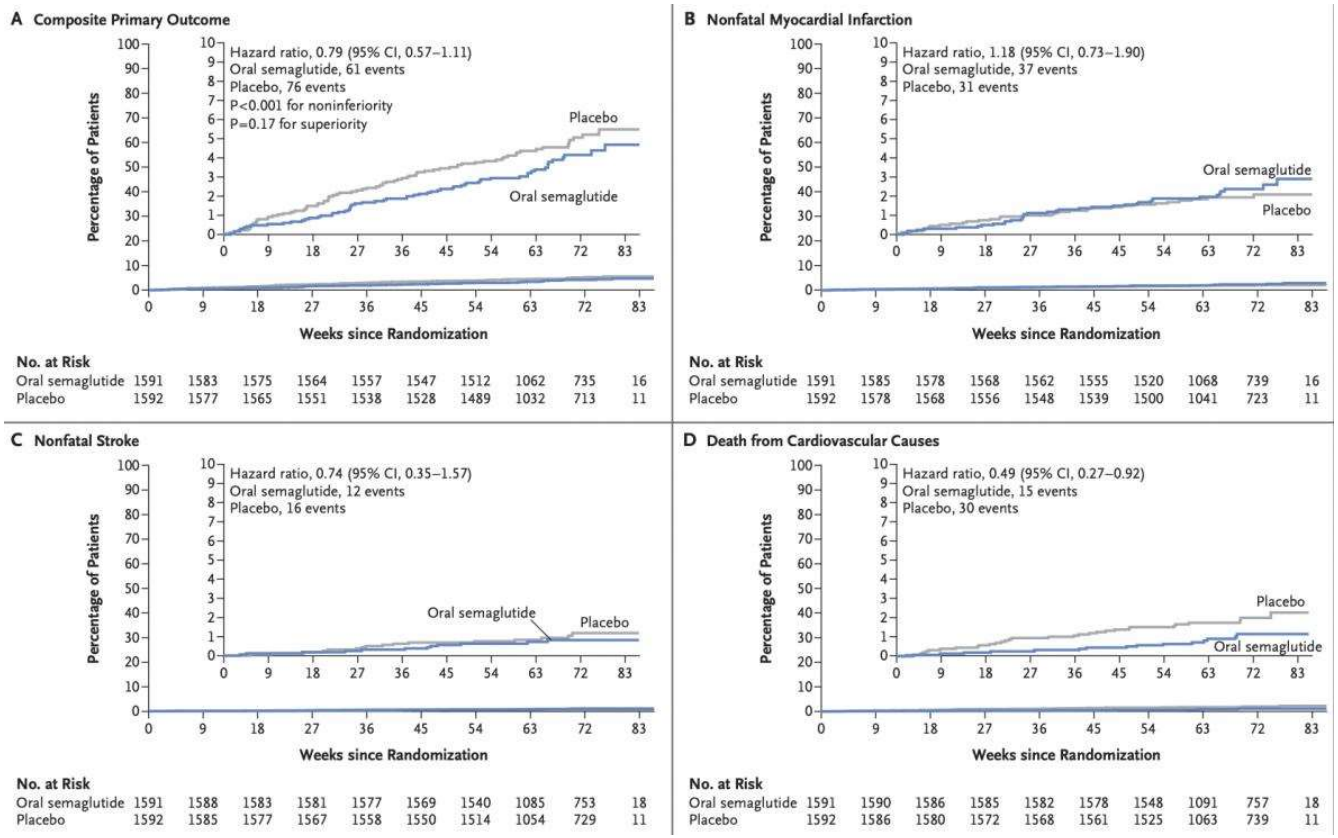
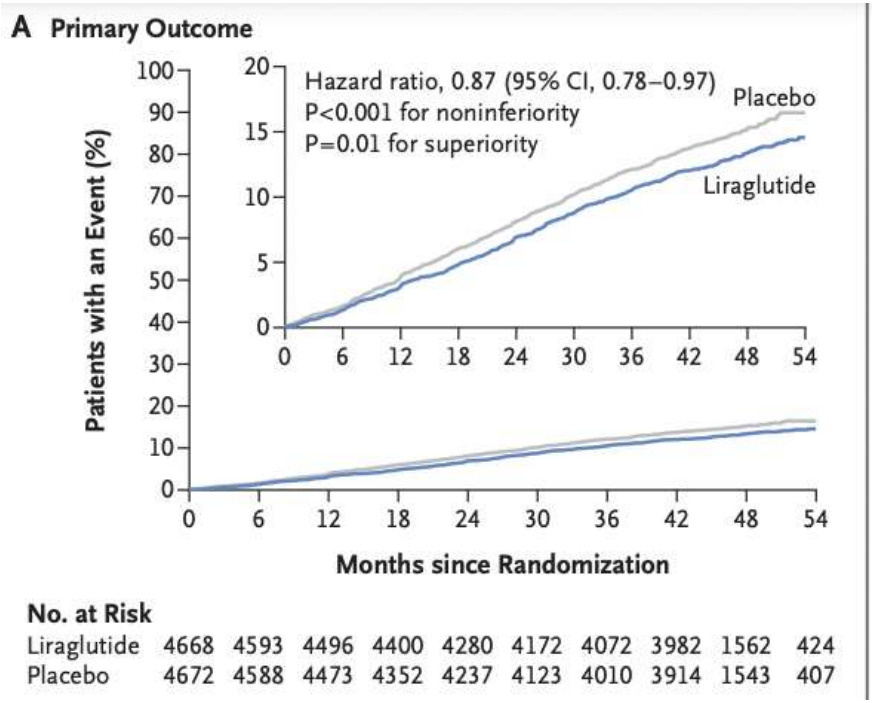
Oral semaglutide

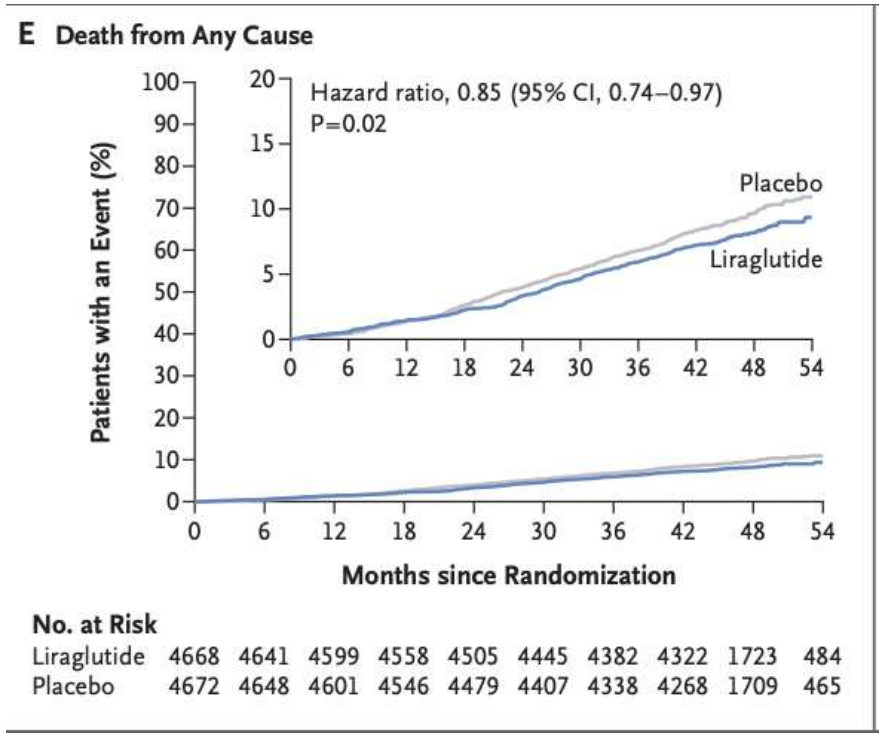
Cardiovascular outcomes



Liraglutide

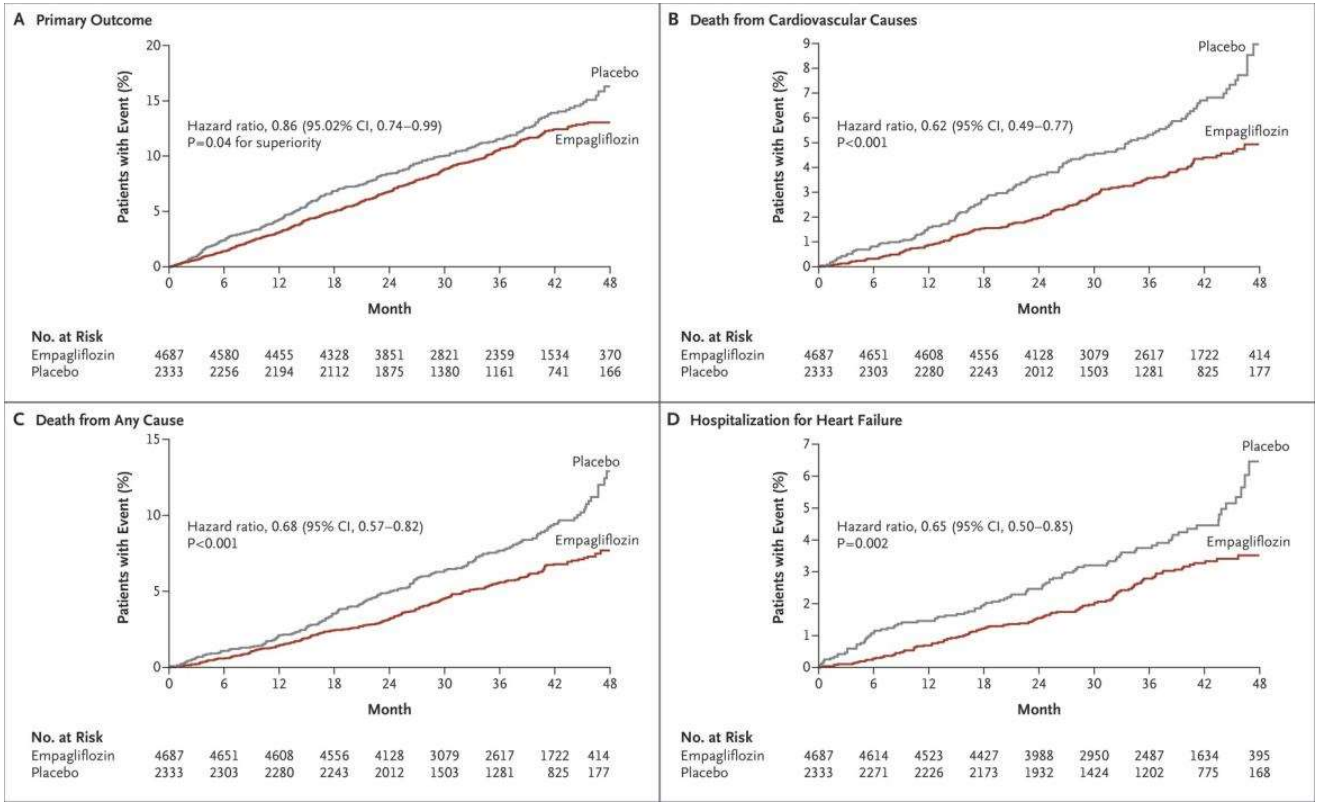
Cardiovascular outcomes

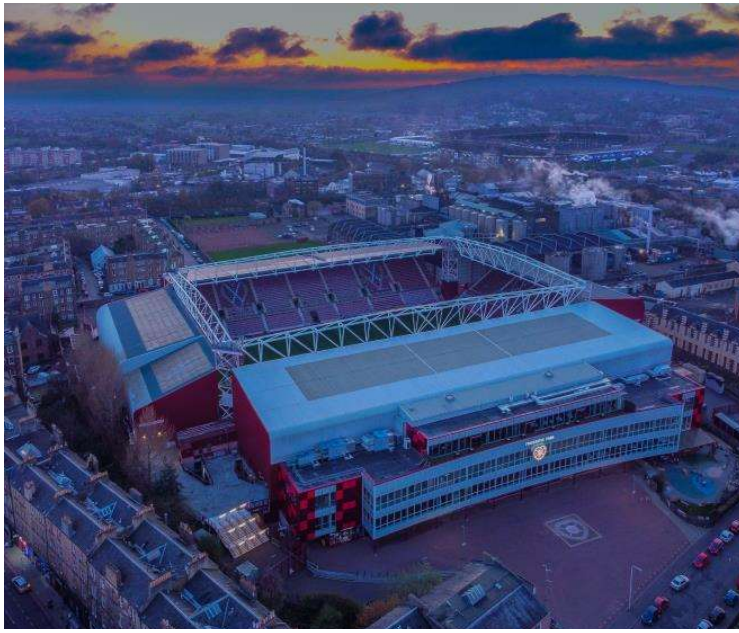




Empagliflozin

Cardiovascular outcomes





Questions?

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