Diabetes medications in the elderly

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Objectives

Diabetes medications in the elderly

1) Appreciate some of the strengths and limitations of the medical evidence around recommendations for T2DM and in particular to the elderly

2) Understand the responsibility of health professionals to incorporate patient values into the decision making process

3) To be able to incorporate the relevant evidence into shared-informed decision making for T2DM

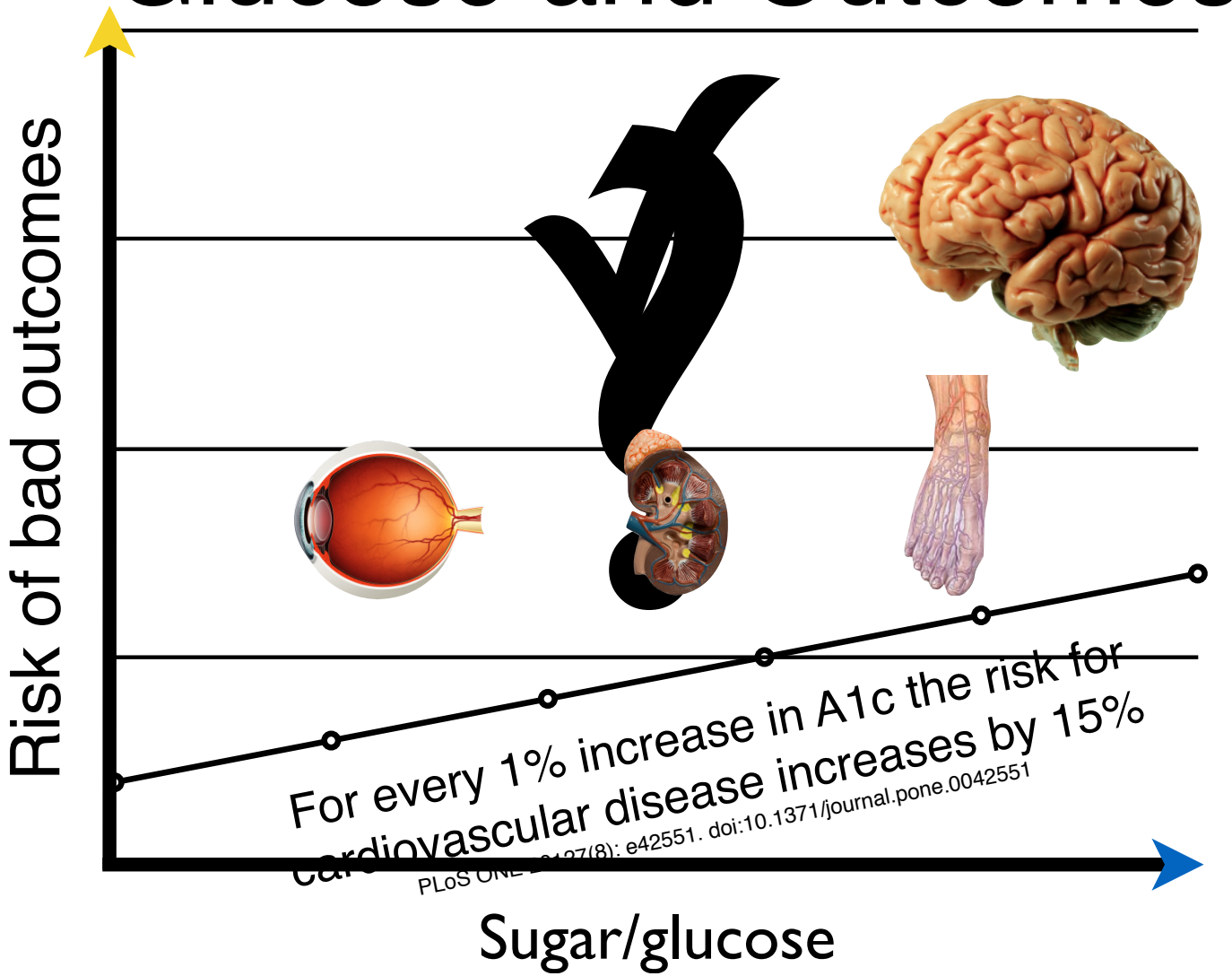
Type-2 diabetes in the elderly

~20% for those 65-69

~25% for those 75-79

~20% for those > 85

Glucose and Outcomes



Major Medical Associations Feud Over Diabetes Guidelines

March 5, 2018 · 5:01 PM ET

CLINICAL GUIDELINES | 6 MARCH 2018

Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

"Clinicians should aim to achieve an HbA1c level **between**

7% and 8% in most patients with type 2 diabetes"

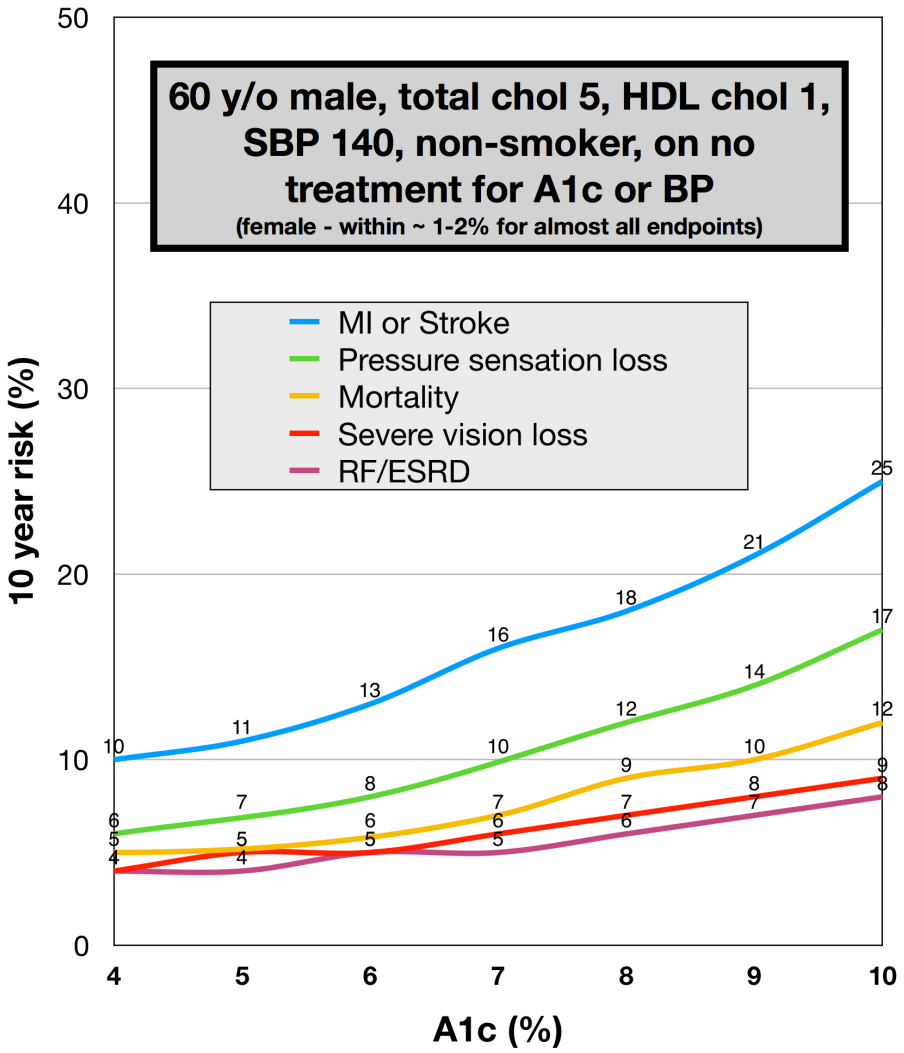
Because of harms - primarily internists

CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – *2018 EXECUTIVE SUMMARY*

"**An A1C level of ≤6.5% is considered optimal** if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time."

Because of benefits - primarily endocrinologists

T2DM risk should not be categorized as YES or NO



https://sanjaybasu.shinyapps.io/recodesi/ - from the ACCORD study

Original Article

Circ Cardiovasc Qual Outcomes. 2016;9:00-00.August 2016

Glycemic Control for Patients With Type 2 Diabetes Mellitus

Our Evolving Faith in the Face of Evidence

René Rodríguez-Gutiérrez, MD, MSc; Victor M. Montori, MD, MSc

"no significant impact of tight glycemic control"

Review

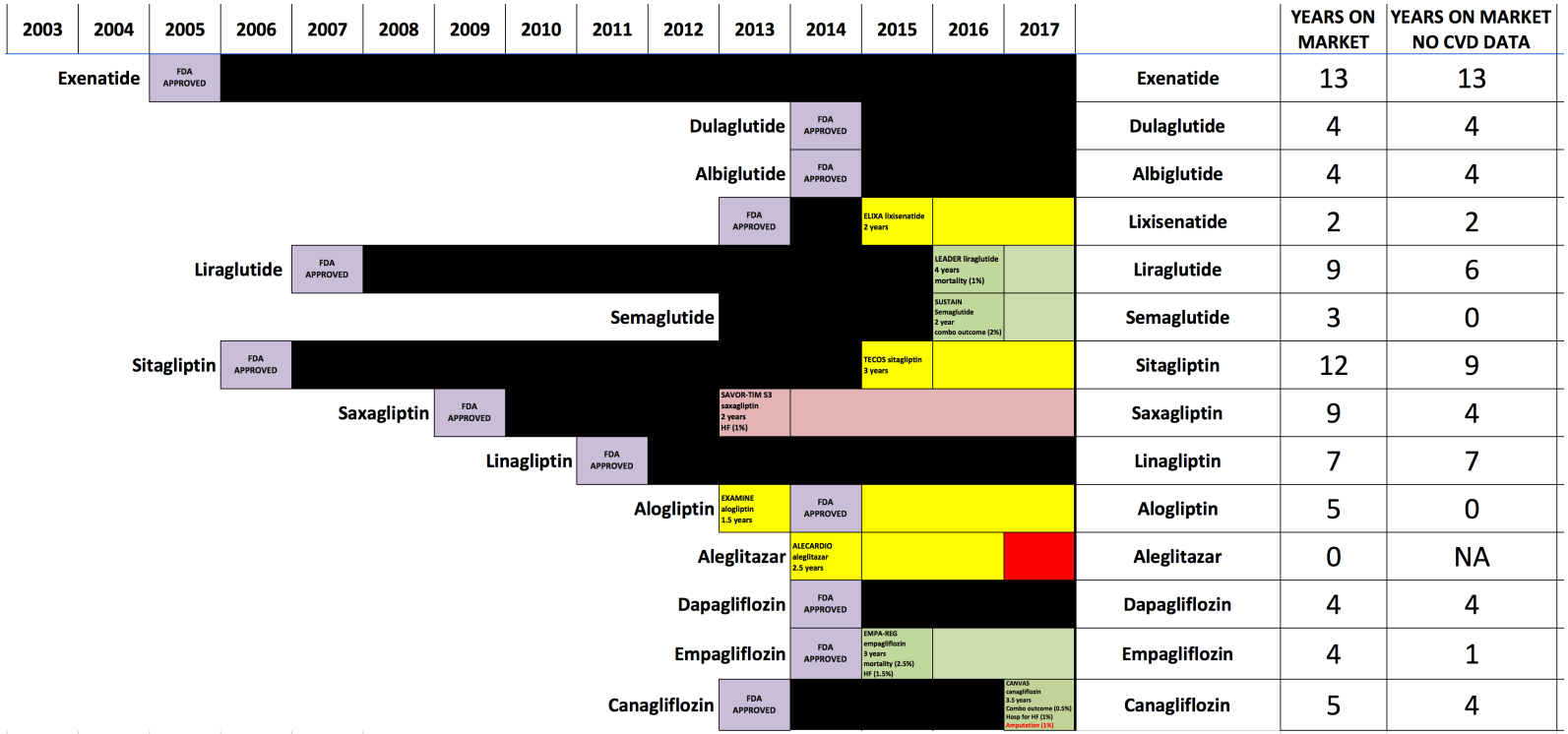
Diabetes Metab 2014 Feb 3. pii: S1262-3636

Effects of pharmacological treatments on micro- and macrovascular complications of type 2 diabetes: What is the level of evidence?

R. Boussageon [a,*], F. Gueyffier [b,c], C. Cornu [b,c,d]

"In 2013, the level of evidence for the clinical efficacy of antidiabetic drugs is disappointing and does not support the millions of prescriptions being written for them"

The History of T2DM Treatments



	YEARS ON MARKET	YEARS ON MARKET NO CVD DATA
Exenatide	13	13
Dulaglutide	4	4
Albiglutide	4	4
Lixisenatide	2	2
Liraglutide	9	6
Semaglutide	3	0
Sitagliptin	12	9
Saxagliptin	9	4
Linagliptin	7	7
Alogliptin	5	0
Aleglitazar	0	NA
Dapagliflozin	4	4
Empagliflozin	4	1
Canagliflozin	5	4

the date the drug was brought to market
the date the key clinical outcome trial(s) were published
the outcome - negative, neutral, positive
colour-coded and calculated the years with and without clinically important outcome evidence

An ~100-year History Lesson

(60 years if you don't include insulin)

30 medications

27 have had regulatory approval - 2 removed

24 have been evaluated in at least 1 RCT assessing impact on important outcomes

MY DEFINITION OF IMPORTANT OUTCOMES

1) microvascular (end-stage renal disease/dialysis, renal death, blindness, clinical neuropathy)

and/or

2) macrovascular (all cause mortality, CVD mortality, non-fatal MI, stroke, amputation, heart failure or a composite CVD endpoint)

Studies Overall

21 RCTs have evaluated 24 of the 29 medications

43% (9/21) of the medications evaluated showed NO OVERALL BENEFIT

40% (8.5/21) SHOWED SOME BENEFIT (on at least one, and TYPICALLY ONLY ONE, clinically important outcome)

17% (3.5/21) SHOWED OVERALL HARM (no benefit and harm for at least one clinically important outcome)

Medication Class	Medication
Insulin	Insulin
Biguanides	Metformin
	Phenformin
Sulfonylureas	Tolbutamide
	Chlorpropamide
	Glyburide/ glibenclamide
	Gliclazide
	Glipizide
	Glimepiride
Glitazones	Rosiglitazone
	Pioglitazone
Meglitinides	Repaglinide
	Nateglinide
Other	Acarbose
	Aleglitazar
GLP's	Exenatide
	Dulaglutide
	Albiglutide
	Lixisenatide
	Liraglutide
	Semaglutide
DPP4's	Sitagliptin
	Saxagliptin
	Linagliptin
	Alogliptin
	Omarigliptin
Gliflozins	Dapagliflozin
	Empagliflozin
	Canagliflozin
	Ertugliflozin

All the large RCTs evaluating the impact of glucose lowering medications on CVD Outcomes

RCTs evaluating the impact of medications on CVD outcomes in T2DM

YEAR	NAME		MEDICATION	RESULT	OUTCOME CHANGED	ABSOLUTE DIFFERENCE/TIME
1970	UGDP	SU	tolbutamide (Orinase)	NEGATIVE	CVD mortality	↑8%/5 years
1971		BG	phenformin (DBI)	NEGATIVE	Mortality	↑ 6%/5-8 years
1976		SU	tolbutamide (Orinase)	NEGATIVE	Fatal MI	↑ 5%/5 years
1982		IN	insulin	NEUTRAL		
1998	UKPDS 33/34	IN,SU	insulin, chlorpropamide, glyburide/glibenclamide, glipizide	NEUTRAL		
1998		IN,SU,BG	metformin, insulin, chlorpropamide, glyburide/glibenclamide, glipizide	NEUTRAL except POSITIVE for metformin	Mortality MI	↓7%/11 years ↓ 6%/11 years
2003	STOP-NIDDM	OTH	acarbose (Precose)	POSITIVE	MI	↓ 1.5%/3 years
2005	PROACTIVE	GLIT	pioglitazone (Actos)	POSITIVE	MI	↓ 1.5%/3 years
2007	RECORD	GLIT	rosiglitazone (Avandia)	NEGATIVE	Heart failure	↑ 1%/4 years
2012	ORIGIN	IN	insulin	NEUTRAL		
2013	EXAMINE	DPP4	alogliptin (Nesina)	NEUTRAL		
2014	SAVOR-TIMI 53	DPP4	saxagliptin (Onglyza)	NEGATIVE	Heart failure	↑ 1%/2 years
2014	ALECARDIO	OTH	aleglitizar	NEUTRAL		
2015	ELIXA	GLP	lixisenatide (Adlyxin)	NEUTRAL		
2015	TECOS	DPP4	sitagliptin (Januvia)	NEUTRAL		
2015	EMPA-REG	GLIF	empagliflozin (Jardiance)	POSITIVE	Mortality Heart failure	↓ 2.5%/3 years ↓ 1.5%/3 years
2016	SUSTAIN 6	GLP	semaglutide (Ozempic)	POSITIVE	Combined outcome	↓ 2%/2 years
2016	LEADER	GLP	liraglutide (Victoza)	POSITIVE	Mortality Combined outcome	↓ 1%/4 years ↓ 2.5%/4 years
2017	CANVAS	GLIF	canagliflozin (Invokana)	POSITIVE	Combined outcome Heart failure Amputations	↓ 2%/3.5years ↓ 1%/3.5 years ↑ 1%/3.5 years
2017	EXSCEL	GLP	exenatide (Byetta)	NEUTRAL		
2017	ACE	OTH	acarbose (Procose)	NEUTRAL		
2017	Omarigliptin	DPP4	omarigliptin	NEUTRAL		
2018	HARMONY	GLP	albiglutide (Tanzeum)	POSITIVE	Combined outcome	↓ 2%/2 years
2018	CARMELINA	DPP4	linagliptin (Tradjenta)	NEUTRAL		
2018	DECLARE-TIMI 58	GLIF	dapagliflozin (Farxiga)	POSITIVE	Combined outcome (primarily heart failure)	↓ 1%/4 years

Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes

A Systematic Review and Meta-analysis **NETWORK MA**

SGLT-2 vs GLP-1 vs DPP-4 vs control (placebo/no treatment)

236 trials - 176,310 subjects - follow up at least 12 weeks

~55% males, ~55 y/o, ~A1c 8.1, ~30 BMI

Outcomes - all-cause mortality, cardiovascular mortality, heart failure, myocardial infarction, unstable angina, stroke, adverse events, hypoglycemia

JAMA. 2018;319(15):1580-1591. doi:10.1001/jama.2018.3024

Outcomes compared to control - all trials
ABSOLUTE differences (%)

	All cause mortality	CV mortality	Heart failure	MI	Unstable angina	Stroke	Any Hypo-glycemia*	Adverse events leading to withdrawal
DPP-4 inhibitor	0.1 (–0.3 to 0.6)	0.0 (–0.3 to 0.4)	0.4 (0.0 to 0.8)	–0.2 (–0.5 to 0.0)	0.0 (–0.2 to 0.3)	0.0 (–0.2 to 0.4)	4.9 (2.0 to 8.4)	0.2 (-0.5 to 1)
GLP-1 agonist	–0.6 (–1.0 to –0.3)	–0.5 (–0.8 to –0.1)	–0.2 (–0.5 to 0.1)	–0.2 (–0.5 to 0.1)	0.1 (–0.3 to 0.2)	–0.2 (–0.5 to 0.0)	7.4 (4.2 to 11.1)	4.7 (3.3 to 6.5)
SGLT-2 inhibitor	–1.0 (–1.5 to –0.6)	–0.8 (–1.1 to –0.3)	–1.1 (–1.3 to –0.8)	–0.6 (–0.9 to –0.1)	0.0 (–0.3 to 0.3)	–0.2 (–0.4 to 0.2)	4.0 (1.0 to 7.6)	0.5 (-0.2 to1.5)

* no difference in major hypoglycaemia

Outcomes compared to control - CV outcome trials
ABSOLUTE differences (%)

	CV mortality, nonfatal MI and non fatal stroke
DPP-4 inhibitor	0.0 absolute #s not provided
GLP-1 agonist	–1.0 (–1.0 to –0.3)
SGLT-2 inhibitor	–1.3 (–2.3 to –0.3)

SGLT-2 = 6% risk of genital infections
DPP-4 = 0.1% risk of acute pancreatitis

Generic Name	Brand name	Strength	Dosing	90 Day Cost (unless otherwise noted)	Coverage
HYPOGLYCEMIC AGENTS					
Biguanides					
Metformin	Glucophage	500mg	2 BID	**$30**	BC / IA covered
Metformin SR	**Glumetza SR**	1000mg	2 QD	**$255**	NC by BC or IA
Sulfonylureas					
Glyburide	Diabeta	5mg	BID	**$25**	BC / IA covered
Gliclazide, Gliclazide MR	Diamicron/MR	80mg/30mg MR	BID, 2 QD MR	**$30**	BC / IA covered
Meglitinides					
Repaglinide	Gluconorm	1mg	TID	**$35**	BC / IA covered
Dipeptidylpeptidase-4 Inhibitors (DPP-4)					
Linagliptin	**Trajenta**	5mg	QD	**$265**	SA req'd for BC and IA
Saxagliptin	**Onglyza**	5mg	QD	**$295**	SA req'd for BC and IA
Sitagliptin	**Januvia**	100mg	QD	**$310**	SA req'd for BC and IA
Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors					
Empagliflozin	**Jardiance**	10mg	QD	**$270**	SA req'd for BC and IA
Canagliflozin	**Invokana**	100mg	QD	**$280**	SA req'd for BC and IA
Glucagon-like Peptide 1 Agonist (GLP-1)					
Liraglutide	**Victoza**	1.2mg SQ	QD	**$575**	NC by BC or IA
Liraglutide	**Victoza**	1.8mg SQ	QD	**$855**	NC by BC or IA
Insulin (Prices may vary between pharmacies, relative differences likely consistent. Max allowable price for 1500 Units of penfill insulin)					
Regular insulin	**Novolin Toronto/ Humulin R**	100U/mL	As dir	**$60**	BC / IA covered
Long-acting insulin	**Novolin NPH/Humulin N**	100U/mL	As dir	**$65**	BC / IA covered
Rapid-acting insulin	**Novorapid/Humalog**	100U/mL	As dir	**$75**	BC / IA covered
Basal insulin (Glargine)	Basaglar	100U/mL	As dir	**$90**	BC covered, NC by IA
Basal insulin (Glargine)	**Toujeo**	300U/mL	As dir	**$110**	NC by BC or IA
Basal insulin (Glargine)	**Lantus**	100U/mL	As dir	**$115**	BC / IA covered
Basal insulin (Detemir)	**Levemir**	100U/mL	As dir	**$130**	BC / IA covered
OBESITY					
Orlistat	**Xenical**	120mg	TID	**$505**	NC by BC or IA
Liraglutide	**Saxenda**	3mg SQ	QD	**$1,165**	NC by BC or IA

LEGEND:
BC = Alberta Blue Cross, IA = Indian Affairs, NC = Not covered, SA = special authorization, SR = sustained release, OTC = over the counter, SQ = subcutaneous injection, SS=Social Services

https://www.acfp.ca/wp-content/uploads/2018/03/ACFPPricingDoc2018.pdf

Let's extrapolate the best case example to 10 years

~2% absolute benefit over ~3.5 years - few new agents primarily only in secondary prevention

~6% absolute benefit over 10 years

in the best case example at least 94% of people will get no benefit, some will get harm (hypoglycemia, genital infections, Gi disturbance), and all will experience the inconvenience and cost of treating for 10 years

~3500 pills or injections

the new agents cost ~ $12,000 for 10 years - basal insulin ~$4,000, metformin ~$1,200 plus any monitoring costs

NOBODY will feel better because of these treatments

Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events

Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)

Nov 13, 2017

"Canagliflozin reduced cardiovascular outcomes with no statistical evidence of heterogeneity of the treatment effect across the primary and secondary prevention groups"

Secondary

"Canagliflozin reduced cardiovascular outcomes with no statistical evidence of heterogeneity of the treatment effect across the primary and secondary prevention groups"

NEJM Journal Watch

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INFORMING PRACTICE

Nov 15, 2017

Canagliflozin Works as Both Primary and Secondary Prevention in Patients with Diabetes Type 2

Joel M. Gore, MD reviewing Mahaffey KW et al. Circulation 2017 Nov 13

P&T Community

THE ONLINE RESOURCE FOR P&T DECISION MAKERS

CURRENT ISSUE OF P&T

November 2017

Invokana Demonstrates Cardiovascular Benefit for Type-2 Diabetes Patients

Outcomes Improve for Those With and Without a History of Prior CV Events

DIABETES IN CONTROL

News and information for Medical Professionals.

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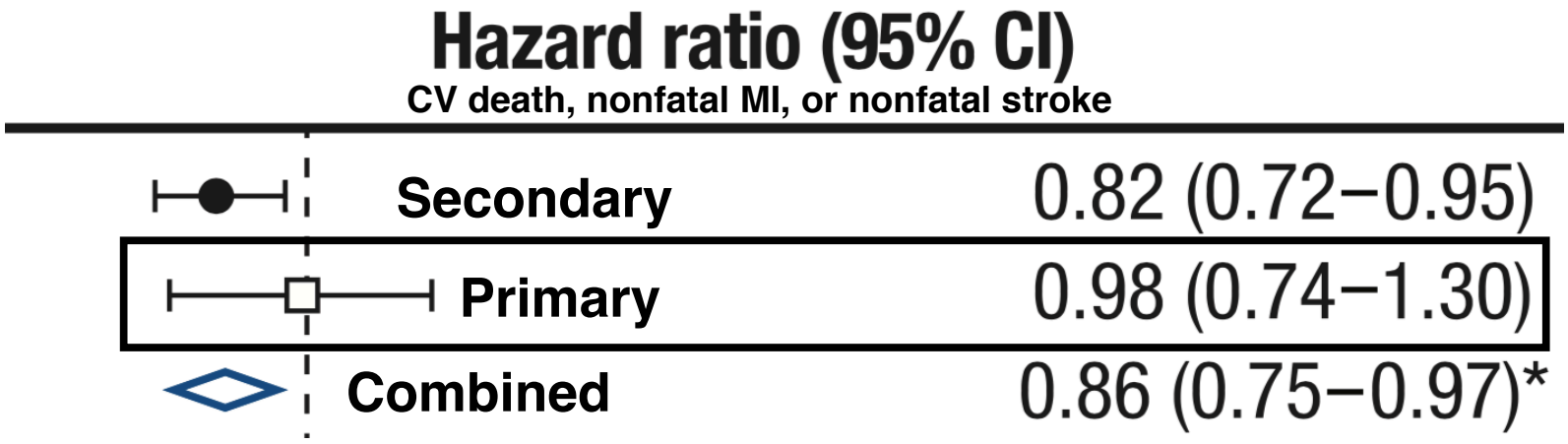
premise. The results showed that the SGLT-2 inhibitor was effective in reducing the risk of CV outcomes in patients with and without a prior history of cardiovascular disease. Patients in the

	Number of participants	Patients per 1000 patient-years		Hazard ratio (95% CI)		Interaction *P* value
		Canagliflozin	Placebo			
CV death, nonfatal MI, or nonfatal stroke	796	34.1	41.3	Secondary	0.82 (0.72–0.95)	0.18
	215	15.8	15.5	Primary	0.98 (0.74–1.30)	
	1011	26.9	31.5	Combined	0.86 (0.75–0.97)*	



Effect of Sodium-Glucose Cotransport-2 Inhibitors on Blood Pressure in People With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of 43 Randomized Control Trials With 22 528 Patients

Mohsen Mazidi, PhD; Peyman Rezaie, MSc; Hong-Kai Gao, MD, PhD; Andre Pascal Kengne, MD, PhD

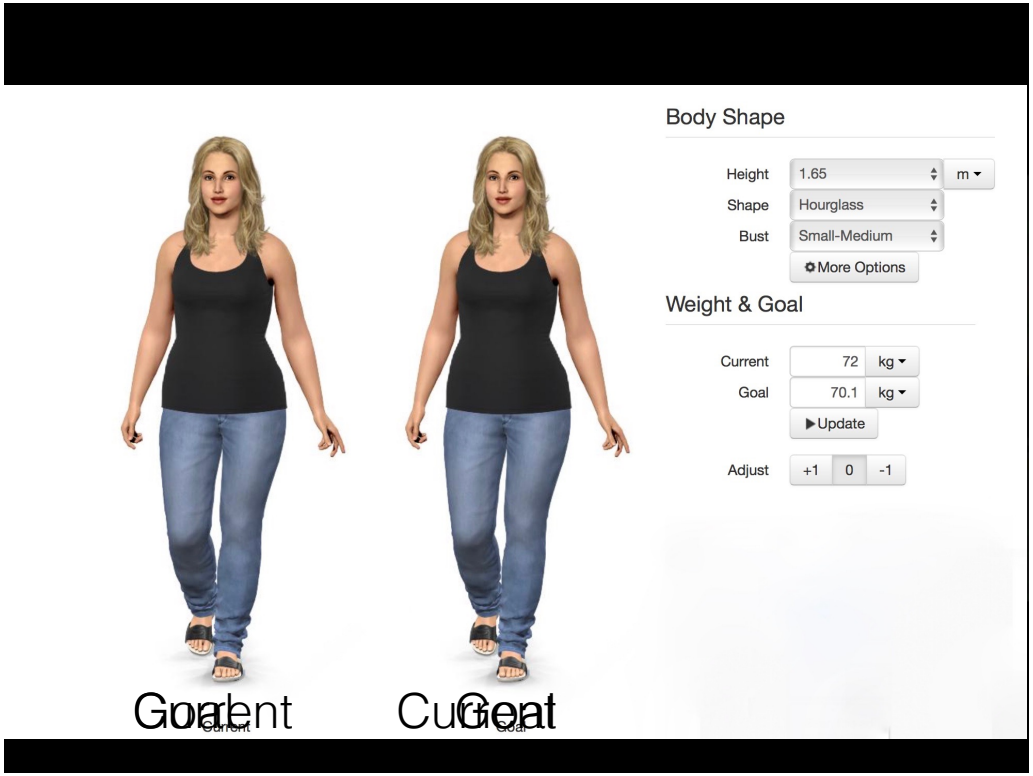
J Am Heart Assoc. 2017;6:e004007. DOI: 10.1161/JAHA.116.004007

Effect on systolic blood pressure

⬇ 2.46 mmHg

Weight

⬇1.88 kg



Additional issues in the elderly

Can J Diabetes 42 (2018) S283–S295

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

2018 Clinical Practice Guidelines

Diabetes in Older People

Older ~70

Diabetes Canada Clinical Practice Guidelines Expert Committee

Personalized strategies are needed to avoid overtreatment of the frail elderly.

In the older person with diabetes and multiple comorbidities and/or frailty, strategies should be used to strictly prevent hypoglycemia, which include the choice of antihyperglycemic therapy and a less stringent A1C target

Sulphonylureas should be used with caution because the risk of hypoglycemia increases significantly with age.

DPP-4 inhibitors should be used over sulfonylureas because of a lower risk of hypoglycemia.

Long-acting basal analogues are associated with a lower frequency of hypoglycemia than intermediate-acting or premixed insulin in this age group

Can J Diabetes 2018;42:S283–S295

Clinical Frailty Scale

1. Very fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2. Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3. Managing well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4. Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5. Mildly frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6. Moderately frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7. Severely frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8. Very severely frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. Terminally Ill – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia,** recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia,** they cannot do personal care without help.

Can J Diabetes 2018;42:S283–S295

Table 2
Guideline recommendations for key clinical outcomes for older people with diabetes from Diabetes Canada (DC), American Diabetes Association (ADA) and International Diabetes Federation (IDF)

Measure	ADA	DC	IDF
A1C	Healthy: <7.5% Complex/Intermediate: <8.0% Very Complex/Poor Health: <8.5%	Functionally independent: ≤ 7.0% Functionally dependent: 7.1–8.0% Frail and/or dementia: 7.1–8.5% End of life: A1C measurement not recommended. Avoid symptomatic hyperglycemia and any hypoglycemia.	Functionally independent: 7.0%–7.5% Functionally dependent: 7.0%–8.0% Sub-level frail: <8.5% Sub-level dementia: <8.5% End of life: avoid symptomatic hyperglycemia
Blood Pressure	Healthy: <140/80 mmHg Complex/Intermediate: <140/80 mmHg Very Complex/Poor Health: <150/90 mmHg	Functionally independent with life expectancy >10 years: <130/80 mmHg Functionally dependent, orthostasis or limited life expectancy: individualize BP targets	Functionally independent: <140/90 mmHg Functionally dependent: <140/90 mmHg Sub-level frail: <150/90 mmHg Sub-level dementia: <140/90 mmHg End of life: strict BP control may not be necessary
LDL-C	<1.8 mmol/L	<2.0 mmol/L or >50% reduction from baseline	<2.0 mmol/L and adjusted based on CV risk

Adapted from ADA (42) and IDF (40).
A1C, glycated hemoglobin; *BP*; blood pressure; *CV*, cardiovascular; *LDL-C*, low density lipoprotein cholesterol.

Diabetes Care program of Nova Scotia

D/C drugs that result in blood glucose levels less than 7.0 mmol/L or HbA1c levels below 8% in the severely frail

Blood glucose targets below 20 mmol/L (as long as the patient is asymptomatic) and HbA1c levels below 12% are advocated in severely frail individuals.

Intensive glucose control

is associated with increased risk of severe hypoglycemia (RR=2.18, 95% CI 1.53 to 3.11) and increased risk of adverse drug events (hospitalizations and life-threatening events)

risk of hypoglycemia and its consequences is known to be increased in older persons

does not reduce risk of all-cause or cardiac mortality; however, it can reduce nonfatal MI risk, and risk of microvascular complications

Can Fam Physician 2017;63:832-43

How to decrease hypoglycemia

there is no hurry to lower glucose

remember renal/liver age issues

higher A1c threshold

use very low doses

sulphonylureas - avoid

DPP-4 lower risk of hypoglycaemia - most “evidence” in the elderly

regular diets vs diabetic diets

avoid sliding scale insulin protocols

more value in dec BP than glucose

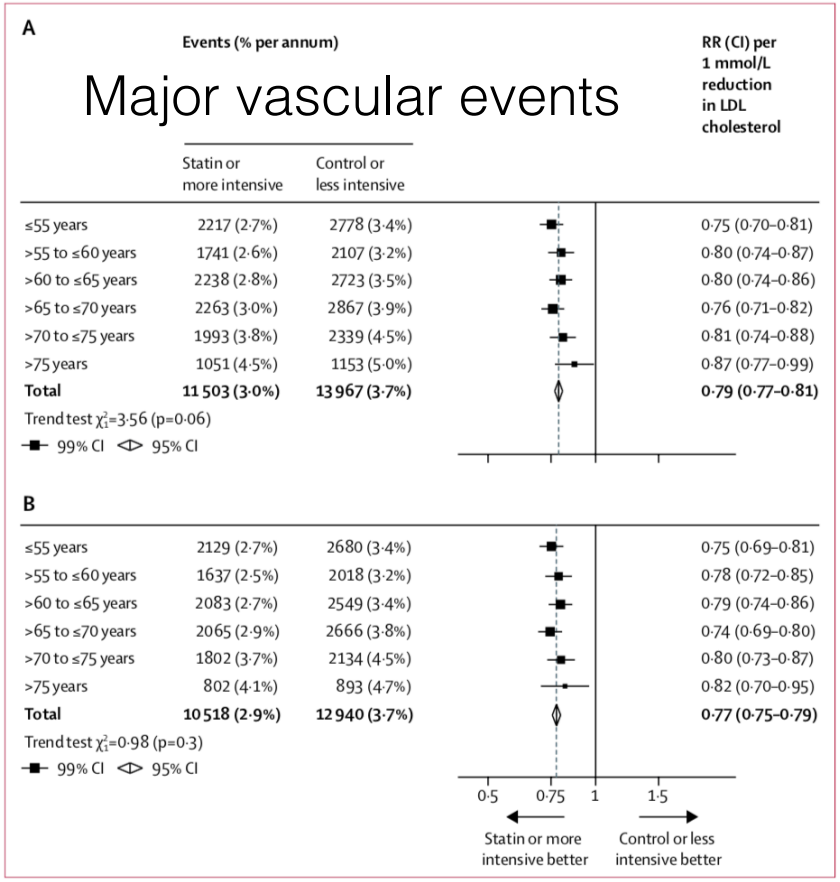
most get no clinical benefit from treatment

get sick or don’t eat - stop meds

reduce complexity - memory problems

Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials

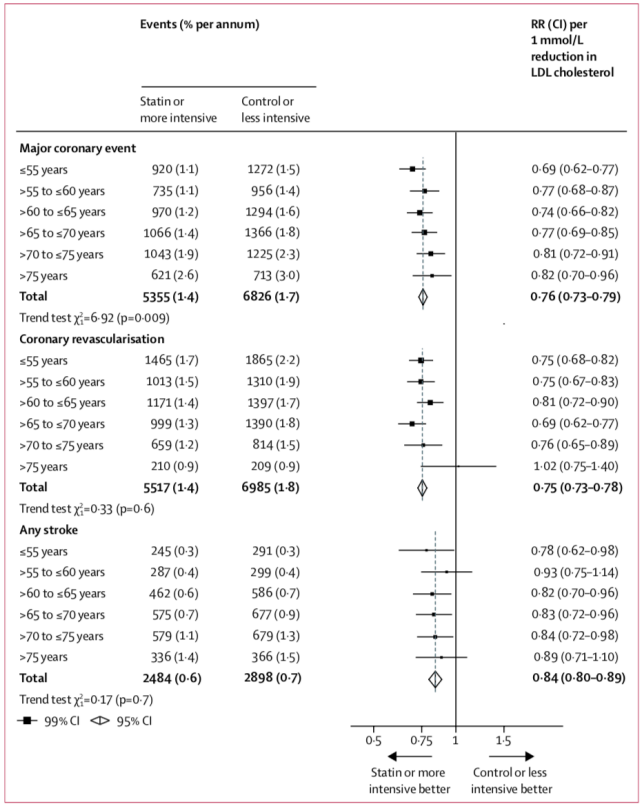
*Cholesterol Treatment Trialists' Collaboration**



Lancet 2019;393:407–15

Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials

*Cholesterol Treatment Trialists' Collaboration**



	Events (% per annum)		RR (CI) per 1 mmol/L reduction in LDL cholesterol
	Statin or more intensive	Control or less intensive	
Major coronary event			
≤55 years	920 (1·1)	1272 (1·5)	0·69 (0·62–0·77)
>55 to ≤60 years	735 (1·1)	956 (1·4)	0·77 (0·68–0·87)
>60 to ≤65 years	970 (1·2)	1294 (1·6)	0·74 (0·66–0·82)
>65 to ≤70 years	1066 (1·4)	1366 (1·8)	0·77 (0·69–0·85)
>70 to ≤75 years	1043 (1·9)	1225 (2·3)	0·81 (0·72–0·91)
>75 years	621 (2·6)	713 (3·0)	0·82 (0·70–0·96)
Total	**5355 (1·4)**	**6826 (1·7)**	**0·76 (0·73–0·79)**
Trend test χ^2_1=6·92 (p=0·009)			
Coronary revascularisation			
≤55 years	1465 (1·7)	1865 (2·2)	0·75 (0·68–0·82)
>55 to ≤60 years	1013 (1·5)	1310 (1·9)	0·75 (0·67–0·83)
>60 to ≤65 years	1171 (1·4)	1397 (1·7)	0·81 (0·72–0·90)
>65 to ≤70 years	999 (1·3)	1390 (1·8)	0·69 (0·62–0·77)
>70 to ≤75 years	659 (1·2)	814 (1·5)	0·76 (0·65–0·89)
>75 years	210 (0·9)	209 (0·9)	1·02 (0·75–1·40)
Total	**5517 (1·4)**	**6985 (1·8)**	**0·75 (0·73–0·78)**
Trend test χ^2_1=0·33 (p=0·6)			
Any stroke			
≤55 years	245 (0·3)	291 (0·3)	0·78 (0·62–0·98)
>55 to ≤60 years	287 (0·4)	299 (0·4)	0·93 (0·75–1·14)
>60 to ≤65 years	462 (0·6)	586 (0·7)	0·82 (0·70–0·96)
>65 to ≤70 years	575 (0·7)	677 (0·9)	0·83 (0·72–0·96)
>70 to ≤75 years	579 (1·1)	679 (1·3)	0·84 (0·72–0·98)
>75 years	336 (1·4)	366 (1·5)	0·89 (0·71–1·10)
Total	**2484 (0·6)**	**2898 (0·7)**	**0·84 (0·80–0·89)**
Trend test χ^2_1=0·17 (p=0·7)			

***Figure 3*: Effects on components of major vascular events per mmol/L reduction in LDL cholesterol in all studies, by age at randomisation**

Data from participants with missing baseline data included in the totals. RR=rate ratio.

Webfigure 6: Effects on ANY DEATH per mmol/L reduction in LDL cholesterol, by age at randomisation

a) All studies

	Events (% p.a.) Statin/more	Events (% p.a.) Control/less	RR (CI) per 1 mmol/L reduction in LDL–C	Trend test
≤ 55 years	689 (0.8)	810 (0.9)	0.83 (0.72 – 0.95)	
>55, ≤ 60 years	844 (1.2)	885 (1.3)	0.97 (0.85 – 1.09)	
>60, ≤ 65 years	1451 (1.7)	1694 (2.0)	0.85 (0.78 – 0.93)	
>65, ≤ 70 years	2016 (2.5)	2215 (2.8)	0.89 (0.82 – 0.96)	χ^2_1=4.20 (p=0.04)
>70, ≤ 75 years	2153 (3.9)	2202 (3.9)	0.96 (0.89 – 1.04)	
>75 years	1551 (6.2)	1638 (6.6)	0.93 (0.85 – 1.03)	
Total	**8704 (2.2)**	**9444 (2.3)**	**0.91 (0.88 – 0.93)**	

b) Excluding four trials that exclusively included participants with heart failure or on dialysis

	Events (% p.a.) Statin/more	Events (% p.a.) Control/less	RR (CI) per 1 mmol/L reduction in LDL–C	Trend test
≤ 55 years	544 (0.6)	649 (0.8)	0.82 (0.71 – 0.95)	
>55, ≤ 60 years	662 (1.0)	725 (1.1)	0.92 (0.80 – 1.06)	
>60, ≤ 65 years	1144 (1.4)	1347 (1.7)	0.84 (0.76 – 0.93)	
>65, ≤ 70 years	1576 (2.1)	1776 (2.4)	0.87 (0.79 – 0.95)	χ^2_1=2.38 (p=0.1)
>70, ≤ 75 years	1610 (3.1)	1695 (3.3)	0.93 (0.85 – 1.02)	
>75 years	850 (4.1)	869 (4.3)	0.91 (0.78 – 1.06)	
Total	**6386 (1.7)**	**7061 (1.8)**	**0.88 (0.85 – 0.91)**	

Data on participants with missing baseline data included in totals.

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Deprescribing antihyperglycemic agents in older persons

Evidence-based clinical practice guideline

In those on antihyperglycemics >65

risk for hypoglycaemia (tight control, advancing age, insulin, sulfonlyurea etc)

Uncertainty of clinical benefit due to frailty, dementia etc

Reduce dose - especially those renally eliminated
(metformin, sitagliptin)

Switch agents - sulfonlyureas to non-sulfonlyureas - reducing the dose (particularly of prandial insulin) MIGHT minimize hypoglycemia risk, or using insulin detemir or glargine instead of isophane or mixed insulin MIGHT reduce risk of nocturnal hypoglycemia

Antihyperglycemics and Hypoglycemia Risk

Drug	Causes hypoglycemia?
Alpha-glucosidase inhibitor	No
Dipeptidyl peptidase-4 (DPP-4) inhibitors	No
Glucagon-like peptide-1 (GLP-1) agonists	No
Insulin	Yes (highest risk with regular insulin and NPH insulin)
Meglitinides	Yes (low risk)
Metformin	No
Sodium-glucose linked transporter 2 (SGLT2) inhibitors	No
Sulfonylureas	Yes (highest risk with glyburide and lower risk with gliclazide)
Thiazolidinediones (TZDs)	No

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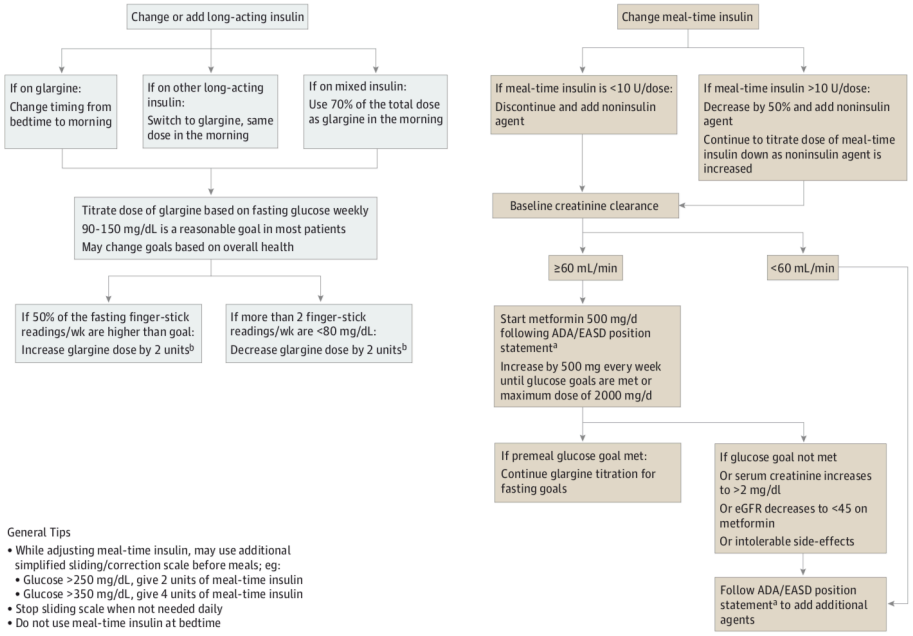
Simplification of insulin regimen

Figure. Algorithm for Insulin Regimen Simplification



Insulin regimen simplification is achieved in this algorithm by changing to or adding glargine as basal insulin and adding noninsulin agents to replace meal-time insulins. Long-acting insulins include insulin detemir (Levemir; Novo Nordisk) and Neutral Protamine Hagedorn insulin. Meal-time insulins include insulin lispro (Humalog; Lilly), insulin aspart (NovoLog; Novo Nordisk), and insulin glulisine (Apidra; Sanofi-Aventis) All patients were 65 years or older with type 2 diabetes, took 2 or more insulin injections/d, and had at least 1 episode of hypoglycemia (glucose level <70 mg/dL) during a 5-day period of continuous glucose monitoring.

[a] Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (http://www.ncbi.nlm.nih.gov/pubmed/25538310). Further simplification agents were chosen based on risk of hypoglycemia, cost, adverse-effect profile, effect on weight, and effectiveness, as recommended.

[b] If fasting glucose levels are higher than the goal but prelunch or dinner glucose levels reach the goal, change the glargine dose to bedtime at the same dose.

65 patients > 65
on 2 or more injections/day
with a history of hypoglycemia
8 months - single arm

Similar glucose control
Cut duration of hypoglycaemia by 2/3
(as measured by
continuous glucose control)

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So if some medications have been shown to lower glucose but not change outcomes, and for some the change is at most 1%/ year what the !@#$% should you do?

Emphasize, EMphasize, EMPhasize physical activity and eating "healthy" food

Don't emphasize targets - an A1c of 7-8 is quite reasonable - even higher in the elderly - focus on not causing hypoglycaemia

The medications with the best of the weakest evidence are metformin, and then just in secondary prevention empagliflozin/canagliflozin, maybe liraglutide

They all cause side effects

We don't really know about long-term adverse effects

The new agents are not inexpensive