Initiation of Glucose lowering medication in the management of type2 diabetes /metformin

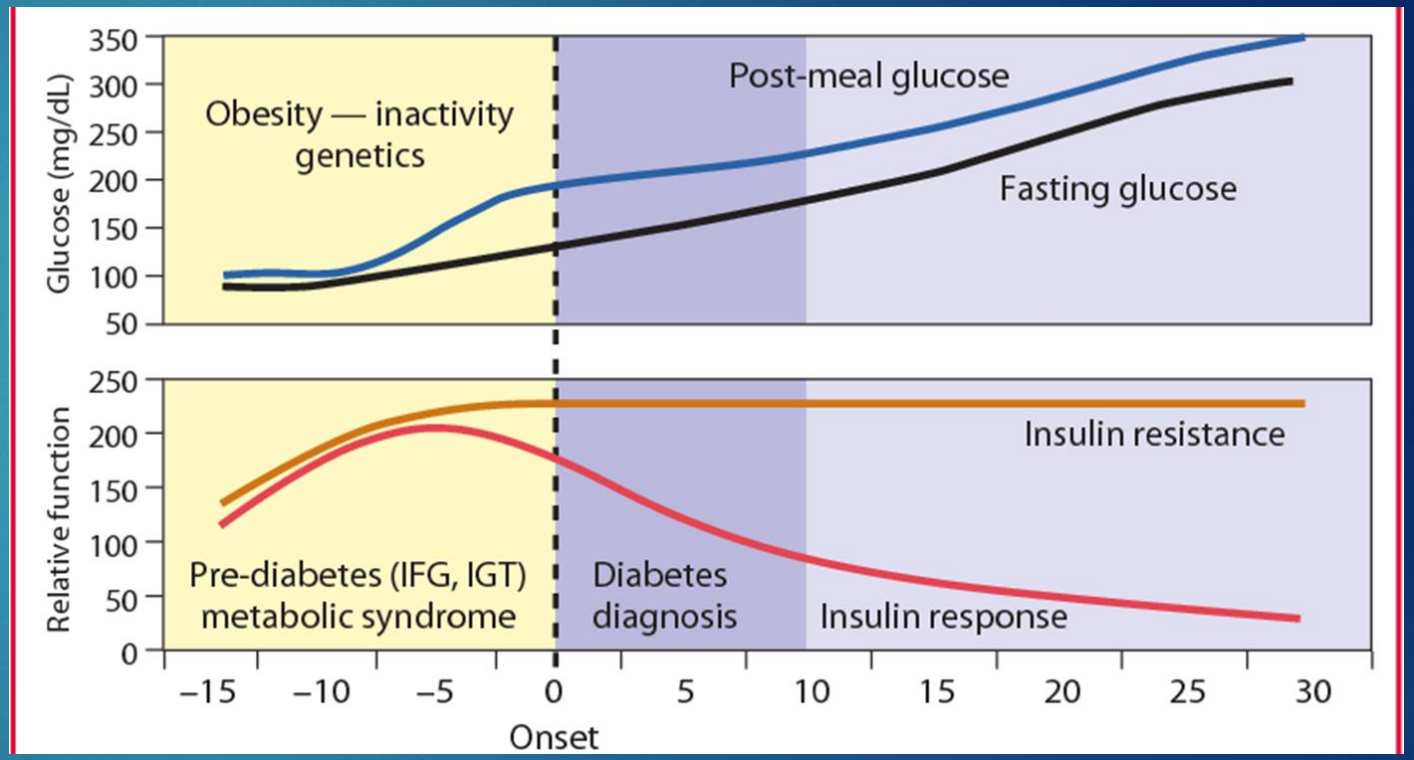
NOOSHIN AHMADI
ENDOCRINOLOGIST
LABBAFINEJAD HOSPITAL

Agenda

- Initiation of glucose lowering agent
- Metformin
- Beneficial effect of metformin
- Side effect of metformin
- Dosing and titration

When to start pharmacological management

- Pharmacotherapy should be started at the time type 2 diabetes is diagnosed, without delay, unless there are contraindications



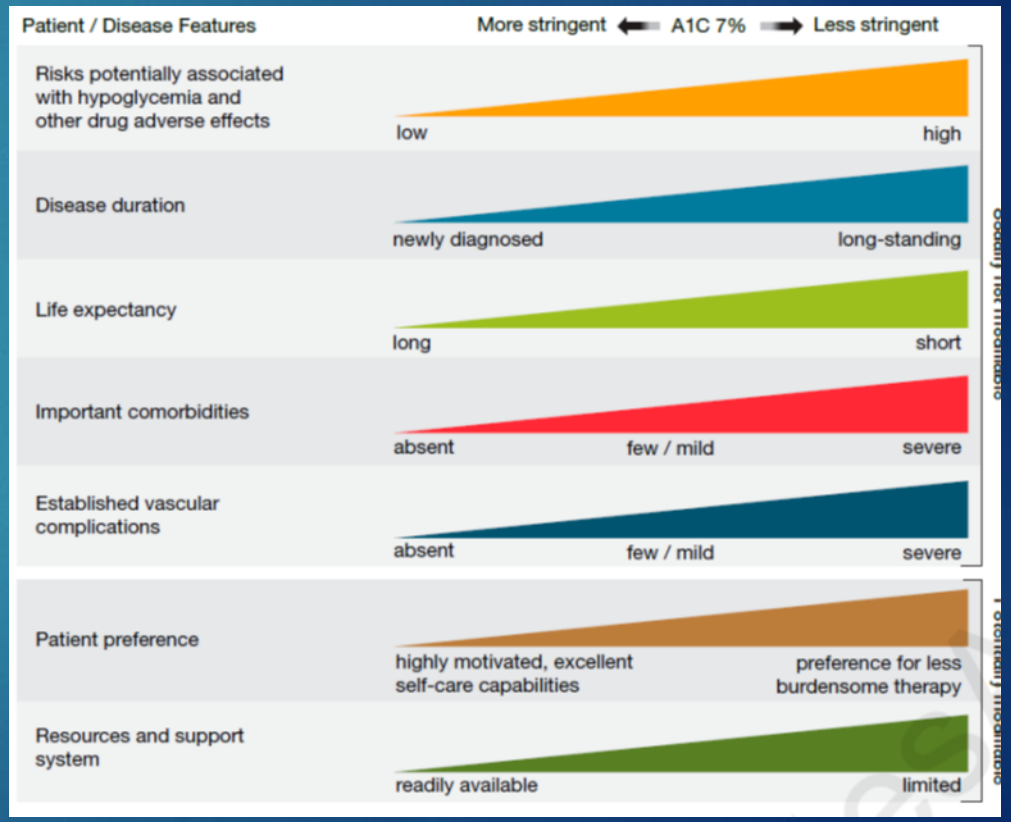
Goal of diabetes treatment

- attempts to achieve near normoglycemia,
- treatment of cardiovascular and other long-term risk factors(smoking cessation; blood pressure control; reduction in serum lipids with a statin; diet, exercise, and weight loss or maintenance)

multifactorial person-centered approach

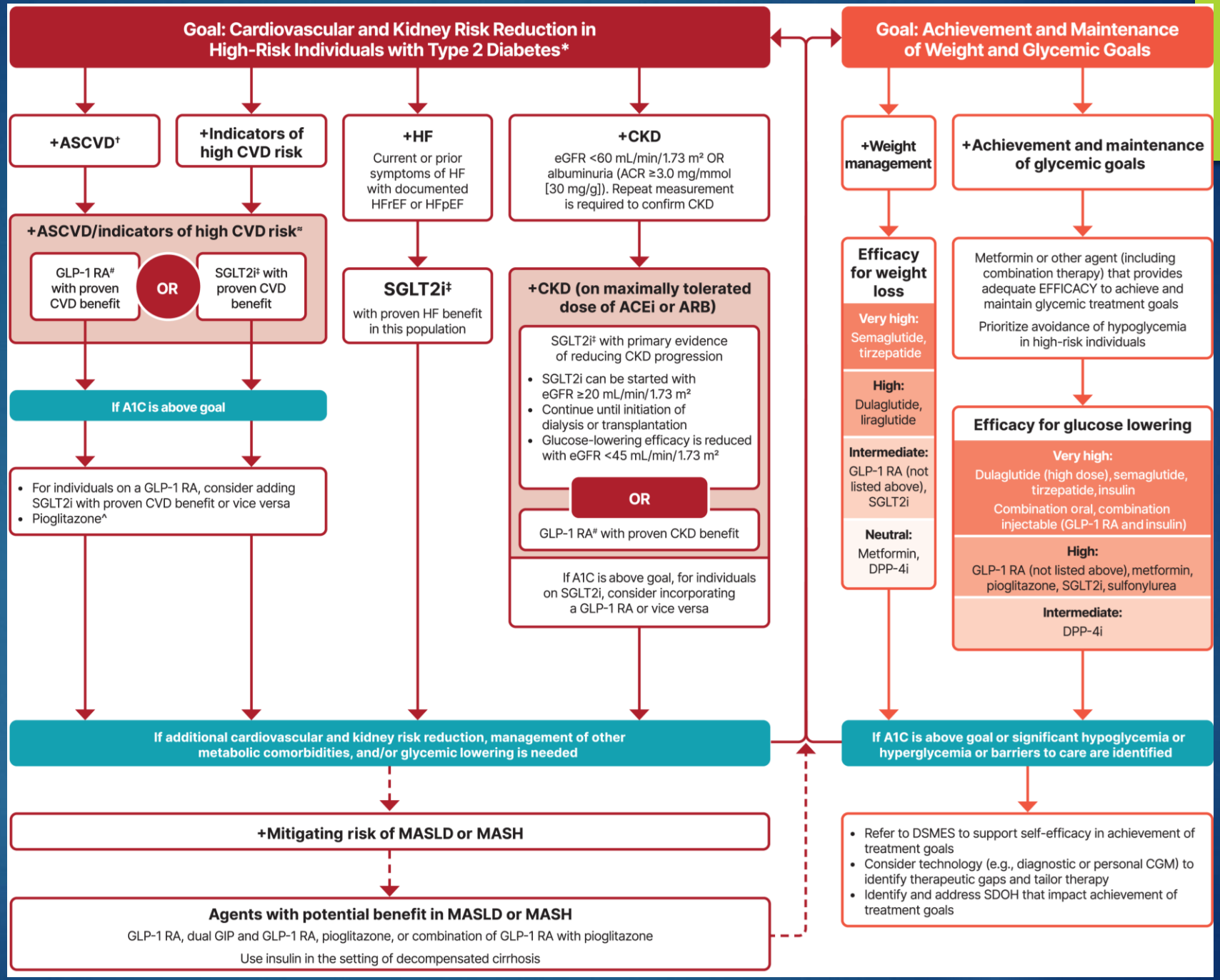
Person-specific factors that affect choice of treatment include:

- individualized glycemic goal
- weight goals, impact on weight
- hypoglycemia and cardiorenal protection
- side effect profiles of medications
- complexity of regimen
- Access and availability of medication
- cost



Choice of Glucose-Lowering Therapy

- achieve treatment goals
- In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or chronic kidney disease (CKD), the treatment regimen should include agents that reduce cardiorenal risk
- Without established cardiovascular or kidney disease Weight management is an impactful component of glucose-lowering management in type 2 diabetes

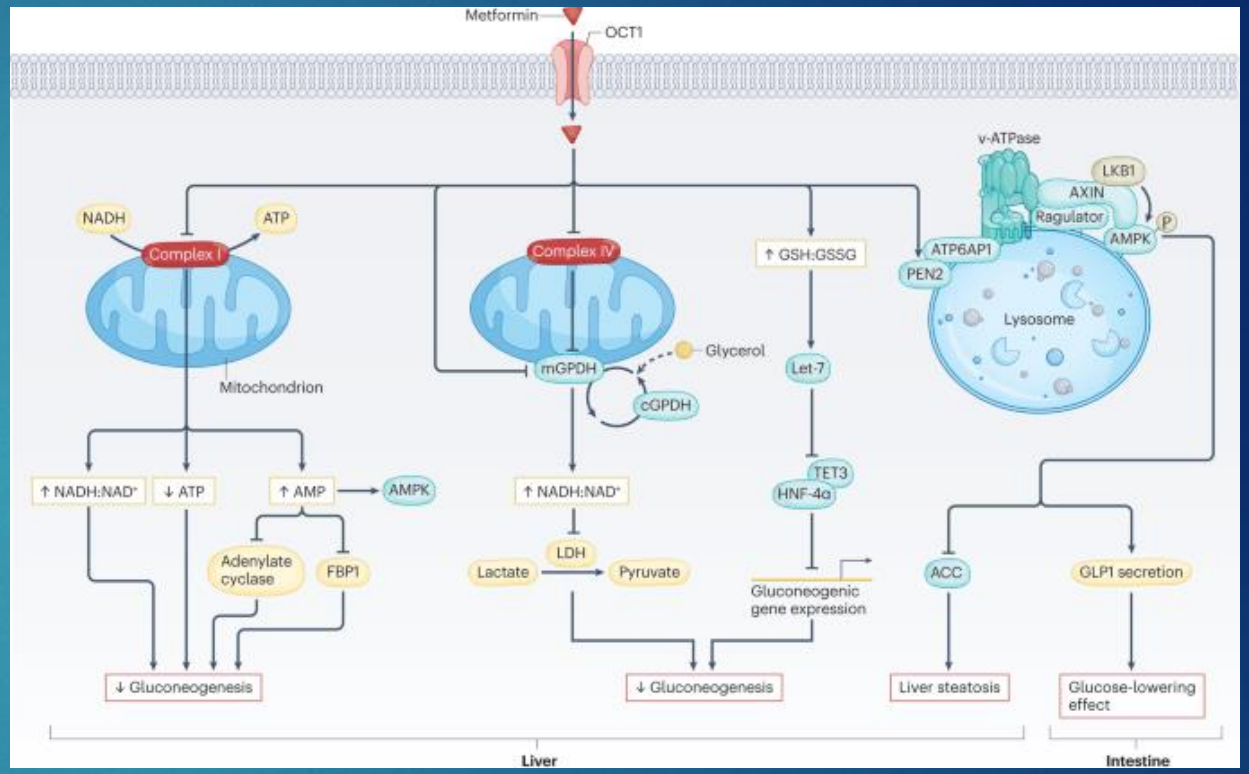

Goal: Cardiovascular and Kidney Risk Reduction in High-Risk Individuals with Type 2 Diabetes*
+ASCVD†
+Indicators of high CVD risk
+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF
+CKD
eGFR <60 mL/min/1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). Repeat measurement is required to confirm CKD
+ASCVD/indicators of high CVD risk¤
GLP-1 RA# with proven CVD benefit
OR
SGLT2i‡ with proven CVD benefit
SGLT2i‡
with proven HF benefit in this population
+CKD (on maximally tolerated dose of ACEi or ARB)
SGLT2i‡ with primary evidence of reducing CKD progression
SGLT2i can be started with eGFR ≥20 mL/min/1.73 m²
Continue until initiation of dialysis or transplantation
Glucose-lowering efficacy is reduced with eGFR <45 mL/min/1.73 m²
OR
GLP-1 RA# with proven CKD benefit
If A1C is above goal
For individuals on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
Pioglitazone^
If A1C is above goal, for individuals on SGLT2i, consider incorporating a GLP-1 RA or vice versa
If additional cardiovascular and kidney risk reduction, management of other metabolic comorbidities, and/or glycemic lowering is needed
+Mitigating risk of MASLD or MASH
Agents with potential benefit in MASLD or MASH
GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone, or combination of GLP-1 RA with pioglitazone
Use insulin in the setting of decompensated cirrhosis
Goal: Achievement and Maintenance of Weight and Glycemic Goals
+Weight management
+Achievement and maintenance of glycemic goals
Efficacy for weight loss
Very high:
Semaglutide, tirzepatide
High:
Dulaglutide, liraglutide
Intermediate:
GLP-1 RA (not listed above), SGLT2i
Neutral:
Metformin, DPP-4i
Metformin or other agent (including combination therapy) that provides adequate EFFICACY to achieve and maintain glycemic treatment goals
Prioritize avoidance of hypoglycemia in high-risk individuals
Efficacy for glucose lowering
Very high:
Dulaglutide (high dose), semaglutide, tirzepatide, insulin
Combination oral, combination injectable (GLP-1 RA and insulin)
High:
GLP-1 RA (not listed above), metformin, pioglitazone, SGLT2i, sulfonylurea
Intermediate:
DPP-4i
If A1C is above goal or significant hypoglycemia or hyperglycemia or barriers to care are identified
Refer to DSMES to support self-efficacy in achievement of treatment goals
Consider technology (e.g., diagnostic or personal CGM) to identify therapeutic gaps and tailor therapy
Identify and address SDOH that impact achievement of treatment goals

metformin

- metformin (1,1-dimethylbiguanide hydrochloride)
- mainly absorbed in the upper small intestine
- Metformin is the only biguanide available in the united state.
- For the past 60 years, has been the most commonly used glucose-lowering agent

Mechanism of action

- decrease hepatic glucose output by inhibiting gluconeogenesis
- increases insulin-mediated glucose utilization in peripheral tissues (such as muscle and liver),
- suppresses lipogenesis and lowers cellular fatty acid synthesis in liver and muscle
- extrahepatic mechanisms including direct actions of the drug on intestinal cells or alterations in the composition and metabolic profile of the gut microbiota
- may play a role in inhibiting cell growth



Metformin: Update on mechanisms of action and repurposing potential. Nature Reviews Endocrinology. 2023 Aug;19(8):460-76.

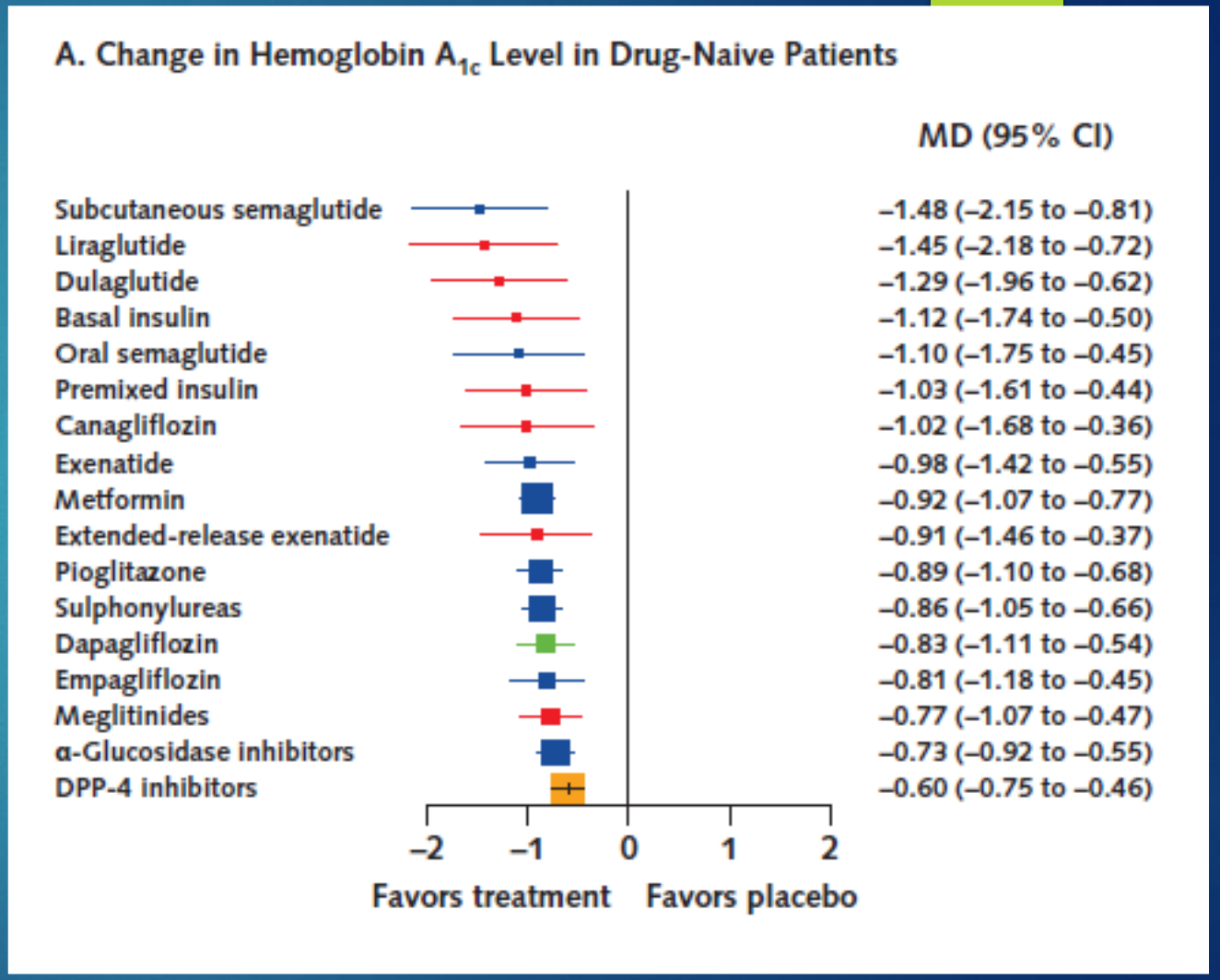
Metformin and HBA1c reduction

- All treatments reduced hemoglobin

A1c level ranging from 1.48% for subcutaneous semaglutide to 0.60% for DPP-4 inhibitors

- All treatments reduced hemoglobin

A1c level to a similar extent with metformin, except for DPP-4 inhibitors

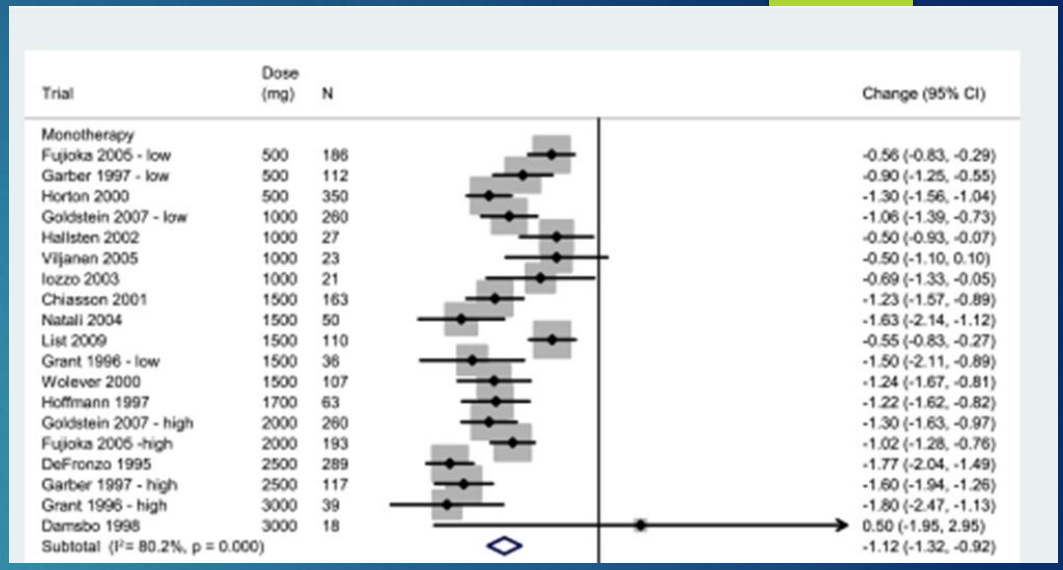


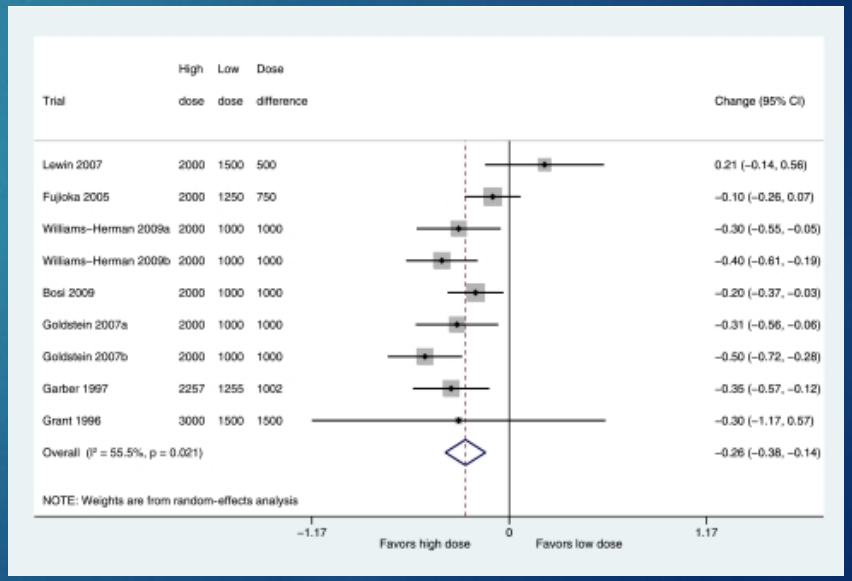
Tsapas A, Avgerinos I, Karagiannis T, Malandris K, Manolopoulos A, Andreadis P, Liakos A, Matthews DR, Bekiari E. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. Annals of internal medicine. 2020 Aug 18;173(4):278-86.

Metformin and HBA1c reduction

- Metformin monotherapy lowered HbA1c by 1.12% (95% CI 0.92–1.32); versus placebo

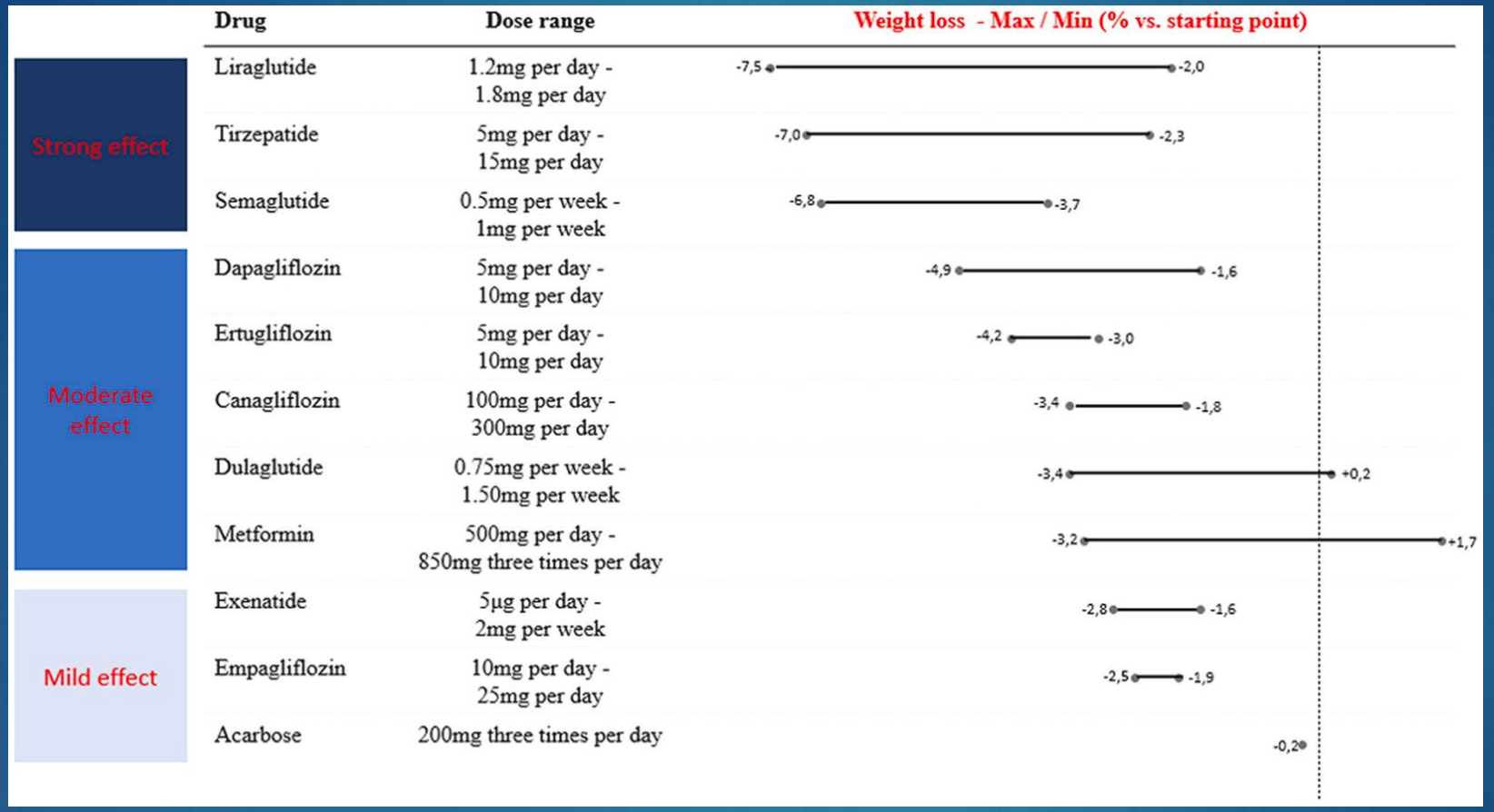
- a significantly greater reduction in HbA1c(0.26% (95% CI 0.14–0.38) using higher doses of metformin compared with lower doses of metformin with no significant increase in side effects.





Hirst JA, Farmer AJ, Ali R, Roberts NW, Stevens RJ. Quantifying the effect of metformin treatment and dose on glycemic control. Diabetes care. 2012 Feb 1;35(2):446-54.

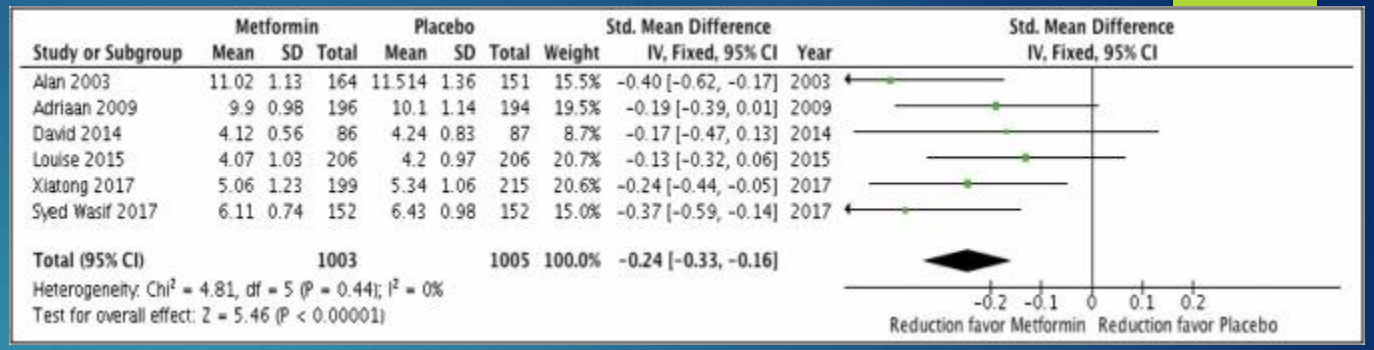
Metformin is associated with less weight gain and a modest weight loss than other agent



Lazzaroni E, Nasr MB, Loretelli C, Pastore I, Plebani L, Lunati ME, Vallone L, Bolla AM, Rossi A, Montefusco L, Ippolito E. Anti-diabetic drugs and weight loss in patients with type 2 diabetes. Pharmacological Research. 2021 Sep 1;171:105782.

Metformin and lipid profile

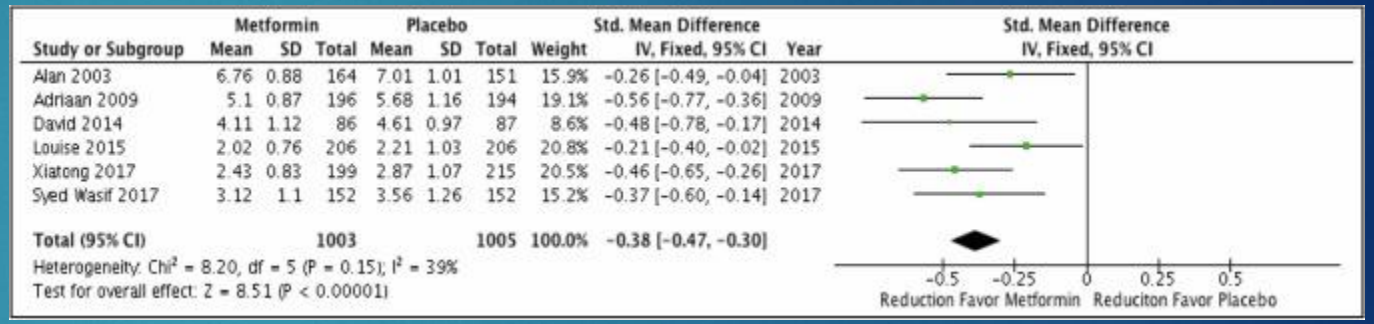
- effect of metformin on the Total Cholesterol, LDL and triglycerides in patients with type 2 diabetes mellitus



Study or Subgroup	Metformin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Alan 2003	11.02	1.13	164	11.514	1.36	151	15.5%	-0.40 [-0.62, -0.17]	2003
Adriaan 2009	9.9	0.98	196	10.1	1.14	194	19.5%	-0.19 [-0.39, 0.01]	2009
David 2014	4.12	0.56	86	4.24	0.83	87	8.7%	-0.17 [-0.47, 0.13]	2014
Louise 2015	4.07	1.03	206	4.2	0.97	206	20.7%	-0.13 [-0.32, 0.06]	2015
Xiatong 2017	5.06	1.23	199	5.34	1.06	215	20.6%	-0.24 [-0.44, -0.05]	2017
Syed Wasif 2017	6.11	0.74	152	6.43	0.98	152	15.0%	-0.37 [-0.59, -0.14]	2017
Total (95% CI)			**1003**			**1005**	**100.0%**	**-0.24 [-0.33, -0.16]**	

Heterogeneity: Chi² = 4.81, df = 5 (P = 0.44); I² = 0%
Test for overall effect: Z = 5.46 (P < 0.00001)

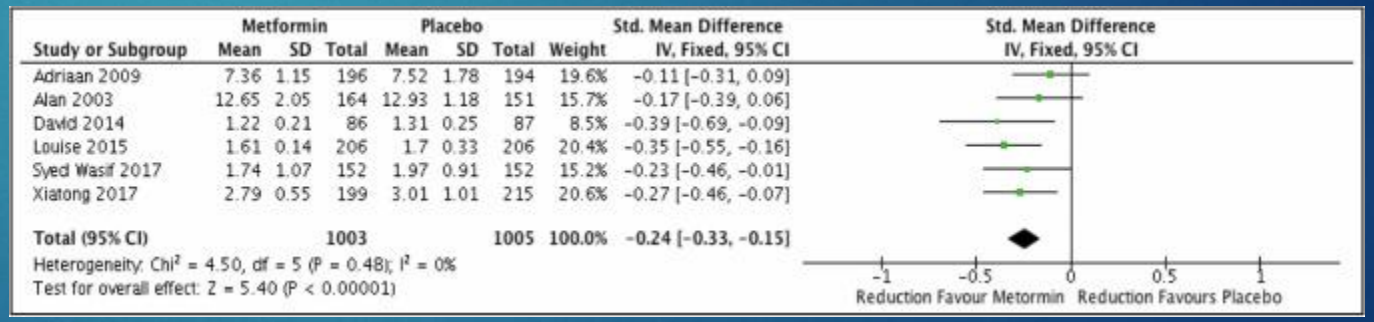
Std. Mean Difference IV, Fixed, 95% CI
-0.2 -0.1 0 0.1 0.2
Reduction favor Metformin Reduction favor Placebo



Study or Subgroup	Metformin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Alan 2003	6.76	0.88	164	7.01	1.01	151	15.9%	-0.26 [-0.49, -0.04]	2003
Adriaan 2009	5.1	0.87	196	5.68	1.16	194	19.1%	-0.56 [-0.77, -0.36]	2009
David 2014	4.11	1.12	86	4.61	0.97	87	8.6%	-0.48 [-0.78, -0.17]	2014
Louise 2015	2.02	0.76	206	2.21	1.03	206	20.8%	-0.21 [-0.40, -0.02]	2015
Xiatong 2017	2.43	0.83	199	2.87	1.07	215	20.5%	-0.46 [-0.65, -0.26]	2017
Syed Wasif 2017	3.12	1.1	152	3.56	1.26	152	15.2%	-0.37 [-0.60, -0.14]	2017
Total (95% CI)			**1003**			**1005**	**100.0%**	**-0.38 [-0.47, -0.30]**	

Heterogeneity: Chi² = 8.20, df = 5 (P = 0.15); I² = 39%
Test for overall effect: Z = 8.51 (P < 0.00001)

Std. Mean Difference IV, Fixed, 95% CI
-0.5 -0.25 0 0.25 0.5
Reduction Favor Metformin Reduciton Favor Placebo



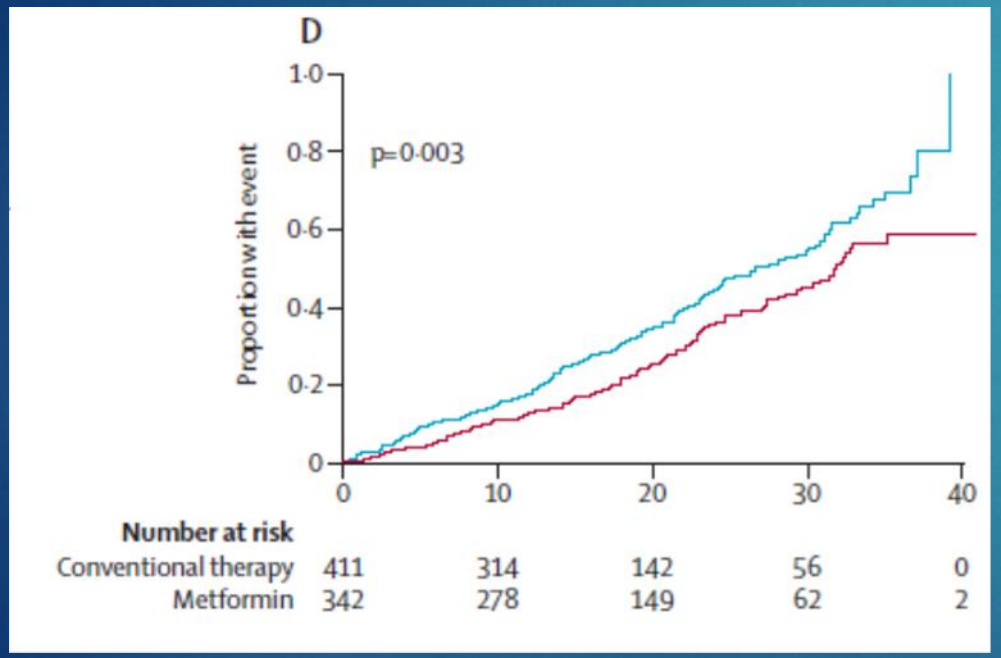
Study or Subgroup	Metformin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Adriaan 2009	7.36	1.15	196	7.52	1.78	194	19.6%	-0.11 [-0.31, 0.09]
Alan 2003	12.65	2.05	164	12.93	1.18	151	15.7%	-0.17 [-0.39, 0.06]
David 2014	1.22	0.21	86	1.31	0.25	87	8.5%	-0.39 [-0.69, -0.09]
Louise 2015	1.61	0.14	206	1.7	0.33	206	20.4%	-0.35 [-0.55, -0.16]
Syed Wasif 2017	1.74	1.07	152	1.97	0.91	152	15.2%	-0.23 [-0.46, -0.01]
Xiatong 2017	2.79	0.55	199	3.01	1.01	215	20.6%	-0.27 [-0.46, -0.07]
Total (95% CI)			**1003**			**1005**	**100.0%**	**-0.24 [-0.33, -0.15]**

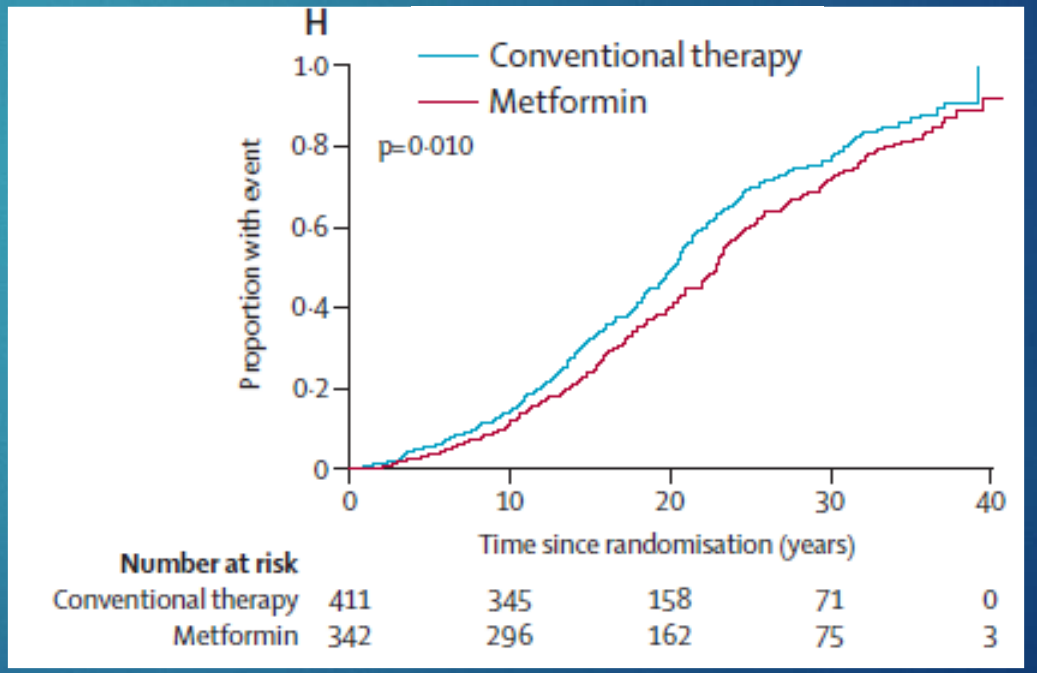
Heterogeneity: Chi² = 4.50, df = 5 (P = 0.48); I² = 0%
Test for overall effect: Z = 5.40 (P < 0.00001)

Std. Mean Difference IV, Fixed, 95% CI
-1 -0.5 0 0.5 1
Reduction Favour Metormin Reduction Favours Placebo

Gillani SW, Ghayedi N, Roosta P, Seddigh P, Nasiri O. Effect of metformin on lipid profiles of type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Journal of Pharmacy and Bioallied Sciences. 2021 Jan 1;13(1):76-82.

The 20-year UK Prospective Diabetes Study showed major clinical benefits(myocardial infarction (D), death from any cause (H) **)for people with newly diagnosed type 2 diabetes randomly allocated to metformin therapy, compared with conventional glycaemic control.**





Post-trial monitoring of a randomised controlled trial of intensive glycaemic control in type 2 diabetes extended from 10 years to 24 years (UKPDS 91). The Lancet. 2024

Early intensive glycaemic control with metformin therapy, compared with conventional glycaemic control, showed overall relative risk reductions of 20% (95% CI 5–32; p=0·010) for death from any cause and 31% (12–46; p=0·003) for myocardial infarction.

	Participants with clinical outcome		Absolute risk		24-year post-trial follow-up		10-year post-trial follow-up	
	Intensive therapy	Conventional therapy	Intensive therapy	Conventional therapy	Relative risk for intensive therapy regimen (95% CI)	p value	Relative risk for intensive therapy regimen (95% CI)	p value
Metformin group								
Any diabetes-related endpoint	245/342 (71·6%)	293/411 (71·3%)	49·6	56·2	0·82 (0·69–0·98)	0·025	0·79 (0·66–0·95)	0·013
Diabetes-related death	128/342 (37·4%)	168/411 (40·9%)	18·1	21·9	0·75 (0·60–0·95)	0·016	0·70 (0·53–0·92)	0·015
Death from any cause	243/342 (71·1%)	301/411 (73·2%)	34·4	49·3	0·80 (0·68–0·95)	0·010	0·73 (0·59–0·89)	0·002
Myocardial infarction	114/342 (33·3%)	164/411 (39·9%)	17·3	23·4	0·69 (0·54–0·88)	0·003	0·67 (0·51–0·89)	0·005
Stroke	46/342 (13·5%)	51/411 (12·4%)	6·7	7·0	0·88 (0·59–1·31)	0·53	0·80 (0·50–1·27)	0·35
Peripheral vascular disease	17/342 (5·0%)	30/411 (7·3%)	2·5	4·1	0·55 (0·31–1·01)	0·053	0·63 (0·32–1·27)	0·19
Microvascular disease	79/342 (23·1%)	88/411 (21·4%)	12·7	13·2	0·91 (0·67–1·24)	0·56	0·84 (0·60–1·17)	0·31

Data are n/N (%), unless otherwise specified. Absolute risk is the number of events per 1000 patient-years. Relative risk was estimated from hazard ratios calculated from proportional hazards modelling. p values were calculated using the log-rank test.

Table: **Clinical outcomes from baseline for participants after up to 24-year post-trial follow-up, and after up to 10-year post-trial follow-up, as previously reported[4]**

Post-trial monitoring of a randomised controlled trial of intensive glycaemic control in type 2 diabetes extended from 10 years to 24 years (UKPDS 91). The Lancet. 2024

Metformin reduces all-cause mortality among patients with metformin therapy vs no-metformin therapy(a) among patients with MI at baseline(b) and among patients with HF at baseline(c)**(meta-analysis were included 40 studies comprising 1,066,408 patients)**

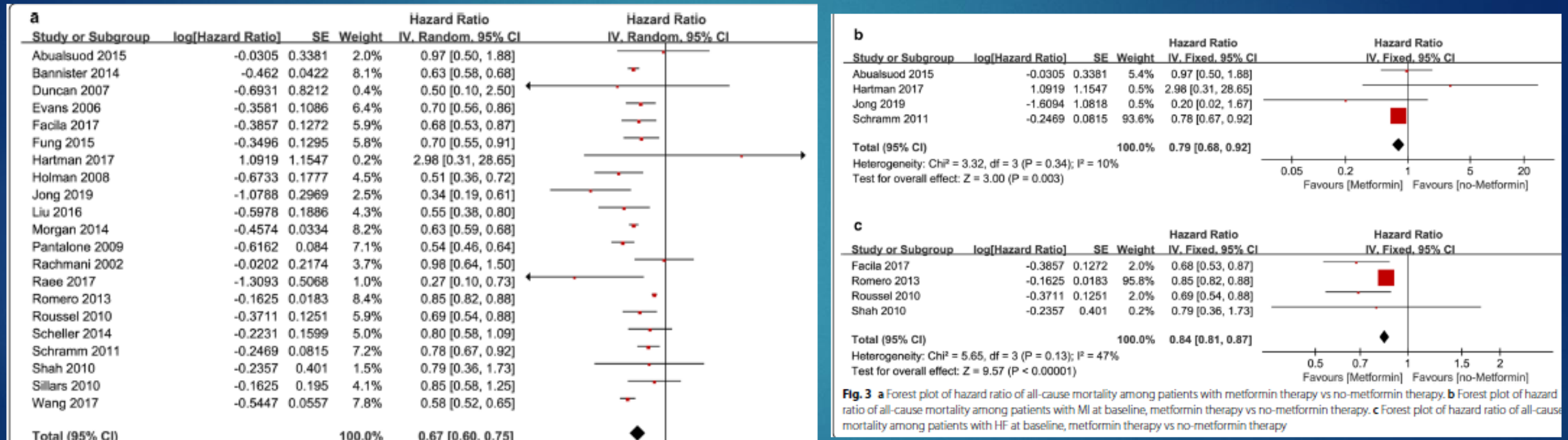


Fig. 3 **a** Forest plot of hazard ratio of all-cause mortality among patients with metformin therapy vs no-metformin therapy. **b** Forest plot of hazard ratio of all-cause mortality among patients with MI at baseline, metformin therapy vs no-metformin therapy. **c** Forest plot of hazard ratio of all-cause mortality among patients with HF at baseline, metformin therapy vs no-metformin therapy

Han Y, Xie H, Liu Y, Gao P, Yang X, Shen Z. Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a systematic review and an updated meta-analysis. Cardiovascular Diabetology. 2019 Dec;18:1-6.

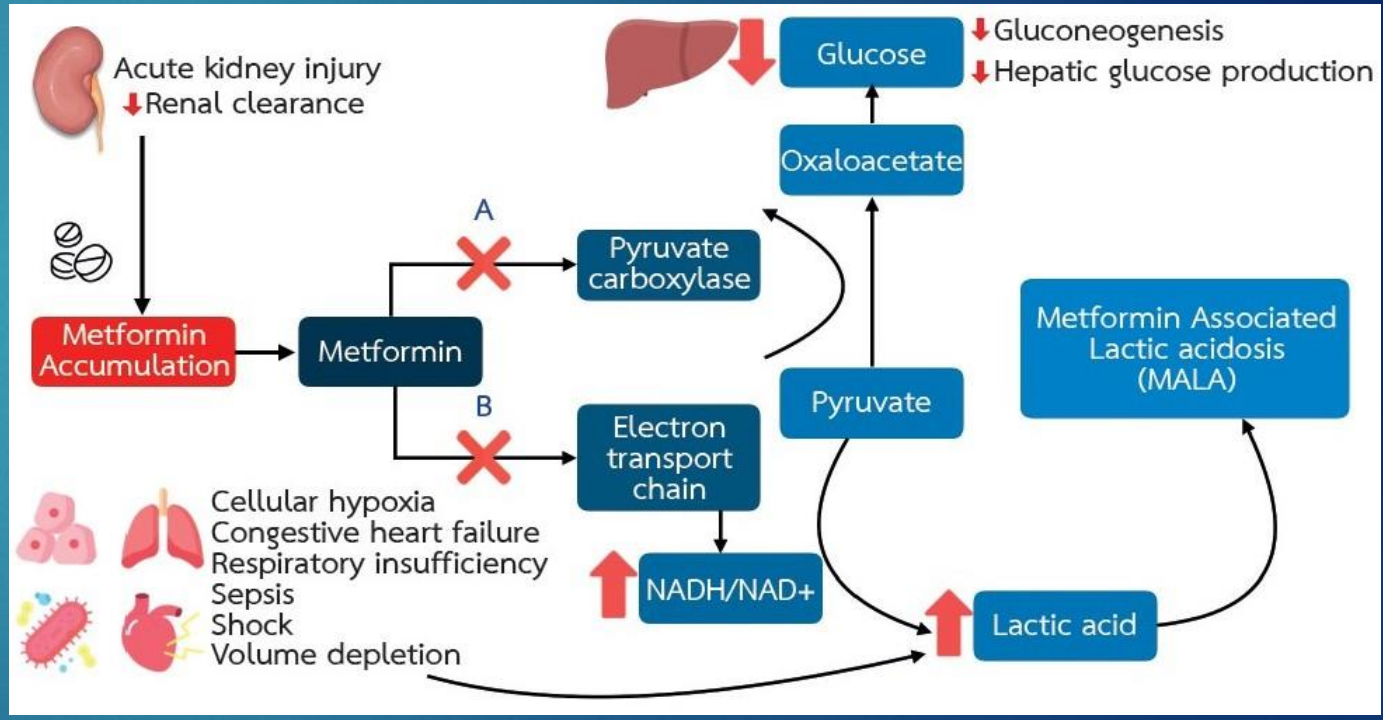
side effects of metformin

- The prevalence of GI adverse effect was as follows:
- diarrhea 6.9% (95% CI: 0.038–0.123),
- bloating 6,2% (95% CI: 0.020–0.177),
- abdominal pain 5,3% (95% CI: 0.003–0.529),
- vomiting 2.4% (95%: CI 0.007–0.075),
- constipation 1.1% (95%: CI 0.001–0.100).
- lead to lower physical and mental HRQoL, which may result in patient nonadherence or physician reluctance to optimally titrate the metformin dose.
- may occur even after prolonged treatment with metformin.
- temporary discontinuation, dose titration or proper intake of medicine.
- switched from immediate-release metformin to metformin-XR experienced fewer GI side effects on comparable doses of the extended-release metformin.

Gastrointestinal adverse events of metformin treatment in patients with type 2 diabetes mellitus: a systematic review and meta-analysis with meta-regression of observational studies. BMC Endocrine Disorders. 2024.

Metformin-associated lactic acidosis:

- Metformin, increases plasma lactate levels in a plasma concentration-dependent manner by inhibiting mitochondrial respiration predominantly in the liver.
- Elevated plasma metformin concentrations (as occur in individuals with renal impairment)
- condition that further disrupts lactate production or clearance (e.g., cirrhosis, sepsis, or hypoperfusion)



DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabolism. 2016 Feb 1;65(2):20-9.

the occurrence of lactic acidosis due to metformin usage is very rare

- Pooled data from 347 comparative trials and cohort studies revealed no cases of fatal or nonfatal lactic acidosis in 70,490 patient-years of metformin use or in 55,451 patients-years in the non-metformin group.
- the true incidence of lactic acidosis per 100,000 patient-years was 4.3 cases in the metformin group and 5.4 cases in the non-metformin group. There was no difference in lactate levels, for metformin compared to non-metformin therapies.

Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane database of systematic reviews. 2010(4).

Metformin and renal failure

- The drug is cleared by renal filtration, and very high circulating levels (e.g., as a result of overdose or acute renal failure) have been associated with lactic acidosis.
- occurrence of this complication is now known to be very rare
- he FDA has revised the label for metformin to reflect its safety in people with eGFR ≥30 mL/min/1.73 m^2

Metformin and renal failure

Table 1—*Proposed recommendations for use of metformin based on eGFR*

eGFR level (mL/min per 1.73 m^2)	Action
≥60	No renal contraindication to metformin Monitor renal function annually
<60 and ≥45	Continue use Increase monitoring of renal function (every 3–6 months)
<45 and ≥30	Prescribe metformin with caution Use lower dose (e.g., 50%, or half-maximal dose) Closely monitor renal function (every 3 months) Do not start new patients on metformin
<30	Stop metformin

Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes care. 2011 Jun 1;34(6):1431-7.

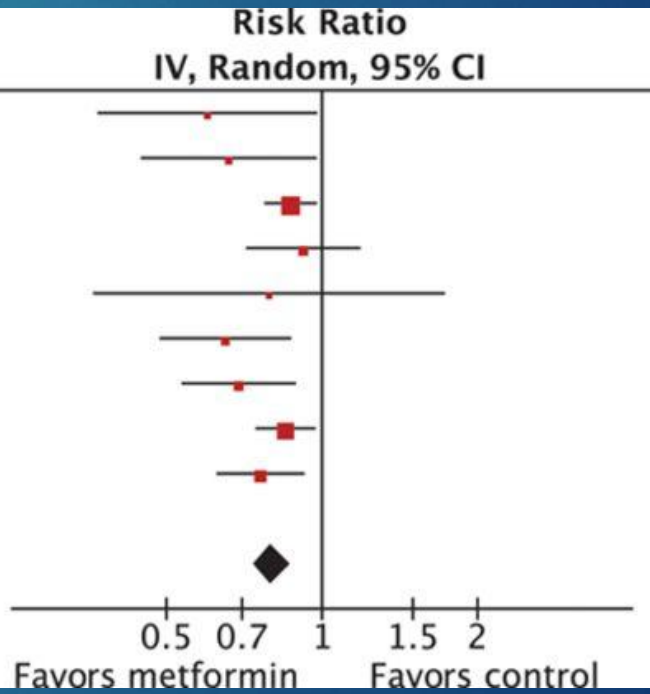
Metformin and heart failure

- Metformin was associated with reduced mortality compared with controls (mostly sulfonylurea therapy): 23% versus 37% (pooled adjusted risk estimates: 0.80; 0.74–0.87; I^2=15%; P<0.001).

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Evans	-0.5108	0.25	2.6%	0.60 [0.37, 0.98]	2005
Eurich	-0.4156	0.2	4.1%	0.66 [0.45, 0.98]	2005
Masoudi	-0.1393	0.06	29.0%	0.87 [0.77, 0.98]	2005
Inzucchi	-0.0834	0.13	8.9%	0.92 [0.71, 1.19]	2005
Shah	-0.2357	0.4	1.1%	0.79 [0.36, 1.73]	2010
MacDonald	-0.4308	0.15	6.9%	0.65 [0.48, 0.87]	2010
Roussel	-0.3711	0.13	8.9%	0.69 [0.53, 0.89]	2010
Andersson	-0.1625	0.0682	24.6%	0.85 [0.74, 0.97]	2010
Aguilar	-0.2744	0.1	13.9%	0.76 [0.62, 0.92]	2011
Total (95% CI)			**100.0%**	**0.80 [0.74, 0.87]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.45$, df = 8 (P = 0.31); $I^2 = 15\%$

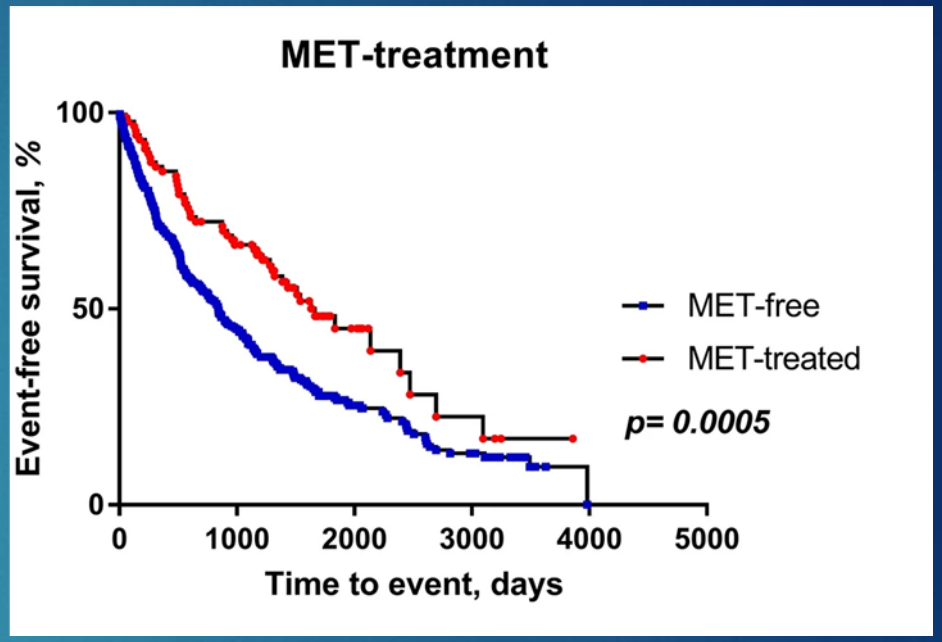
Test for overall effect: Z = 5.35 (P < 0.00001)



Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34 000 patients. Circulation: Heart Failure. 2013 May;6(3):395-402.

Metformin usage in patients with diabetes and heart failure

- A total of 87 stable DM patients treated with metformin with advanced HFrEF , NYHA III/IV, LVEF 23.6 ± 5.8%) followed for a median of 1126 days
- Endpoint: occurrence of death, urgent heart transplantation or mechanical circulatory support implantation.
- MET-treated patients had better event-free survival even after adjustment for BNP, BMI and eGFR
- MET treatment in patients with advanced HFrEF and DM is associated with improved outcome by mechanisms beyond the improvement of blood glucose control.



. Metformin treatment is associated with improved outcome in patients with diabetes and advanced heart failure (HFrEF). Scientific Reports. 2022

Metformin and heart failure

- metformin is at least as safe as other glucose-lowering treatments in patients with diabetes mellitus and HF and even in those with reduced left ventricular ejection fraction or concomitant chronic kidney disease
- Metformin was not associated with increased risk of lactic acidosis.
- Do not use in acute heart failure or in presence of end organ hypoperfusion

metformin in liver failure

- No patients developed metformin-associated lactic acidosis during follow-up.

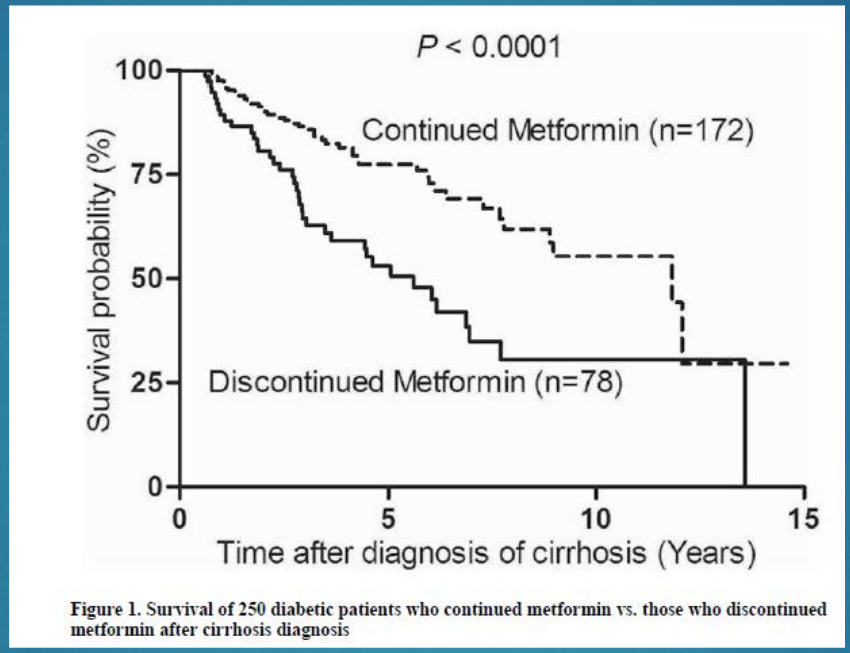
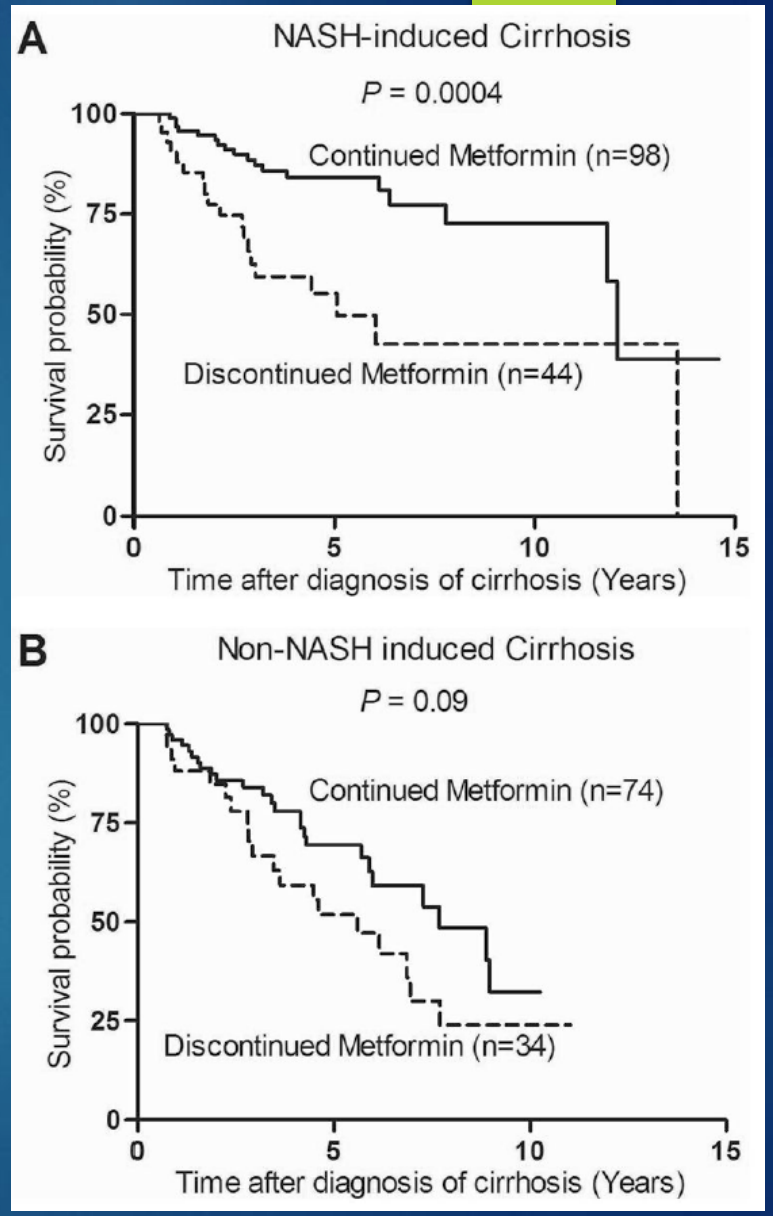


Figure 1. Survival of 250 diabetic patients who continued metformin vs. those who discontinued metformin after cirrhosis diagnosis



Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. Hepatology. 2014

Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease

- adults with type 2 diabetes and chronic kidney disease with eGFR<60 mL/min/1.73m2, congestive heart failure, or chronic liver disease with hepatic impairment;
- Metformin use in patients with moderate chronic kidney disease, congestive heart failure, or chronic liver disease with hepatic impairment is associated with improvements in all cause mortality and major cardiovascular events

Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron CB, Stanifer JW, Mock CK, Wang X, Tang S, Nagi A, Kosinski AS, Williams Jr JW. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Annals of internal medicine. 2017 Feb 7;166(3):191-200.

Metformin and intravenous administration of iodinated contrast media

- hold metformin in patients who are about to receive intravenous iodinated contrast material (with potential for contrast-induced renal failure) if they are at increased risk for lactic acidosis independent of metformin.
- Such patients include those with vascular instability, hypotension, and potential hypoperfusion.
- discontinue metformin prior to any radiologic procedures with intravenous or intra-arterial contrast in patients with eGFR <45 mL/min/1.73 m^2,
- Metformin should not be restarted until eGFR can be retested (usually two to five days after the procedure) and confirmed to be >30 mL/min/1.73 m^2.

Metformin and vitamin B12 deficiency

- not only reduces serum levels of B12, but also progressively increases serum MMA.
- was associated with significant worsening of the NPS.
- Neuropathy prevalence was higher in MET with low B12 levels.
- Long-term use of metformin was associated with biochemical B12 deficiency and .
- Routine testing of vitamin B12 levels in metformin-treated patients should be considered.
- Years of metformin use were associated with increased risk of B12 deficiency

Out M, Kooy A, Lehert P, Schalkwijk CA, Stehouwer CD. Long-term treatment with metformin in type 2 diabetes and methylmalonic acid: post hoc analysis of a randomized controlled 4.3 year trial. Journal of Diabetes and its Complications. 2018 Feb 1;32(2):171-8.
Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ, Bray GA, Schade DS, Temprosa MG, White NH, Crandall JP. Long-term metformin use and vitamin B12 deficiency in the diabetes prevention program outcomes study. The Journal of Clinical Endocrinology & Metabolism. 2016 Apr 1;101(4):1754-61.

Common obstacles to using metformin

Condition	Suggested approach
GI intolerance	• Reduce dose until adverse effects resolve • Consider use of extended-release form
Impaired kidney function	• Use freely if eGFR ≥45 mL/min • Use with caution if eGFR 30-45 mL/min • Do not use if eGFR <30 mL/min
Heart failure	• Acceptable to use with stable, chronic heart failure • Do not use with acute heart failure and evidence of end-organ hypoperfusion
Liver disease	• Acceptable to use with chronic liver disease (including mildly elevated liver enzymes, but intact liver function) • Do not use with functional hepatic failure or acute liver injury

Flory J, Lipska K. Metformin in 2019. Jama. 2019 May 21;321(19):1926-7.

Metformin contraindication

- GFR<30ml/min/1.72m
- Active or progressive sever liver disease unstable
- acute heart failure at risk of hypoperfusion
- Decreased tissue perfusion or hemodynamic instability due to infection or other cause
- Past history of lactic acidosis during metformin therapy

Metformin dosing

- Metformin immediate release 500mg/ 850mg/1000 mg
- Metformin extended release 500/1000/750 mg

Starting dose and titration

immediate-release oral formulation:

- begin with an initial dosage of either 500 mg, once or twice daily.
- The daily dose of metformin is often titrated every week in increments of 500 to minimize any adverse GI effects.
- The typical maintenance dose of the medication is 850 or 1000 mg twice daily

Formulation	Dosage forms	Starting dose	Maximum dose
Metformin, Immediate Release	Tablet, Oral: 500 mg, 850 mg, 1000 mg	500 mg once or twice daily OR 850 mg once daily	Usual maintenance dose: 1 g twice daily OR 850 mg twice daily Maximum: 2.55 g/day

Starting dose and titration

- Extended-release oral formulation:
- begin with an initial dosage of either 500 mg or 1000 mg once daily.
- The daily dose of metformin is often titrated every week in increments of 500 mg
- recommended maximum dose for this formulation is 2000 mg, taken once or twice daily

Metformin, Extended Release	Tablet, Oral: 500 mg, 750 mg, 1000 mg	500 mg once daily OR 1 g once daily	2 g/day

Key point

- treatment plans need to be continuously reviewed for efficacy, side effects, hypoglycemia, and treatment burden
- metformin is considered the initial medication of choice
- Metformin is effective and safe, Inexpensive
- may reduce risk of cardiovascular events and death
- Metformin is not associated with significant risk of hypoglycemia
- Metformin should be continued upon initiation of insulin therapy for ongoing glycemic and metabolic benefits.