Preventing or Delaying Progression of Diabetic Microvascular Complications

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Objectives of Lectures

- Review the pathogenesis & natural history of the long-term microvascular complications of diabetes mellitus
- Demonstrate how improved glucose control protects against risk for DM complications
- Describe the ”protective effects” of various classes of medications which have now been shown to delaying the onset & progression of diabetic CKD, retinopathy, & peripheral neuropathy

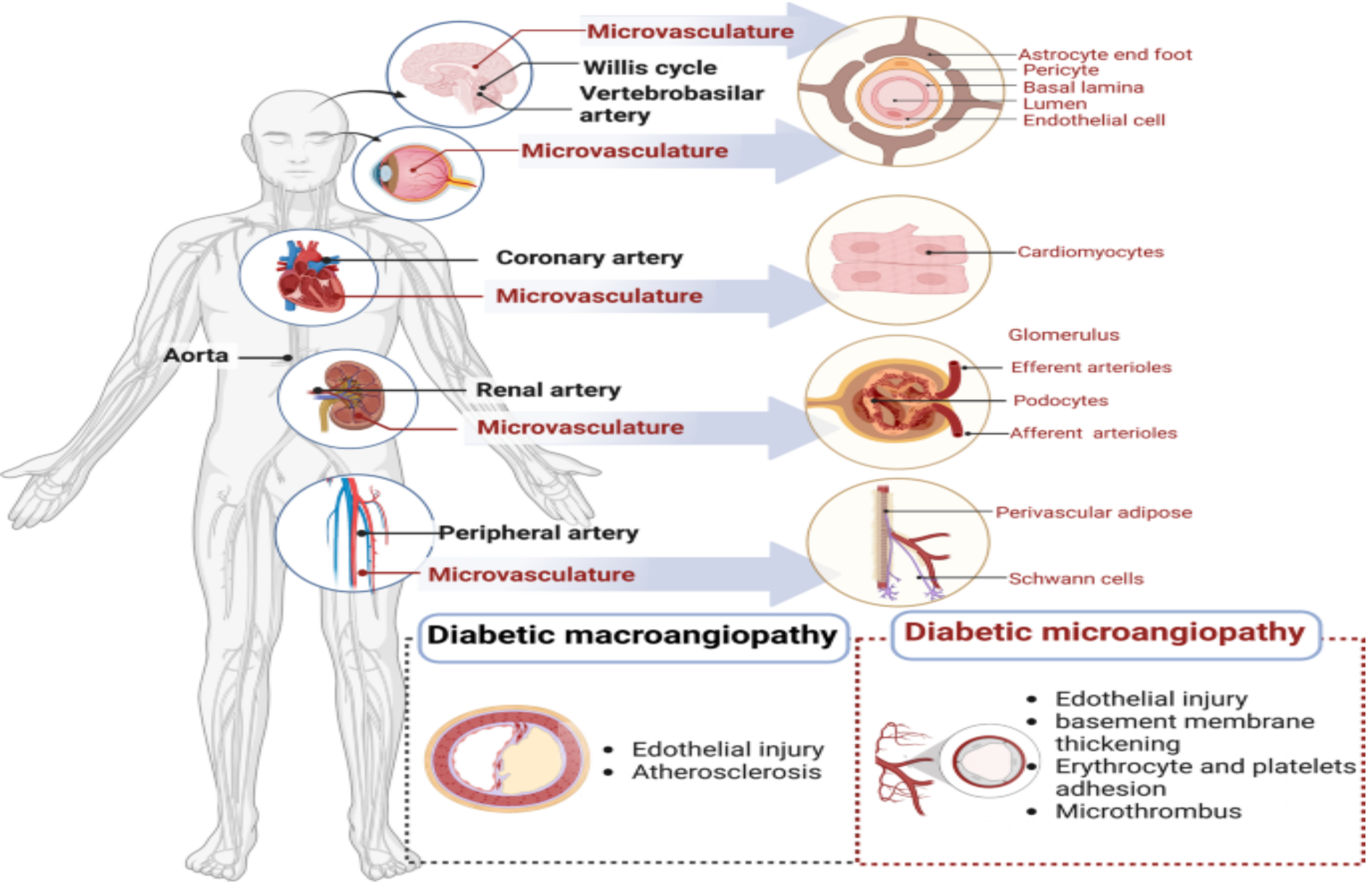
Impact of Diabetes on Overall Morbidity & Mortality

- Persons with diabetes have a 2X-3X higher mortality compared to persons without
- 75% of the increased mortality is due to CV Disease; males are at 2X & females 4X increased risk
- Microvascular complications; CKD, retinopathy & neuropathy also increases risk of premature death…… but are the major causes of long-term disability

Impact of The Microvascular Complications of Diabetes

- Diabetic nephropathy & CKD is leading cause of ESKD, dialysis, & need for renal transplant in the US
- Diabetic neuropathy is a major contributor to diabetic foot disorders (non-healing ulcers & Charcot foot) & leading cause non-traumatic LE amputation in US
- Diabetic retinopathy is the leading cause of preventable blindness in US

Macrovascular & Microvascular Complications of Diabetes



Timing & Clinical Presentation of DM Complications in T2DM

- Most individuals with T2DM have had abnormal CV risk factors for many years before it is diagnosed so may already have preexisting macrovascular disease
- Due to delay in diagnosis of T2DM many also have evidence of microvascular complications; especially early retinopathy & microalbuminuria/CKD

Timing & Clinical Presentation of DM Complications in T1DM

- Most individual with T1DM are younger @ onset so there is a delay in onset of the microvascular complications for 10-15 yrs & macrovascular complications 20-30 yrs
- Onset of diabetes microvascular & macrovascular complications occur @ a much younger age in T1DM; especially nephropathy, retinopathy, & neuropathy

Factors Unique to DM Which Affect Macro & Microvascular Risk

- Hyperinsulinemia (even T1DM)
- The "Dyslipidemia" of DM
- Pro-coagulant state (increased PAI-1 & fibrinogen)
- Glycosylation of endothelial cells, platelets, RBC's, & WBC's (altered platelet function)
- Abnormal RBC rheology from glycosylation & increased blood viscosity

Genetics & Risk for Microvascular Complications

Family history is strongly linked to risk for microvascular complications however the molecular links @ present are still poorly understood

Lyssenko, V. & Vaag, A. Diabetologia. 2023; 66(9): 1601–1613

Microvascular Risk Factors Unique to Diabetes:

"Its the Sugar Stupid!!"

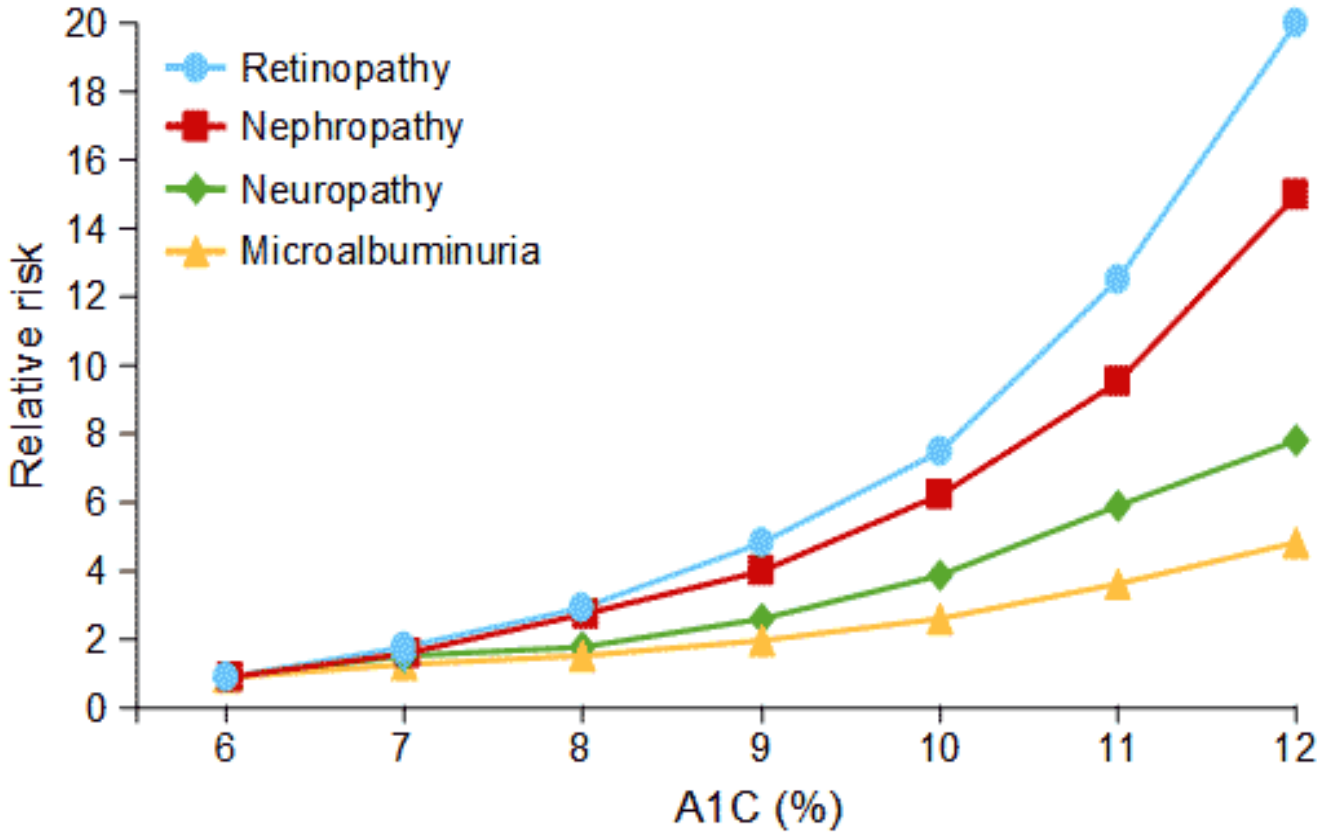
1. Sustained Hyperglycemia leading to direct tissue damage
2. Glycemic Variability (GV) inducing endothelial oxidative stress

The Link Between Hyperglycemia & Diabetes Complications Has Been Proven For > 30 years!

The Diabetes Complication & Control Trial (DCCT) for T1DM

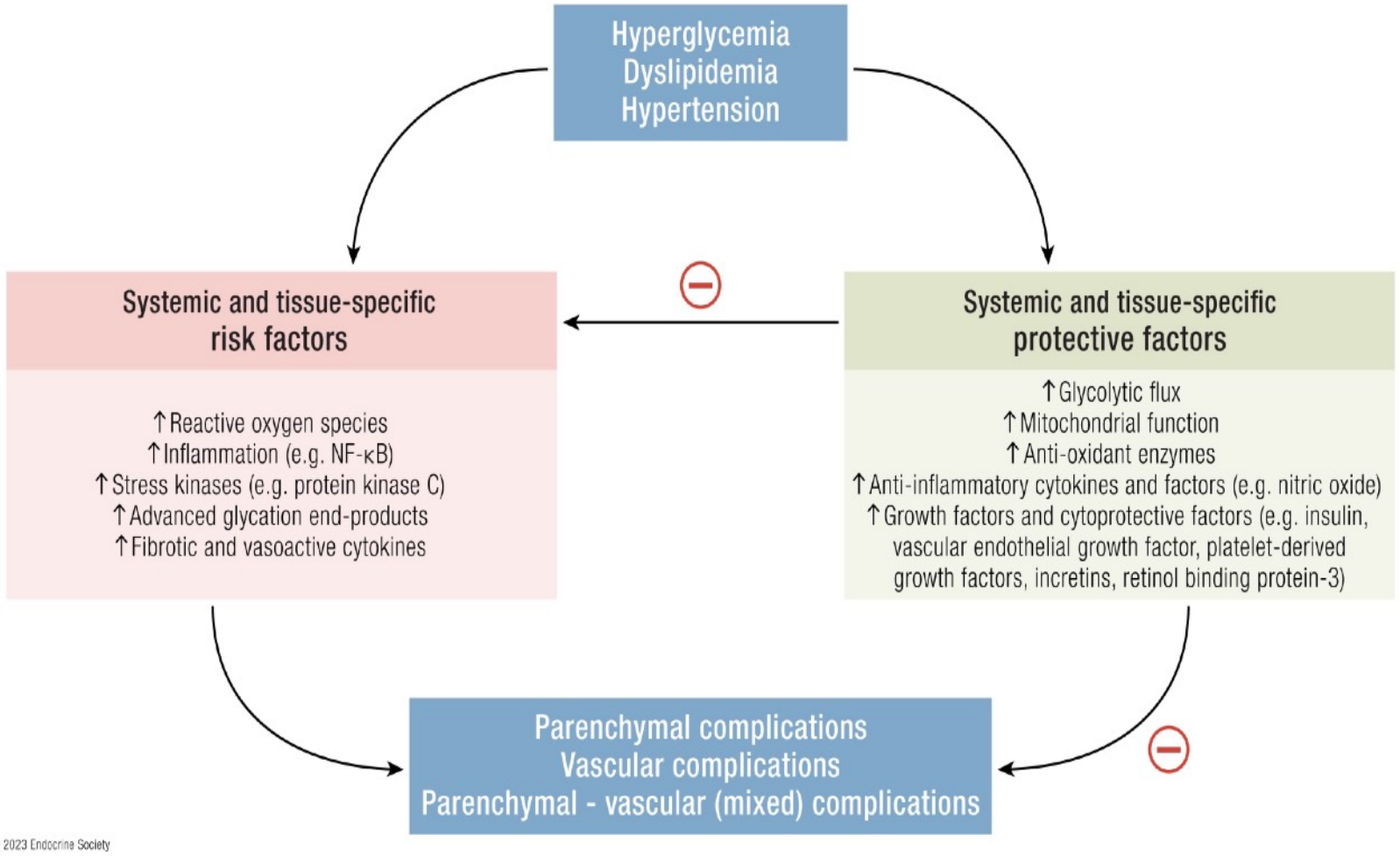
UKPDS & Kumamoto Trials for T2DM

DCCT, A1C, & Risk for Nephropathy, Retinopathy, & Neuropathy



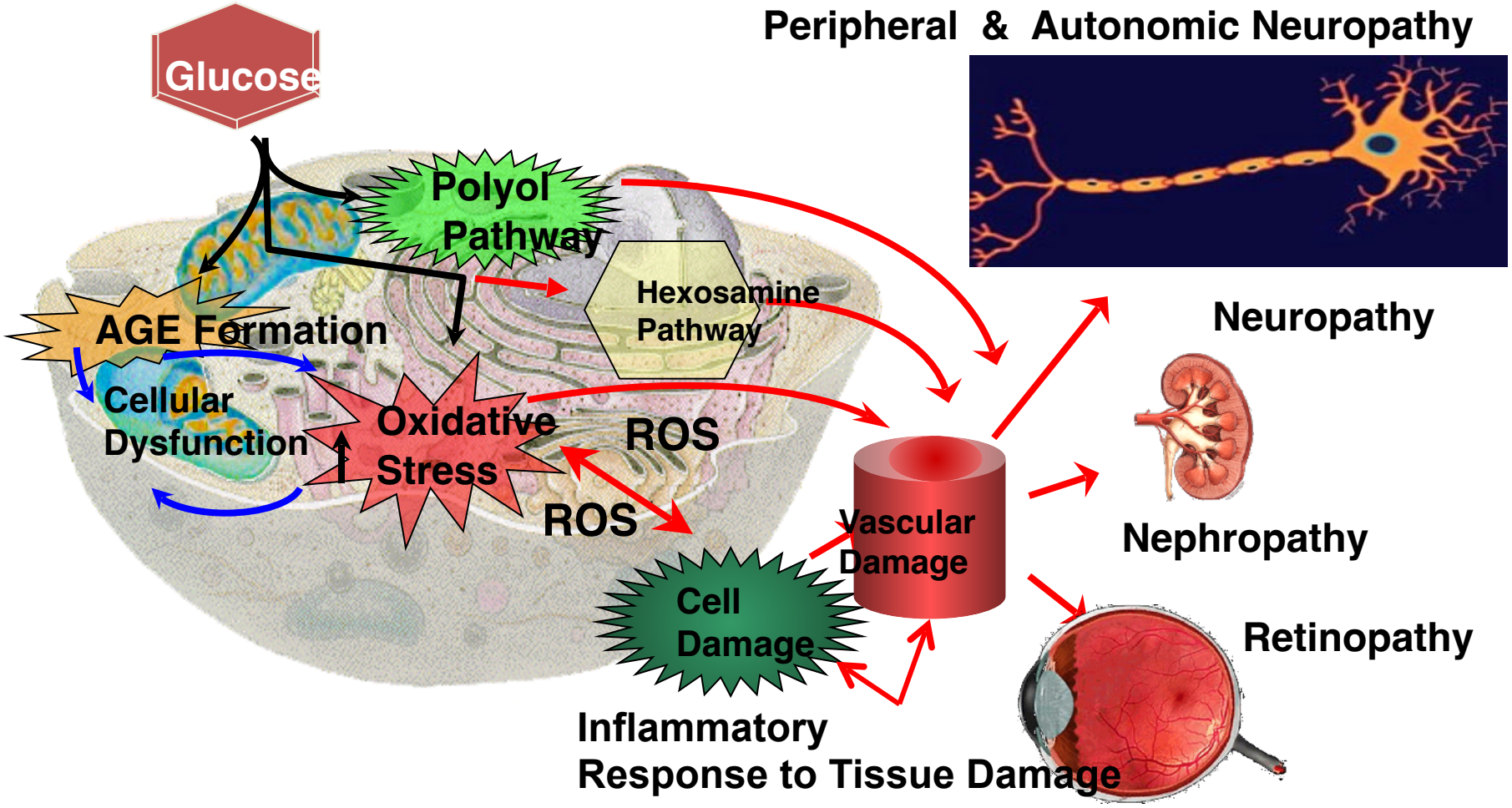
The DCCT Research Group NEJM 1993;329(14):977–986.

Pathogenesis of Diabetic Complications



Yu, G. et. al. Endocrine Reviews, 2023, 00, 1–26

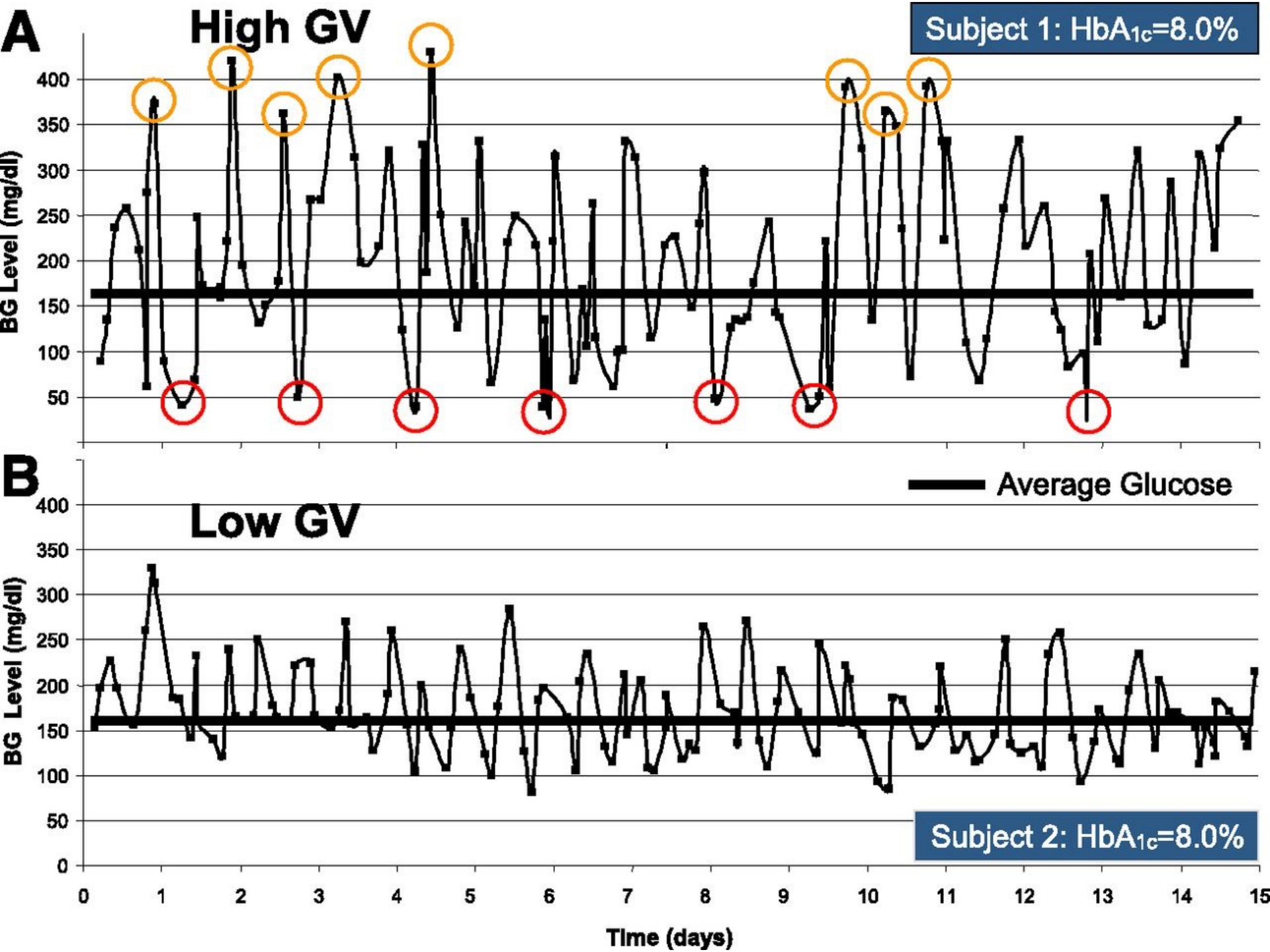
Common Pathways in Diabetes Complications



Glycemic Variability

The frequency & magnitude of daily glucose excursions outside the normal range

(70-140 mg/dl)


A
High GV
Subject 1: HbA1c=8.0%
BG Level (mg/dl)
400
350
300
250
200
150
100
50
B
Low GV
Average Glucose
BG Level (mg/dl)
400
350
300
250
200
150
100
50
0
Subject 2: HbA1c=8.0%
0
1
2
3
4
5
6
7
8
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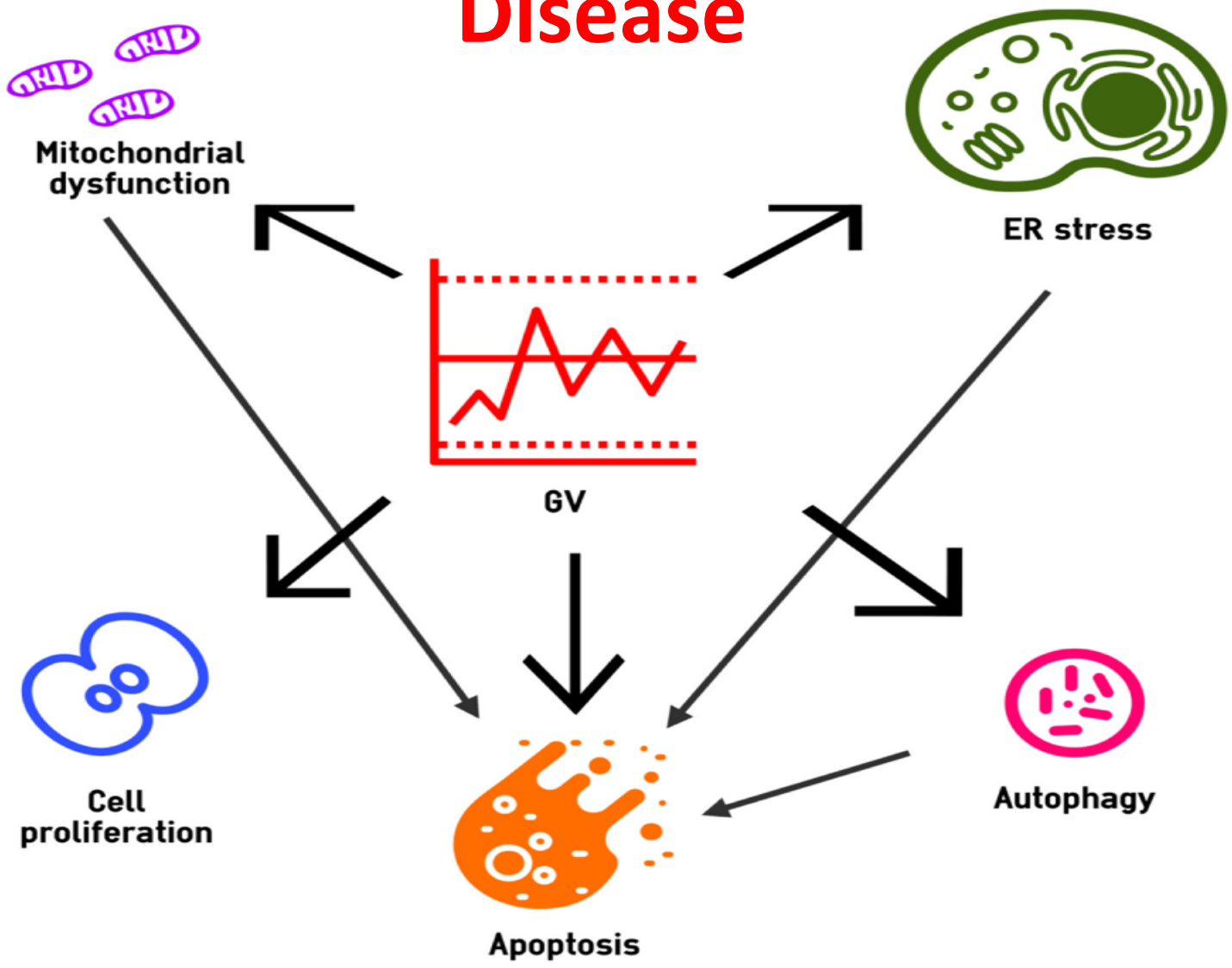
14
15
Time (days)

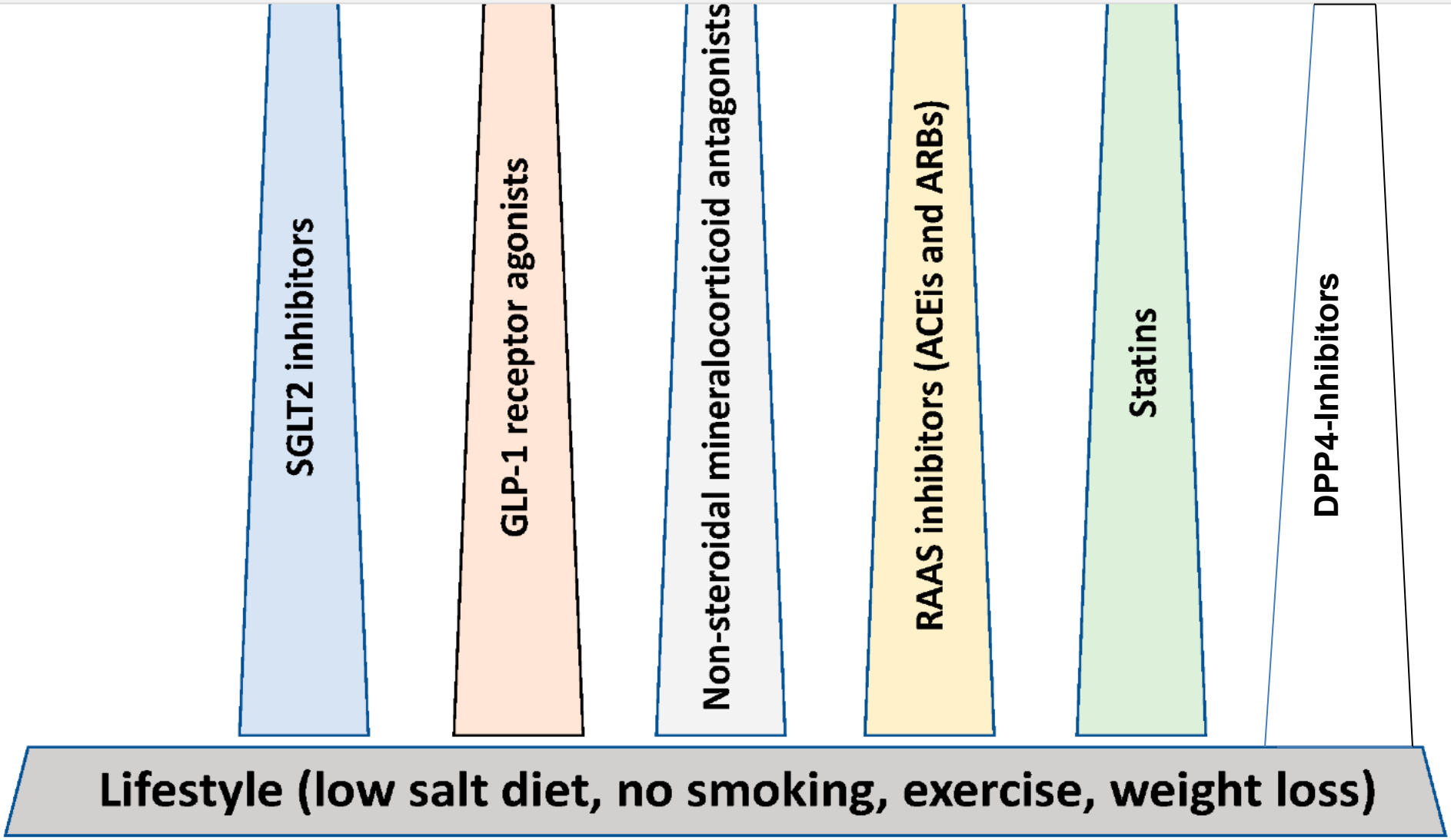
Glycemic Variability Contributes to Endothelial Dysfunction & Microvascular Disease



The Good News:

- End-stage long-term microvascular complications are no longer inevitable!
- With improved glucose control & use of other classes of medications such as; ACE/ ARB's, GLP-1 agonists, & SGLT2-Inhibitors…..
- The natural history of end-organ damage is being altered dramatically

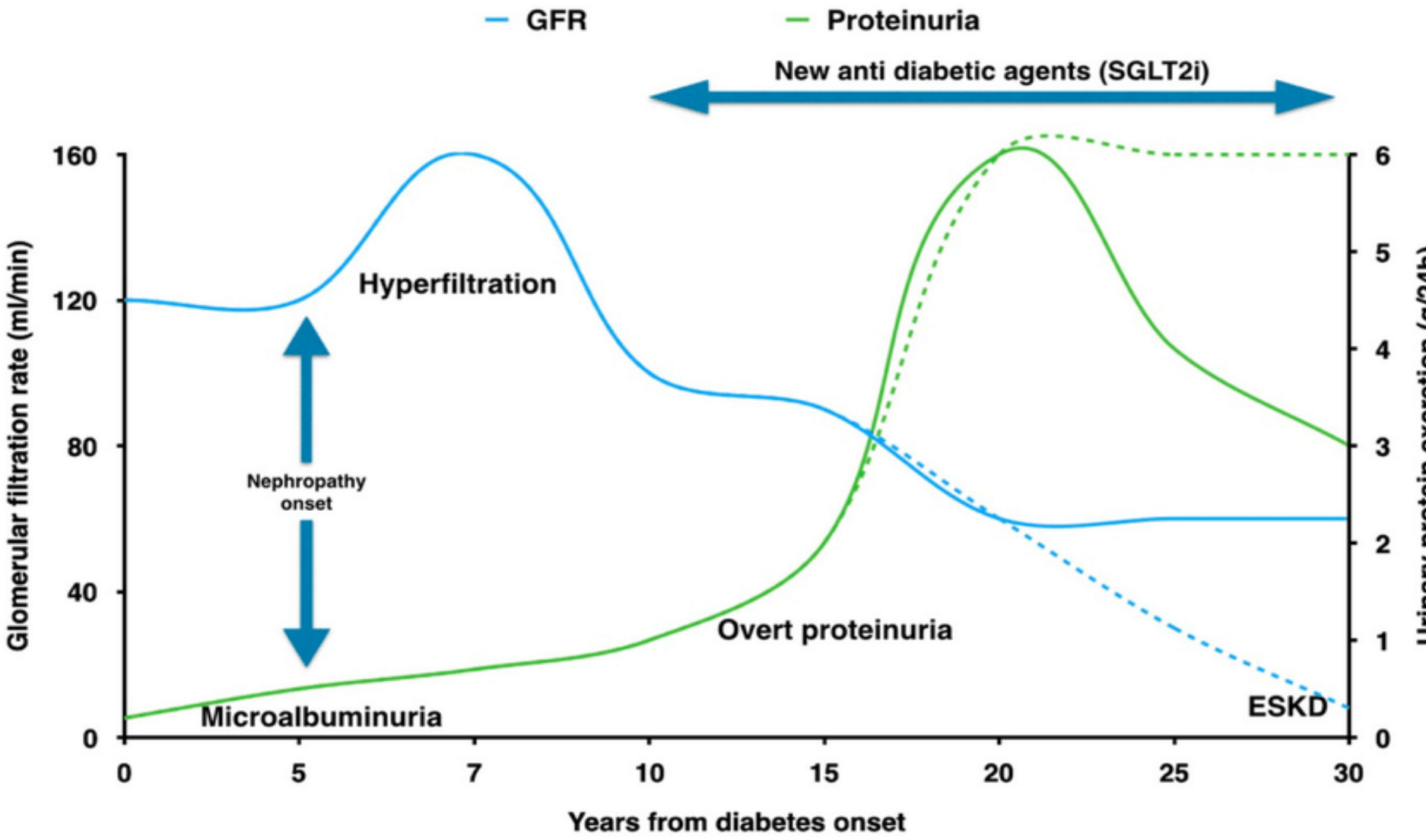
Medications Proven to Reduce Diabetes Complication Risk



The Natural History of Diabetic Nephropathy

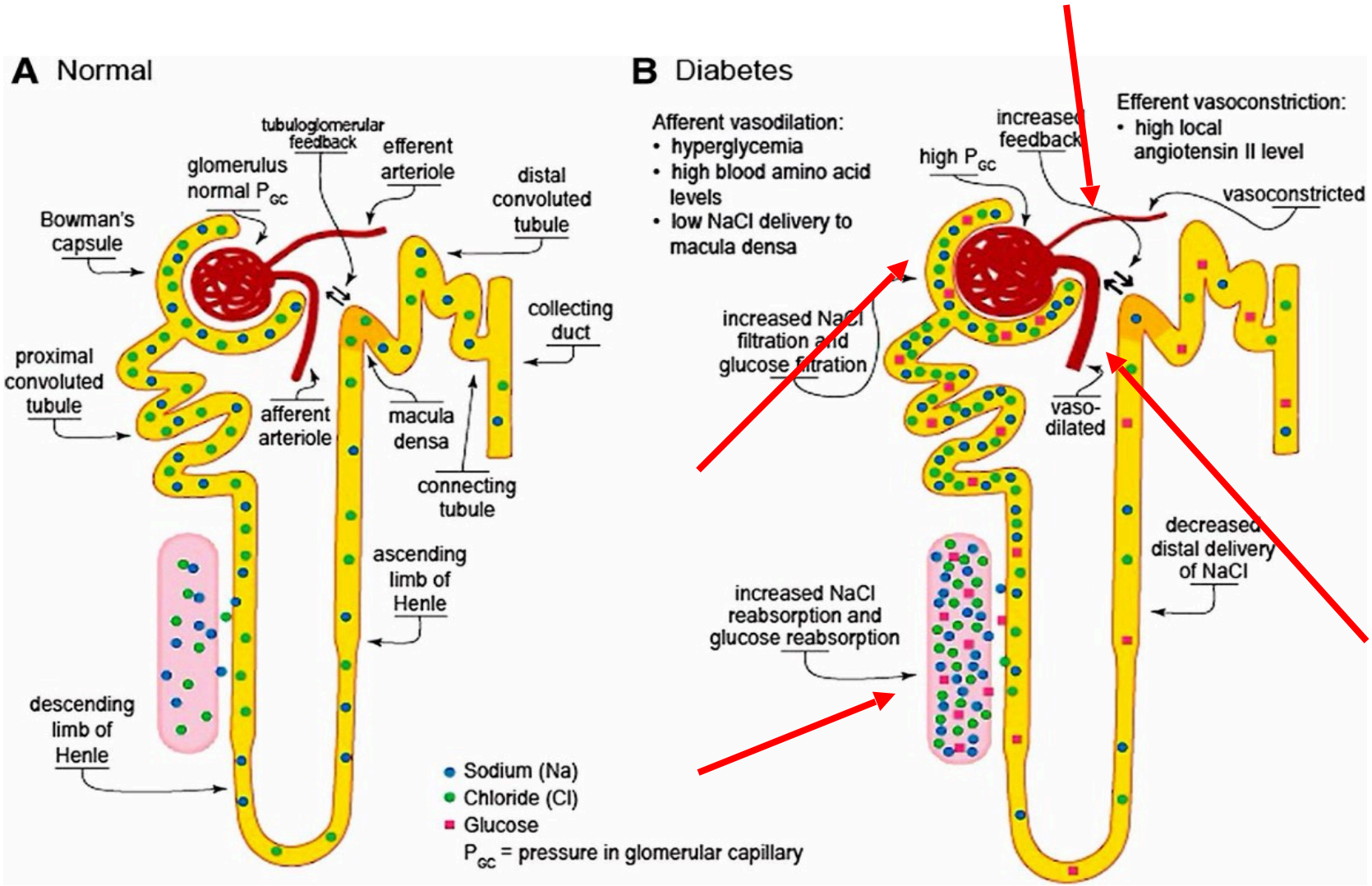
The same processes are going on in other tissues such as retina & nerve

Natural History of Diabetic Nephropathy



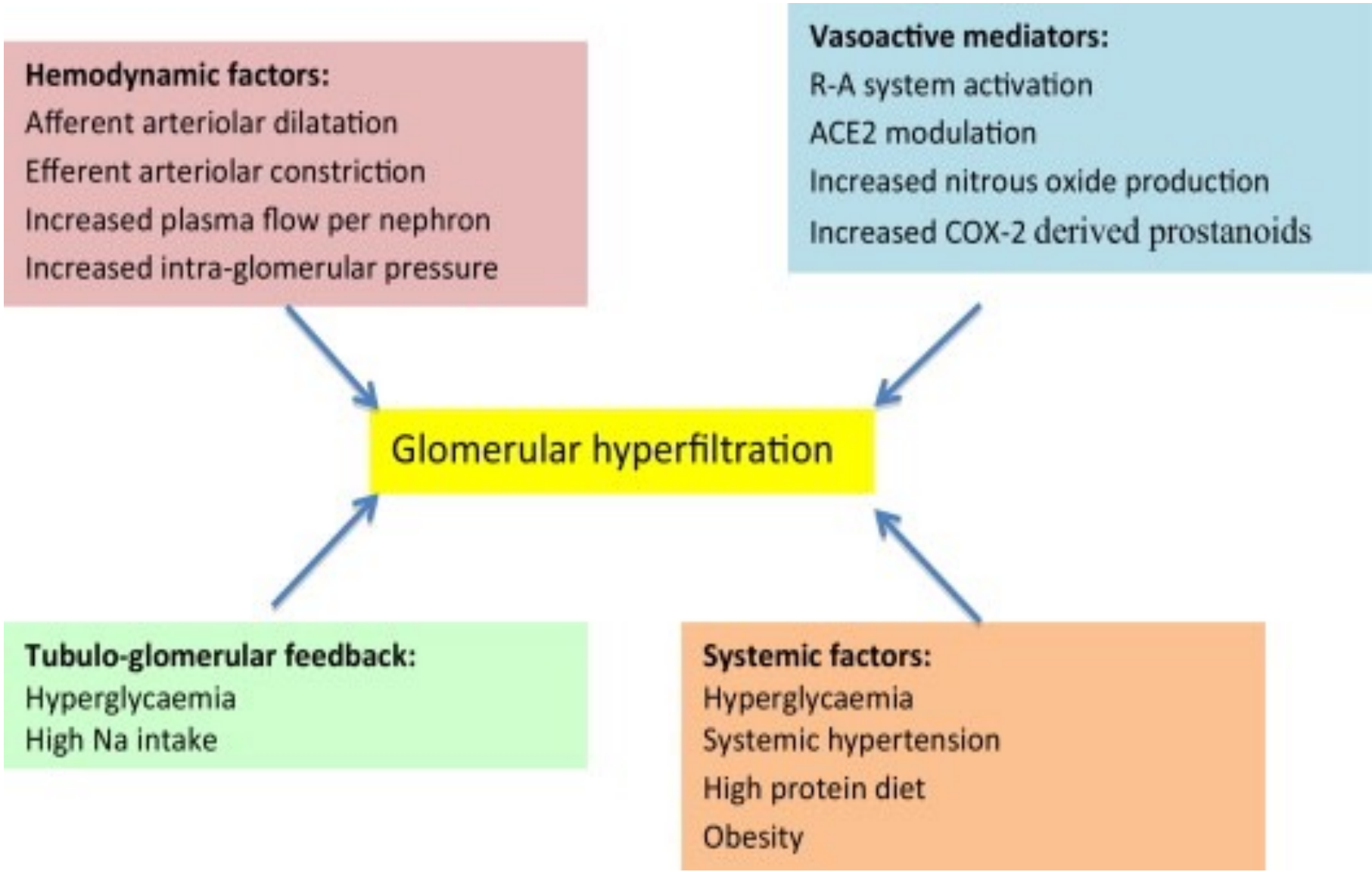
Toregianni, M. et. Al. International Journal of Molecular Sciences 22(11):5425

Hyperglycemia Drives Hyperfiltration in Glomerulus



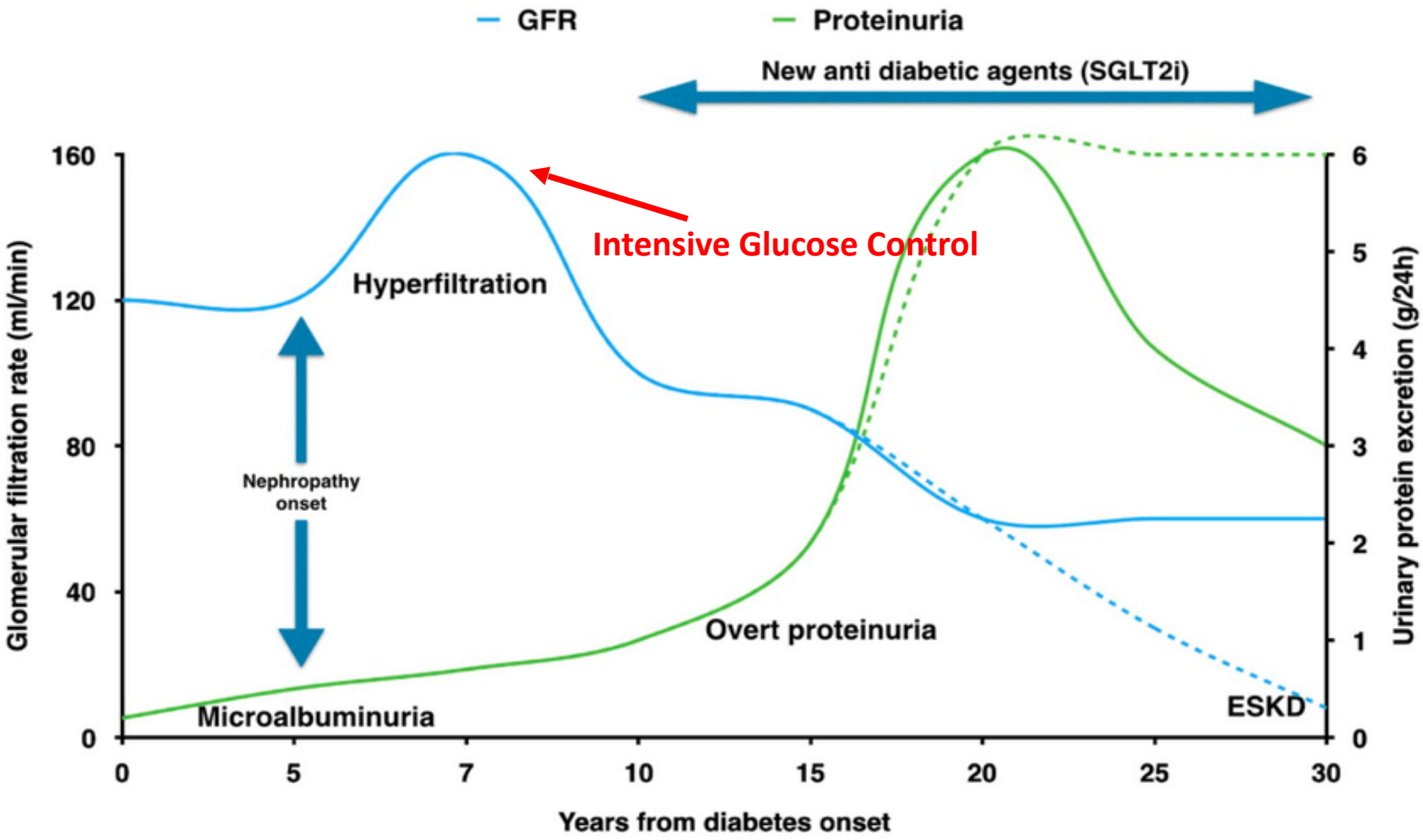
Diabetes. 2016;66(1):14-16. doi:10.2337/dbi16-0056

Hyperfiltration & Diabetic Nephropathy



Premaratne, E. et. al. Diabetes & Metabolism. Vol. 41, Iss. 1, Feb. 2015, PP. 5-17

Natural History of Diabetic Nephropathy

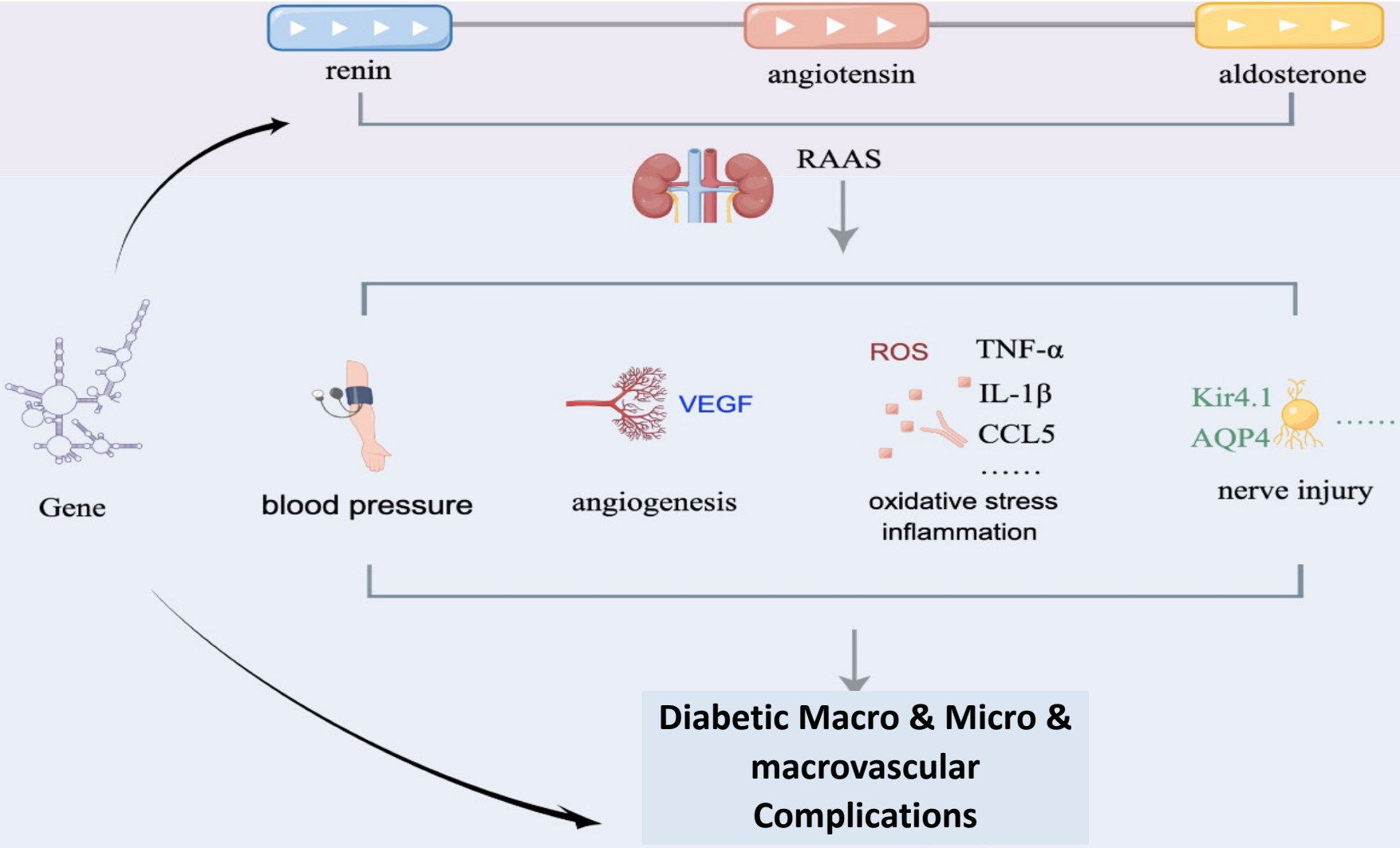


Toregianni, M. et. Al. International Journal of Molecular Sciences 22(11):5425

Reno-Protective Medications

- ACE/ARB/aldosterone antagonists
- Statins
- PCKD9 inhibitors (safe in CKD but no protection data yet)
- Metformin
- SGLT2-inhibitors
- GLP-1 agonists
- DPP4 inhibitors

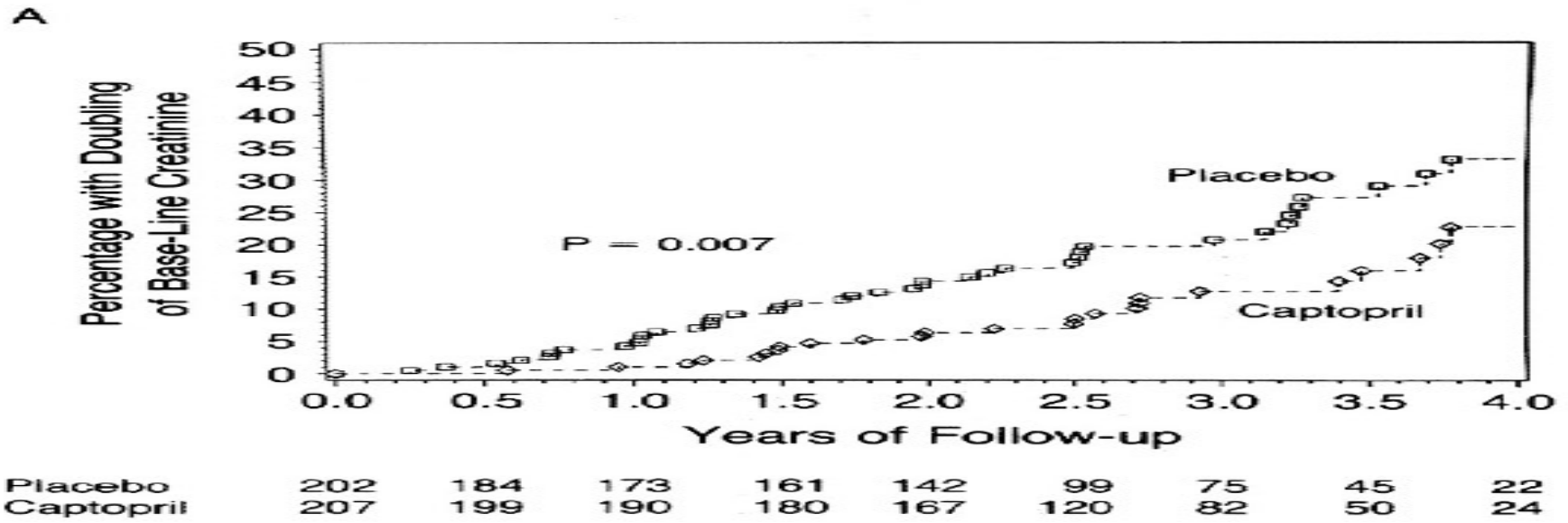
Role of Renin-Angiotensin-Aldosterone in Diabetic Complications

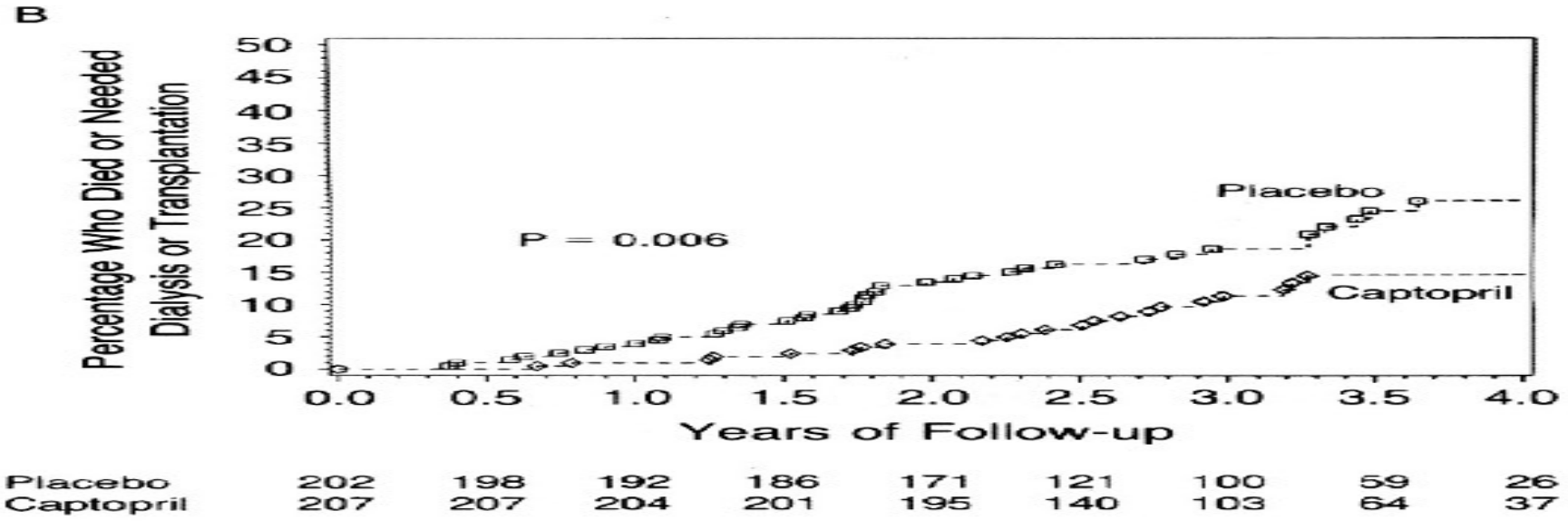


Beta Blockers, ACE/ARB Inhibitors, & Aldosterone Receptor Antagonists Protect Kidney From Long-Term Diabetic Complications

These drugs are clinically proven for preventing & delaying progression of diabetic macro & microvascular complications

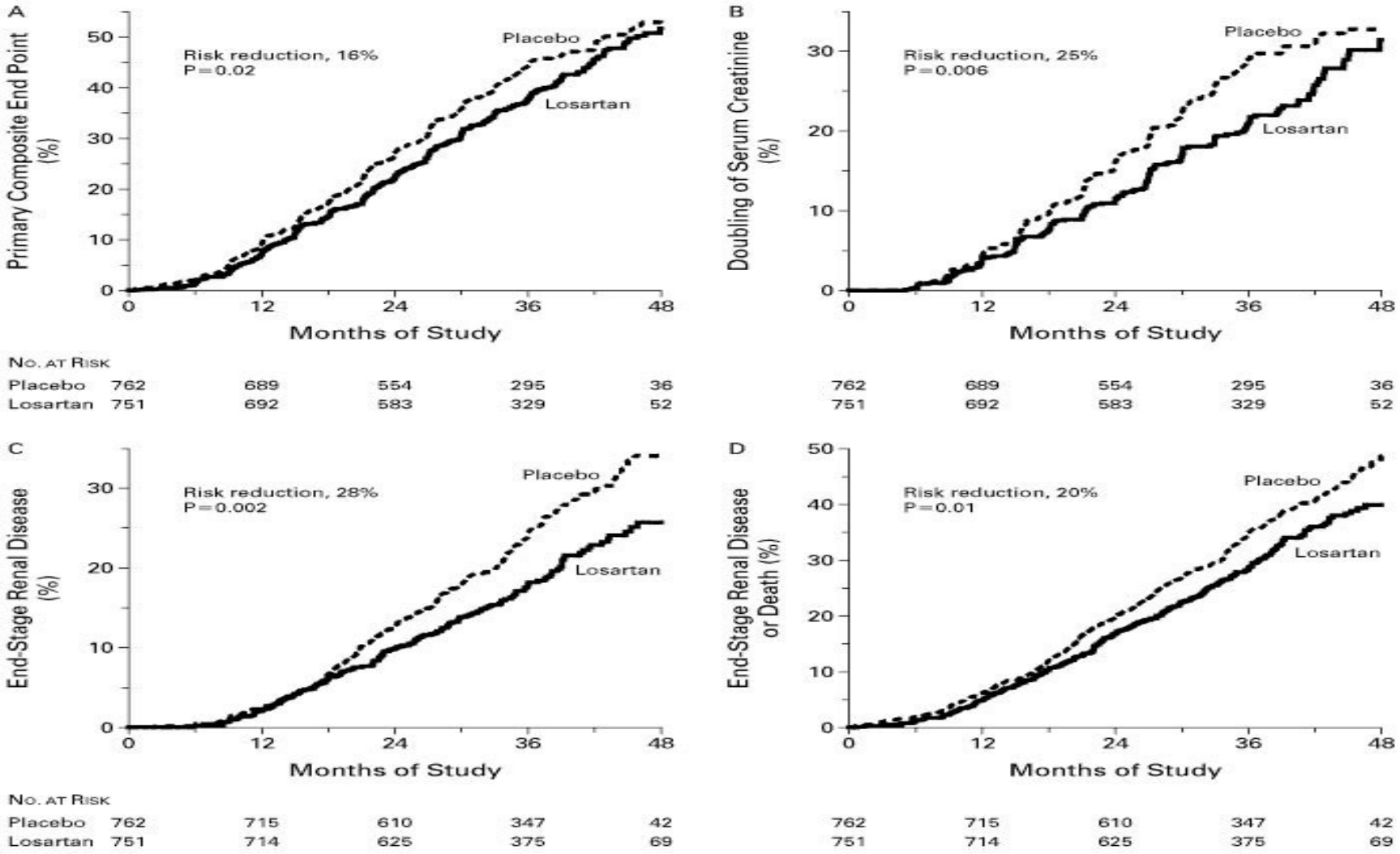
ACE Inhibitors & Renal Protection





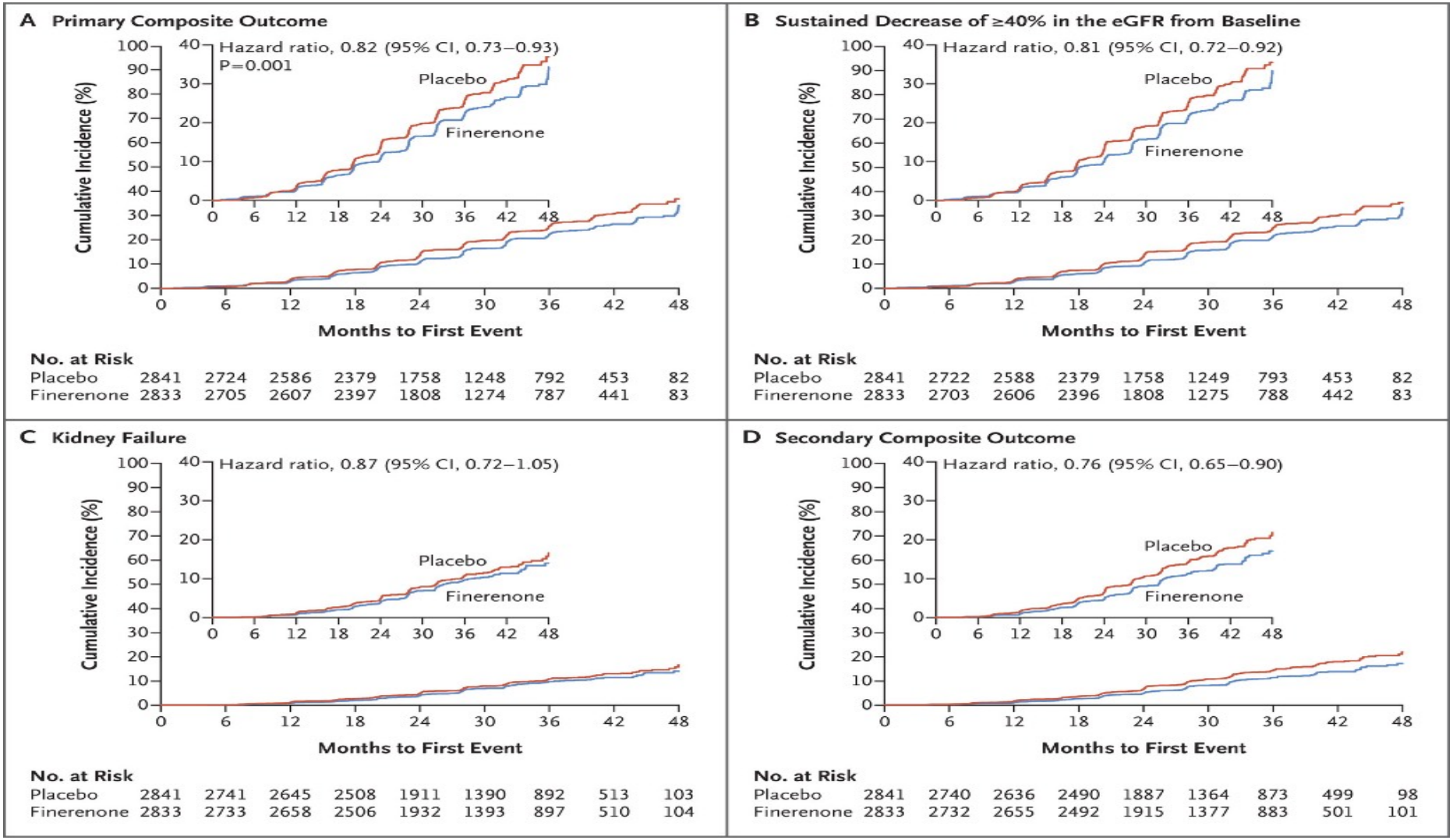
Lewis, E., et. Al. a Engl J Med 1993; 329:1456-1462

Effect of ARB (Losartan) on Renal & CV Outcomes



Brenner, B. et.al. N Engl J Med 2001; 345:861-869

Effect of Finerenone (Aldosterone Antagonist) on CKD Outcomes in T2DM

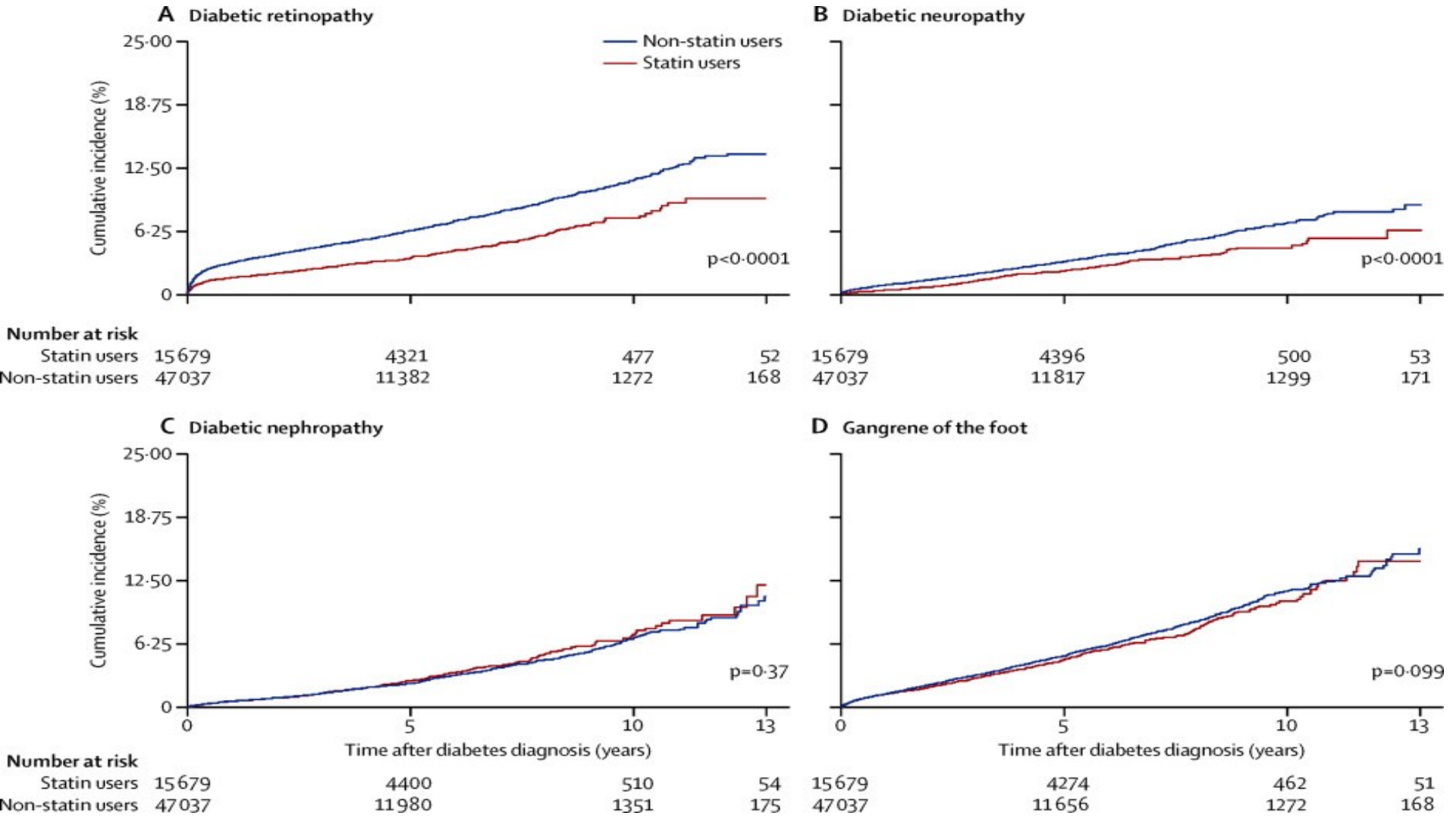


Bakris, G. et. al. N Engl J Med 2020; 383:2219-2229

In Addition to CV Protection….Statins Also Reduce Risk for Developing Diabetic Nephropathy, Retinopathy, & Neuropathy

Zhao, X. et. at. Medicine. 2022 Jun 17; 101(24):
Kang, EYC, et. al. JAMA Ophthalmol. 2019. 6319
Daliri, M. et. al. J Pharm Pharmacol. 2023 Apr 17;75(5):593-611.

Statins Protect Against Diabetic Microvascular Complications



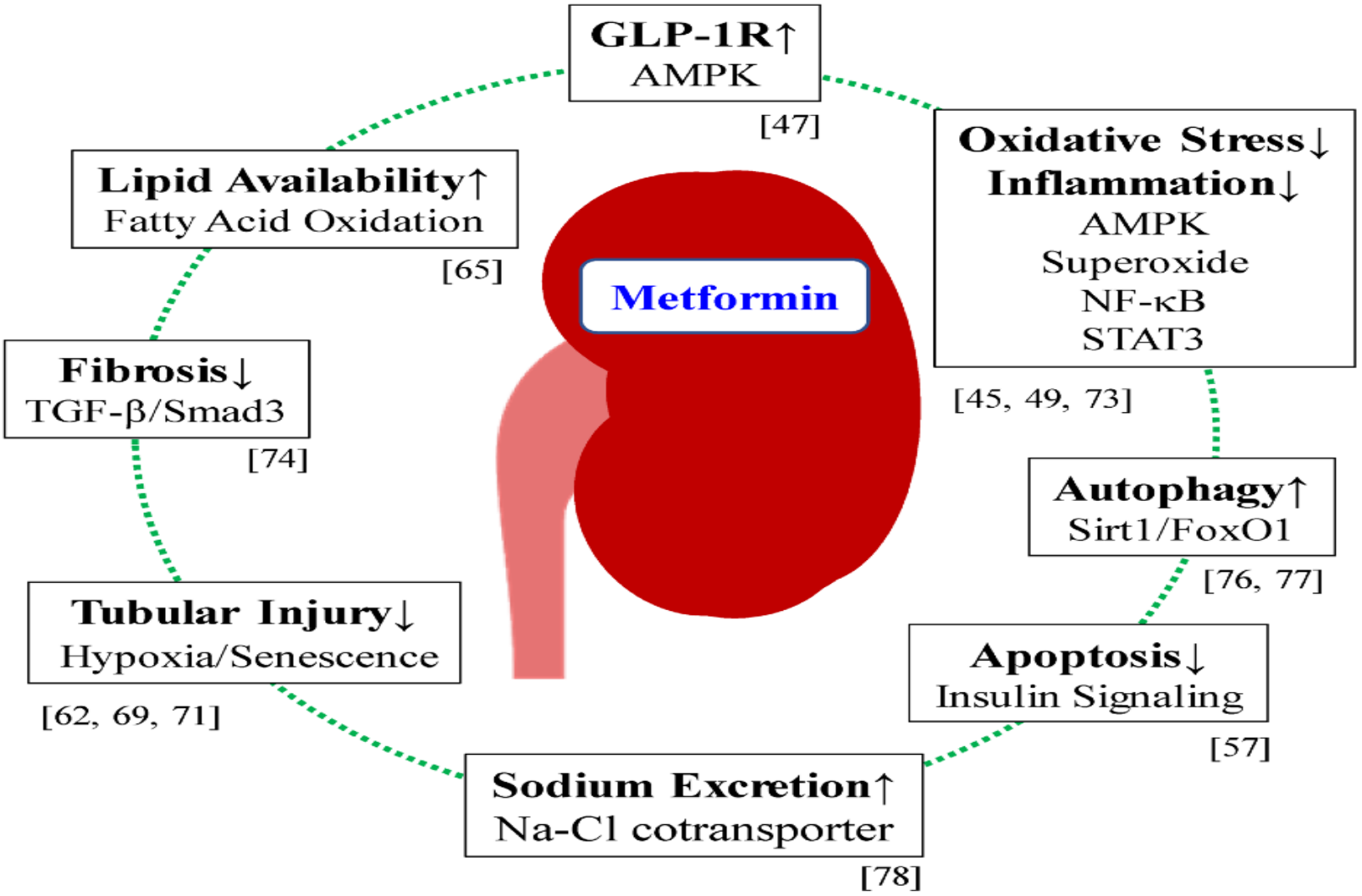
Nielsen, S. & Nordesgaard, B. The Lancet Diab & Endo. Vol. 2 Iss. 11, P 894, Nov 2014

What About Metformin?

Metformin imparts renal protection via multiple pathways including; AMP-activated protein kinase (AMPK) signaling, reducing endogenous ROS generation, & direct antifibrotic effects in renal cells

Pan, Q. et. al. Aging. 2020 May 15; 12(9): 8742–8759.

Reno-Protective Effects of Metformin

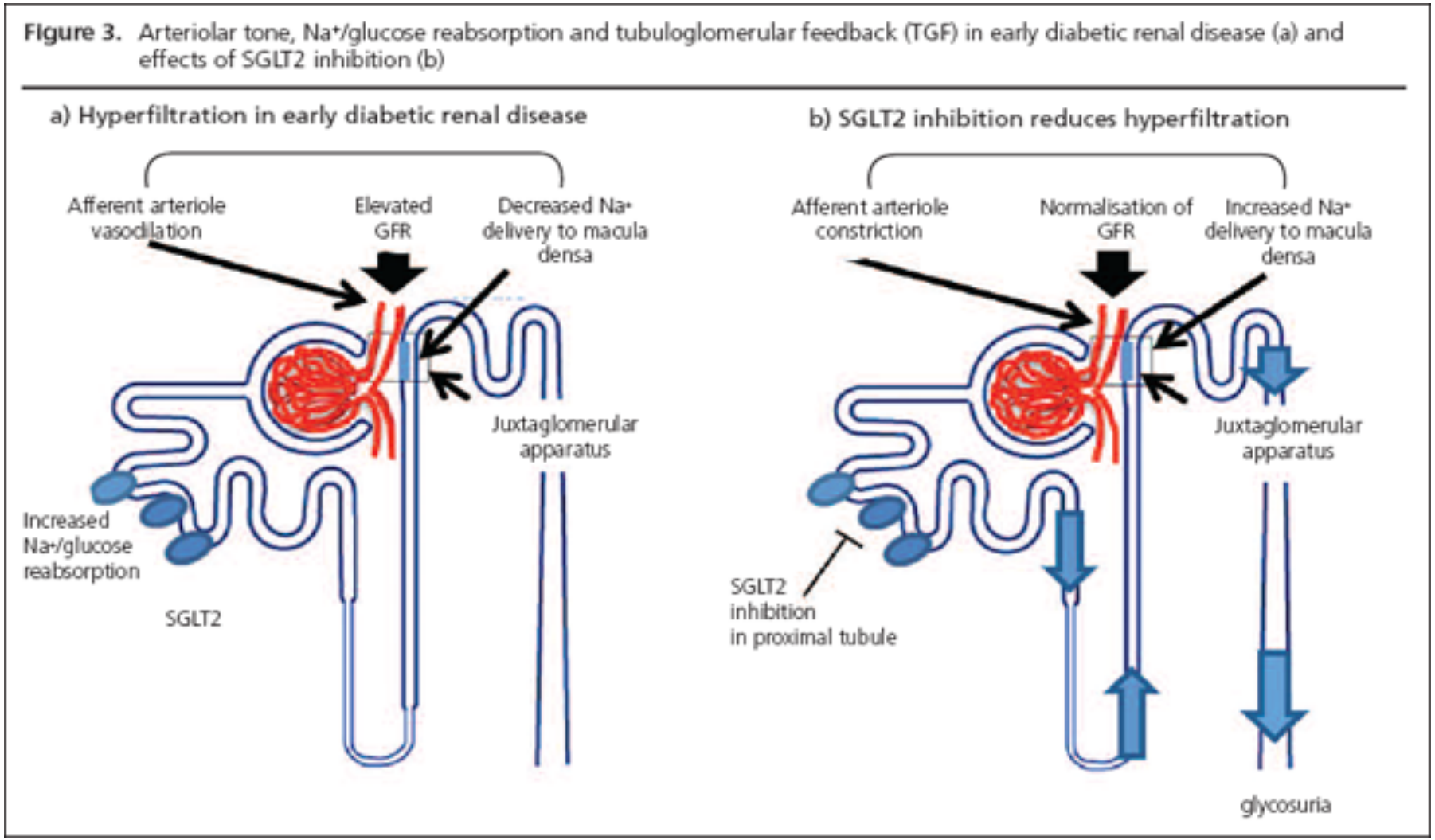


Kawanami, D. et. Al. Int. J. Mol. Sci. 2020, *21*(12), 4239;

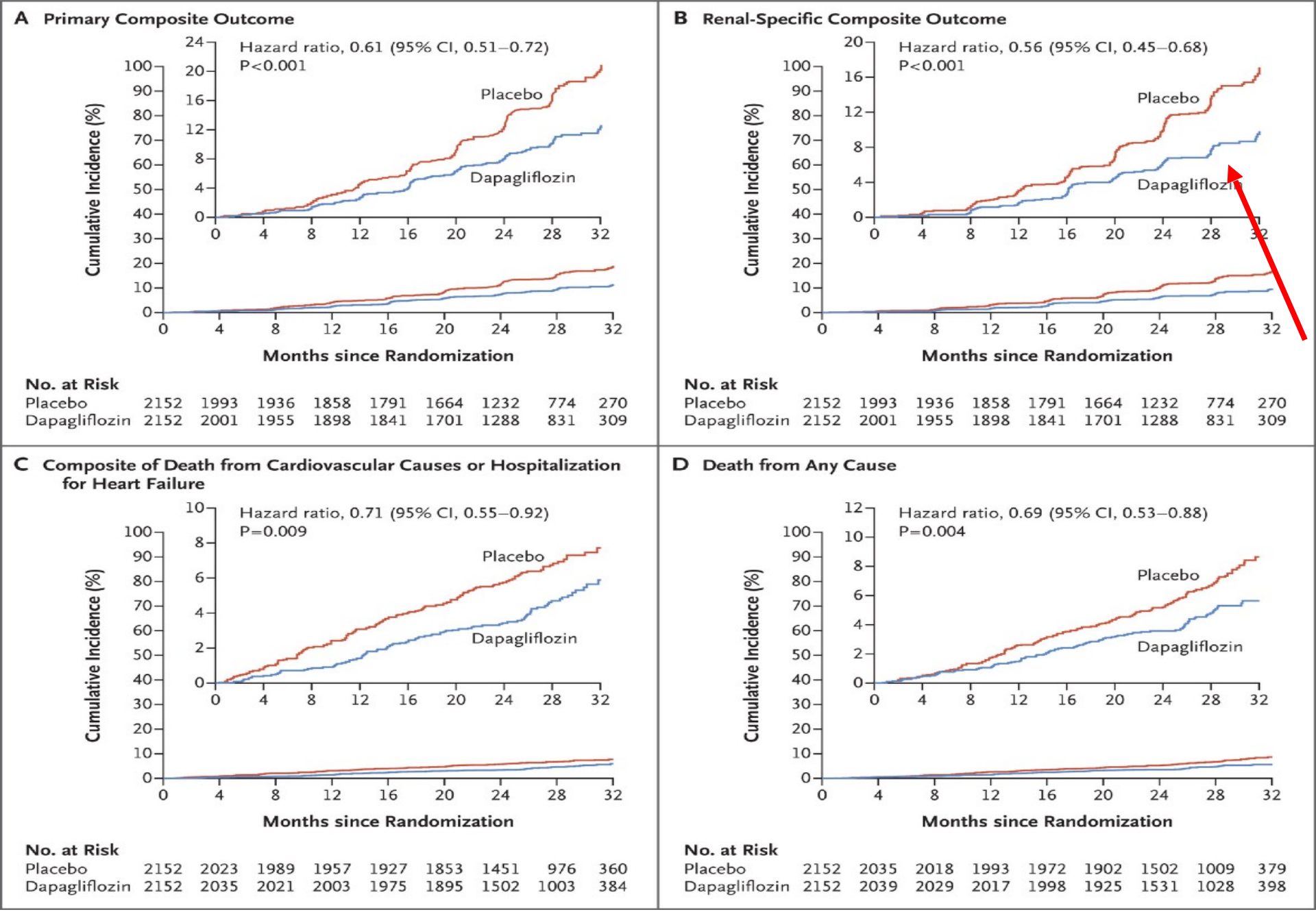
SGLT-2 Inhibitors Protect Against CKD in Diabetes Mellitus

May protect from the first step in diabetic nephropathy; hyperfiltration

SGLT-2 Inhibitors Reduce Renal Hyperfiltration



Maltese, G. et. al. British J of Diabetes, Vol. 15 No. 3 (2015)



Heerspink, H. et. al. N Engl J Med 2020; 383:1436-1446

SGLT-2 Inhibitors Also Protect Against Diabetic Neuropathy & Retinopathy

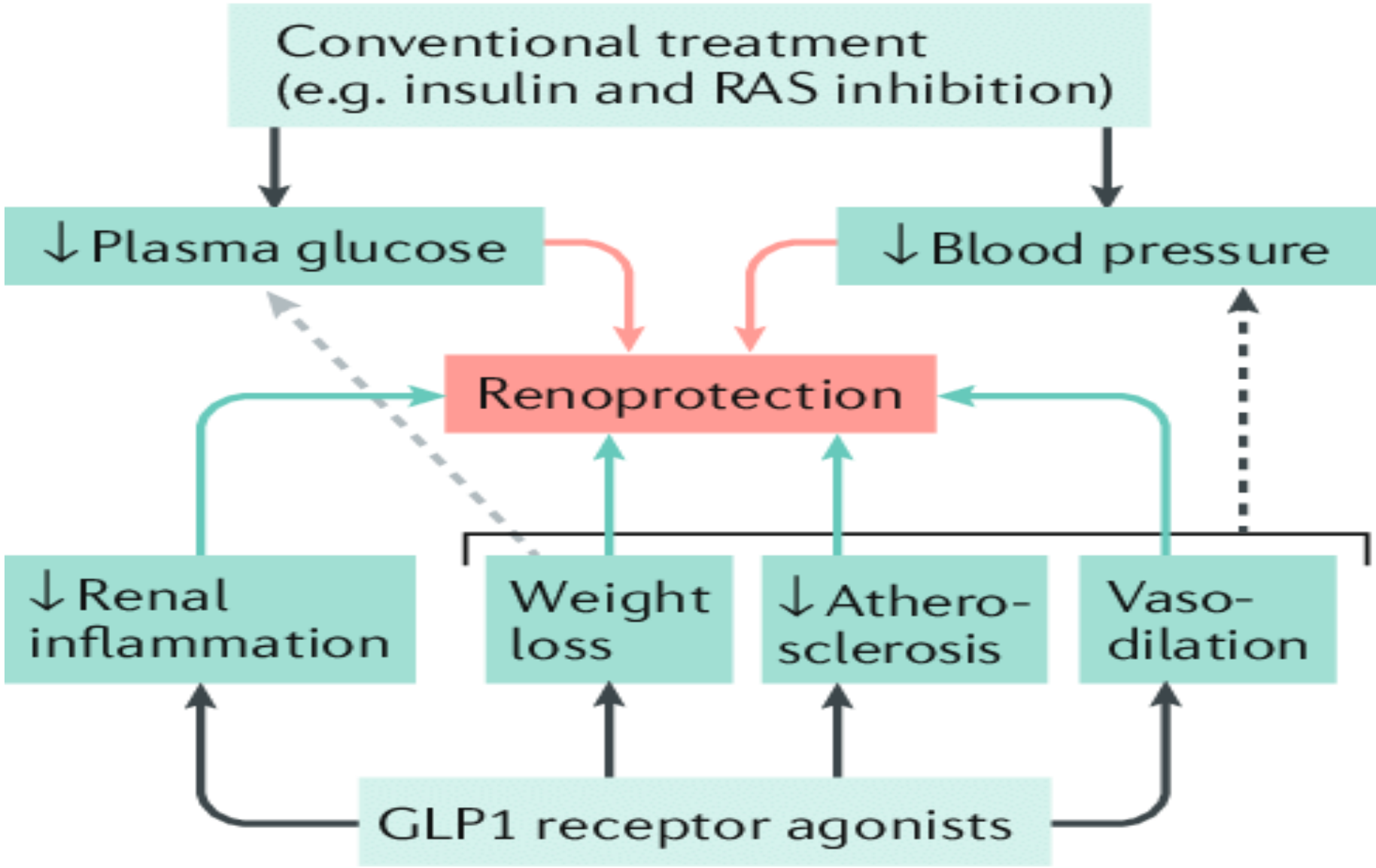
- In addition to the CV & renal protective effects of SGLT-2 inhibitors …….
- They also improve motor nerve conduction velocities[1] & prevent retinal pericyte loss which protects from retinopathy[2]

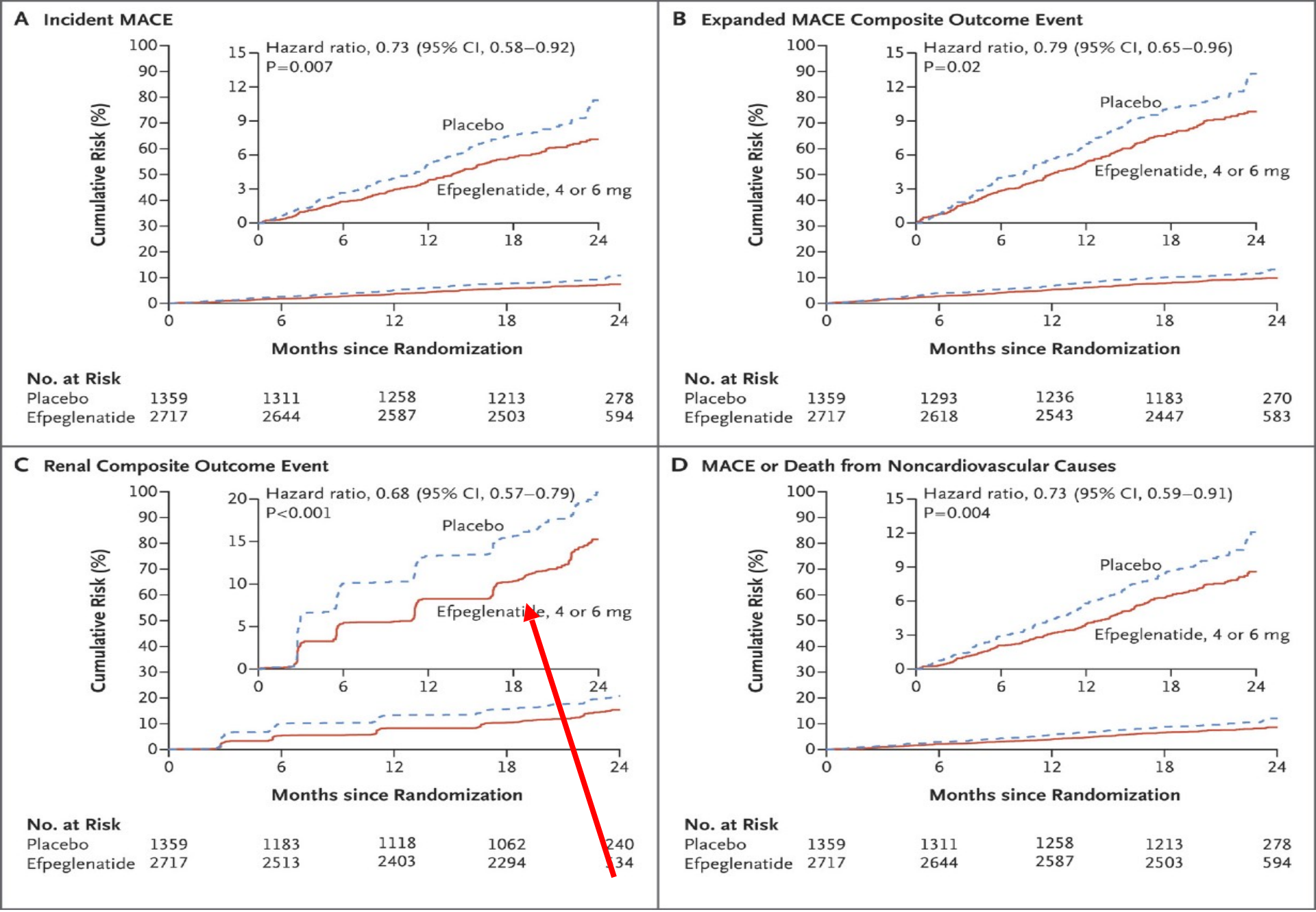
[1]Kandeel, M Front Pharmacol. 2022; 13: 926717
[2]Lahoti, M. et. Al. Cardiovasc Endocrinol Metab. 2021 Mar; 10(1): 3–13.

GLP-1, Dual & Triple Agonists Demonstrate Protection For All Long-Term Diabetes Complications

They also reduce risk of developing diabetes associated cancers!

GLP-1 Agonists & Renal Protection



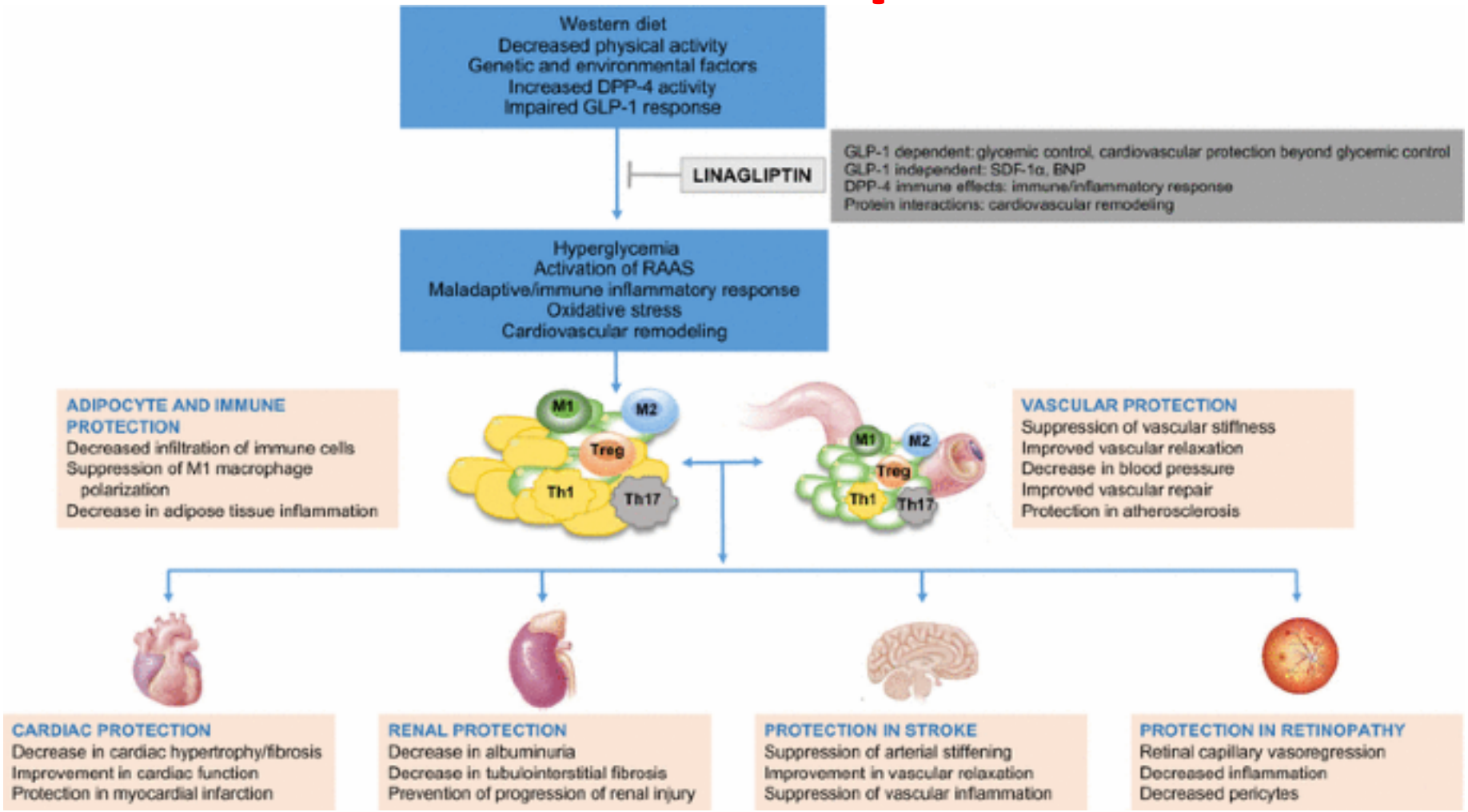


Gerstein, H. et. al. N Engl J Med 2021; 385:896-907

DPP4-Inhibitors Prolong the Half-Life of Endogenous GLP-1

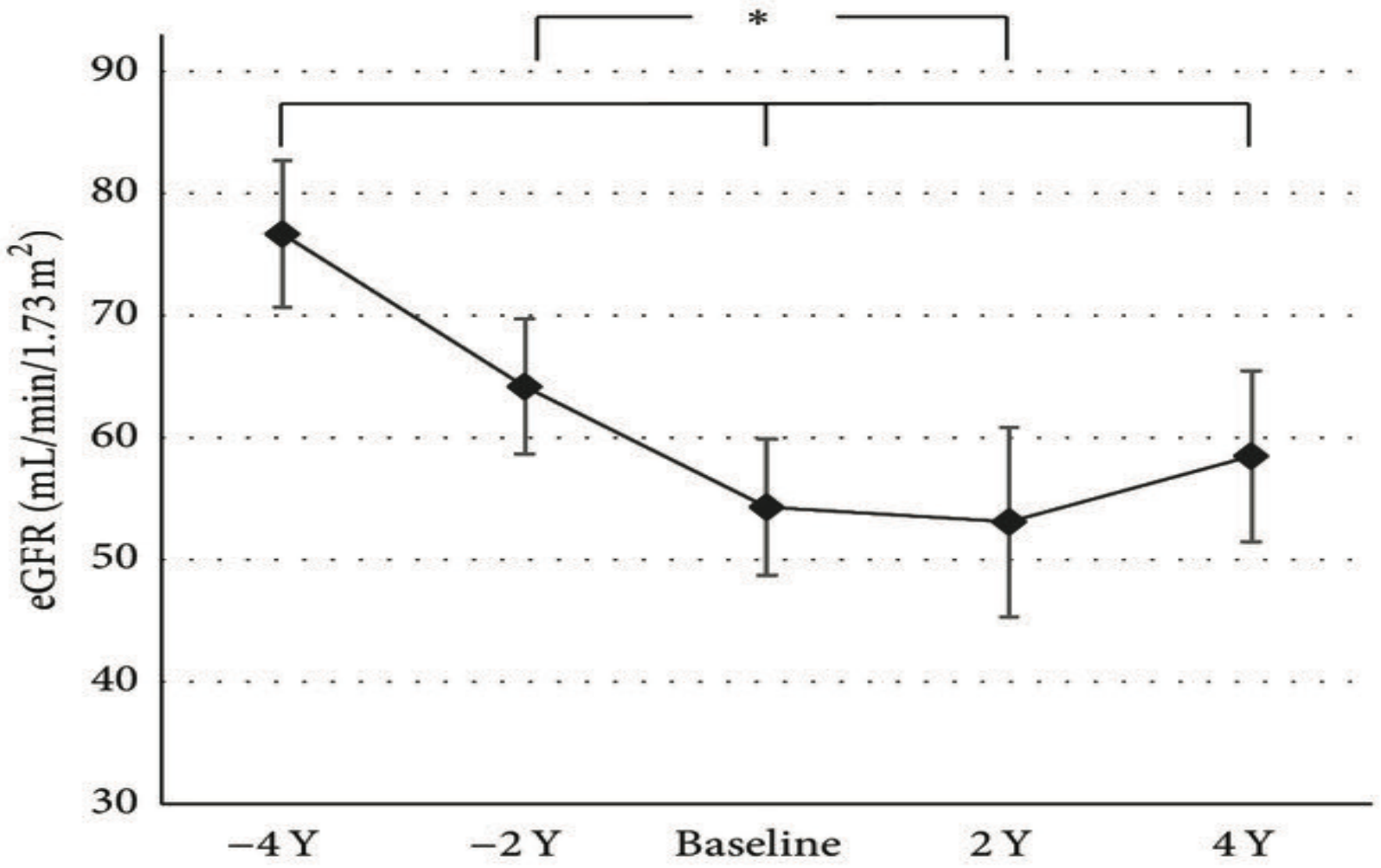
The Are Also Protective Against Diabetic Macrovascular & Microvascular Complications

Protective Effects of DPP4-Inhibitors on Diabetic Complications



Aroor, A. et. Al. Cardiovascular Diabetology volume 17, Article number: 59 (2018)

Renal Protective Effect of DPP-4 Inhibitors in T2DM With Early CKD



Kim, Y-G. et. al. J Diab. Res. 2016; 129-139.

DPP4 Inhibitors in T1DM?

Improve β-cell function, attenuate autoimmune destruction of β-cells & decrease insulin requirements

Penaforte-Saboia, J. et. al. Diabetes Metab Syndr Obes. 2021; 14: 565–573

Conclusions

Multiple Classes of Medications Protect Against Long-Term Diabetic Microvascular Complications

Clinical Approach in 2023 to Preventing the Diabetes Long-Term Complications

We should assume that the trajectory of long-term diabetes complications risk should be altered dramatically if we use these medications earlier to control glucose levels

Routine Monitoring of Persons With Diabetes

- A1C q 3-4 mo
- Annual labs; CMP, lipid profile, TSH, eGFR & urine microalbumin (timed urine GFR & protein once abnormal), 25 (OH) Vitamin D
- Annual dilated eye exam, foot exam, dental exam, & neurofilament testing of LE's for peripheral neuropathy
- Early CV assessment with stress test or coronary artery calcium score

Less than 40% of older adults with diabetes even get routine screening for CKD!

Ferre, S. et. al. Mayo Clinic Proceedings. Vol. 7, Iss. 5, Oct. 2023, Pages 382-391

Target Goals for Long-Term Diabetes Complication Prevention in 2023

- Normalize A1C to <6.5% & reduce glycemic variability (GV) seen on CGM
- Correct dyslipidemia with LDL <70 mg/dl, HDL >55 mg/dl, & TG <100 mg/dl with statins or PCKS9 inhibitors
- Normalize blood pressure to <130/80
- No smoking, encourage regular exercise, & treat any BMI >28?

Earlier Use of Specific Medications For Both Forms of Diabetes

- ACE or ARB with onset of HT, microalbumin, or elevated urinary albumin-to-creatinine ratio (30-299 mg/g creatinine)
- SGLT-2 antagonists for post-prandial glucose control, high GV documented on CGM, albuminuria (GFR >30 ml/min), or CHF
- GLP-1/DPP4 inhibitor for BMI >28 or GFR <60 ml/min

Reducing the Risk of Complications for T1DM

Reducing the Risk in T1DM

- Basal/bolus insulin replacement therapy with "smart" insulin pump/CGM if possible A1C q 3 months & target A1C 6.5-7.0%
- CGM download q 3 months with estimate of time in range & GV
- Early use of SGLT-2 knowing hyperfiltration is first phase of nephropathy; eGFR >110?
- Consider Statin in males >21 YO; however …. in females only if reliably using BCP/IUD
- GLP-1 for BMI >30?

Reducing the Risk of Complications in T2DM

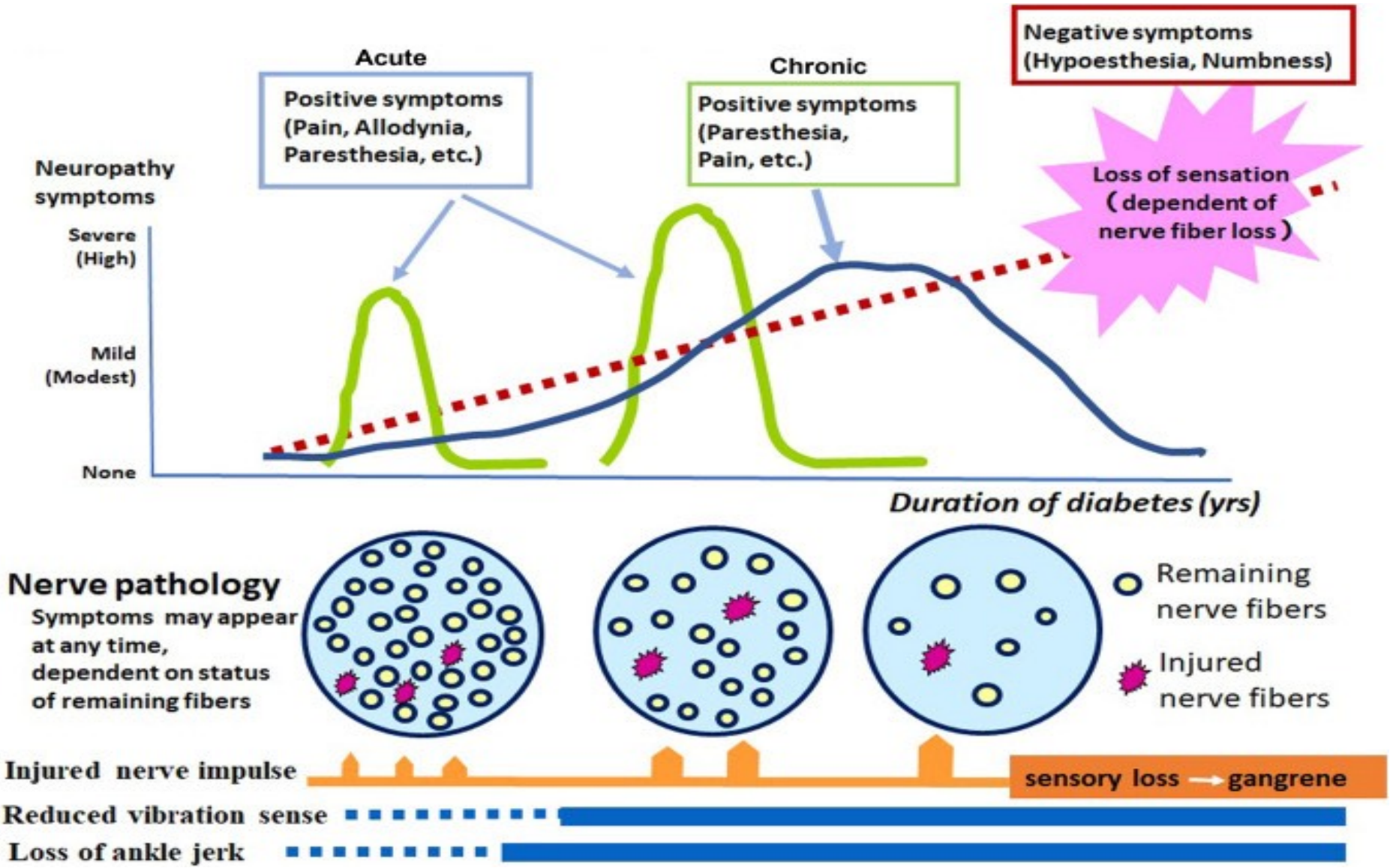
Reducing the Risk Specific to T2DM

- Routine self-glucose monitoring & reporting to office q 4-6 weeks
- Intermittent “Flash CGM” q 3-4 months (pattern analysis) & to R/O hypoglycemia unawareness in older patients with CAD
- Triple meds; GLP-1 agonist + SGLT-2 antagonist + metformin @ diagnosis or before (IGT) to delay onset?
- Basal insulin if A1C >8% on triple meds

Altering the Natural History of Diabetic Nephropathy

- Intensive glucose control is very important
- BP control is even more important
- Identifying early microalbuminuria & intervention with ACE/ARB inhibitor
- SGLT2 antagonists reduce hyperfiltration & may have major early protective effects
- Smoking cessation & other CV risk factor reduction

Natural History of Diabetic Neuropathy



Yagahashi, S. ScienceDirect. PP 11-32, 2022

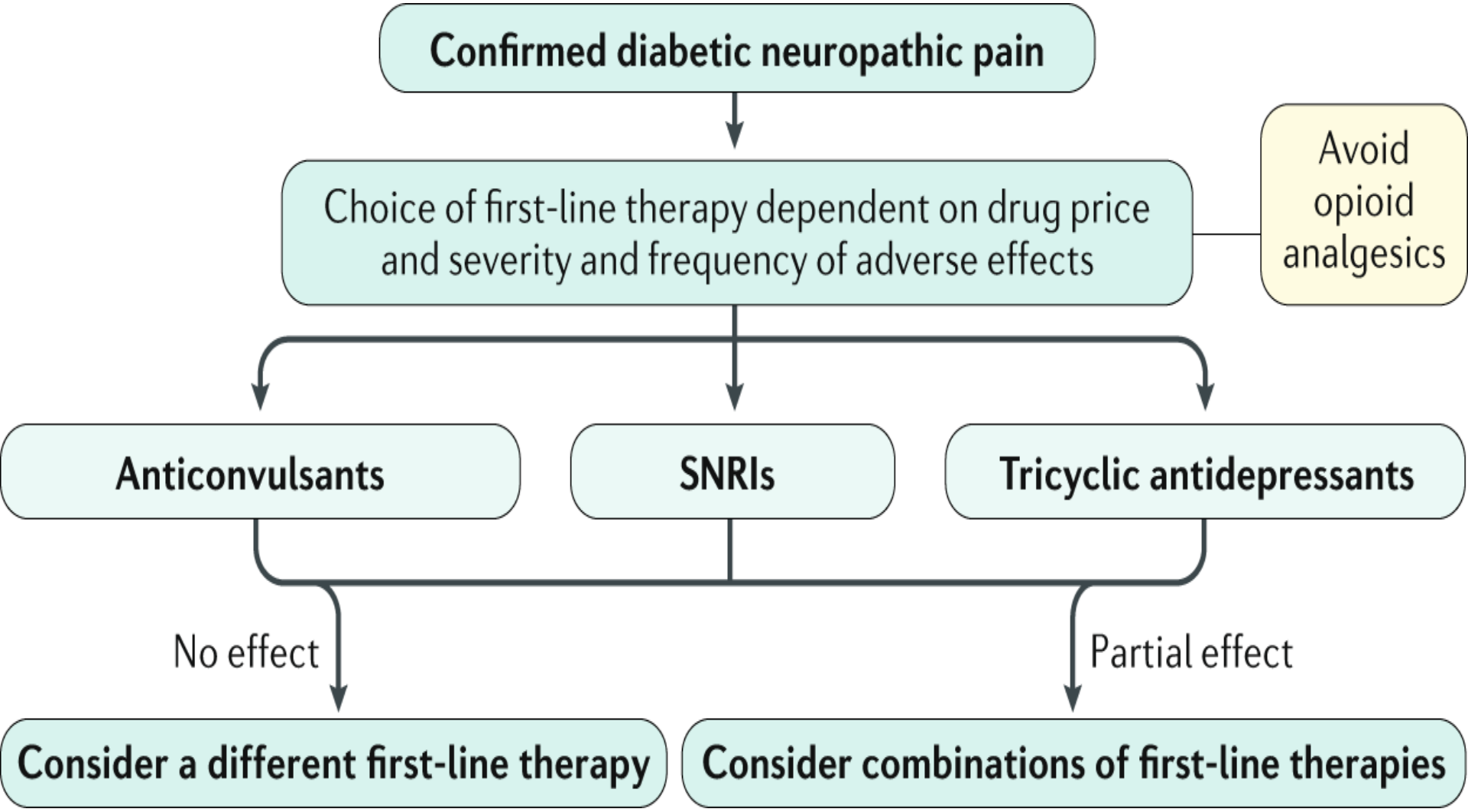
Altering the Natural History of Diabetic Peripheral Neuropathy

- Same as nephropathy but add B-complex multiple vitamin to protect distal nerves
- Intensive glucose control is more effective in patients with T1DM at preventing neuropathy & its complications than T2DM
- Education on self-home monitoring of feet, skin, & use of therapeutic footwear
- Early podiatric referral for nail care & orthotics for deformities

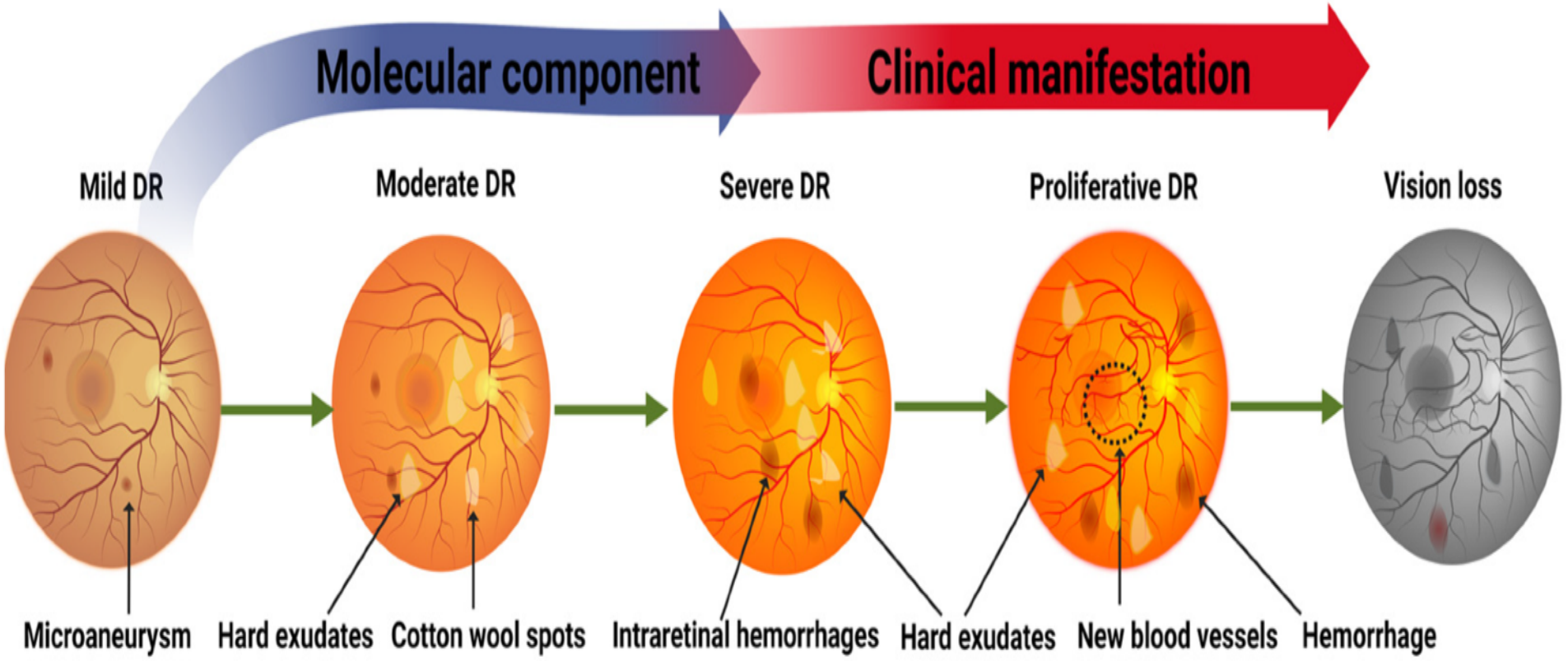
Alpha-Lipoic Acid for Neuropathic Pain?

Multiple controlled, double-blinded clinical trials have failed to demonstrate benefit!!

Management of Severe Diabetic Neuropathic Pain



Natural History of Diabetic Retinopathy

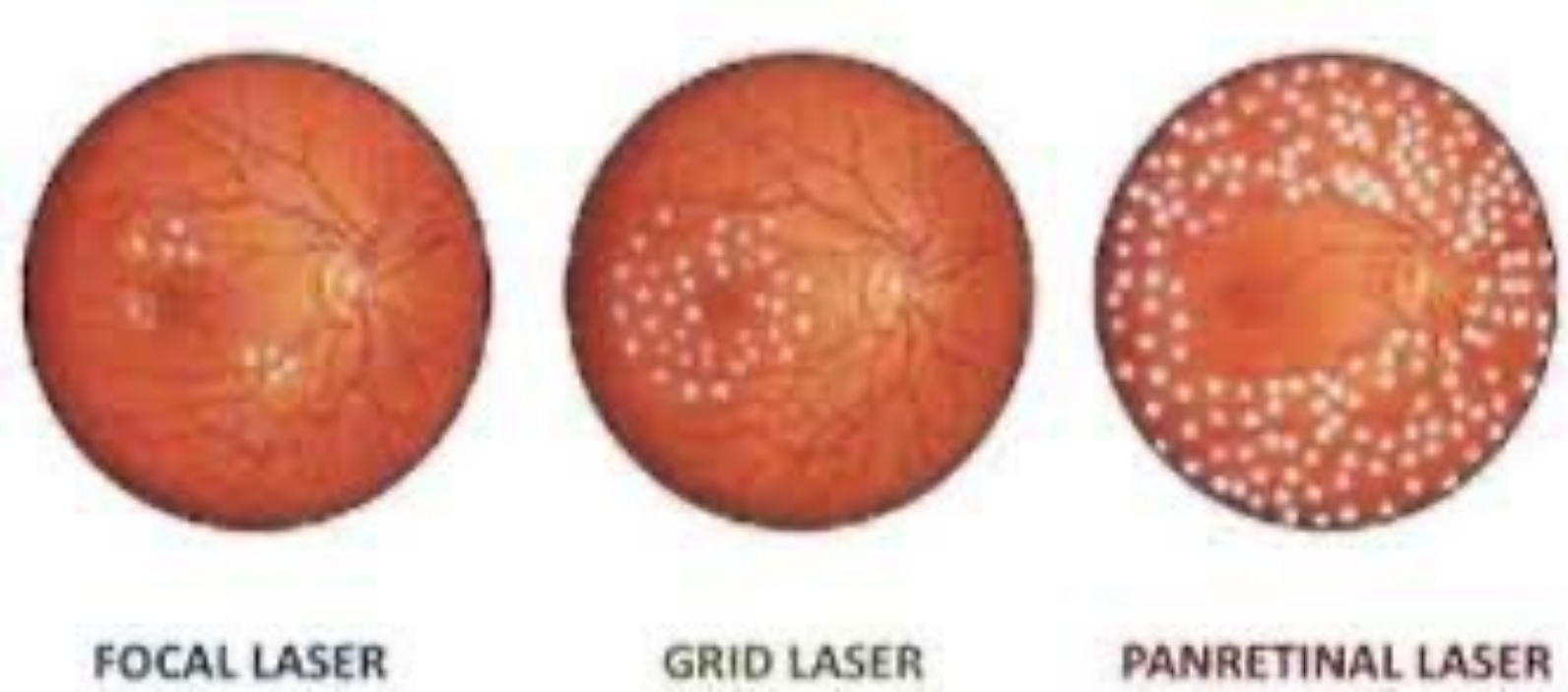


kaushik, V. et.al. nt. J. Mol. Sci. 2023, 24(5), 4408;

Altering the Natural History of Diabetic Retinopathy

- Early, intensive glucose control has been demonstrated to protect against risk for proliferative diabetic retinopathy in T1DM; but not protect from macular edema
- Annual dilated diabetic eye exam to detect early retinopathy
- Early referral to retinal specialist for treatment of non-proliferative diabetic retinopathy (NPDR)

Different Intensities of Laser Treatment of Diabetic Retinopathy



Altering the Natural History of Diabetic Retinopathy

- Early focal laser photocoagulation in non-proliferative diabetic retinopathy (NPDR)
- Focal/grid laser therapy has replaced pan-photocoagulation for proliferative diabetic retinopathy (PDP) due to 50% less vision loss from the less aggressive procedure
- Intravitreal injections of Anti-Vascular Endothelial Growth Factor (VEGF) Agents for retinopathy & macular edema

Conclusions

- DM is associated with increased risk for many acute & chronic complications
- Genetics is the principle non-modifiable risk factor while glucose control is the major modifiable risk factor
- Glucose control can now be achieved in either form of DM with aggressive treatment

Take Home Message

Multiple classes of medications have now been shown to protect against & delay progression of the long-term macrovascular & microvascular complications of diabetes