Updates in Peripheral Arterial Disease Management

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SCHOOL OF MEDICINE

Disclosures

- None

Objectives

- Identify PAD pathophysiology
- Review PAD epidemiology and risk factors
- Describe clinical manifestations of PAD
- Evaluate the latest evidence-based medical treatments

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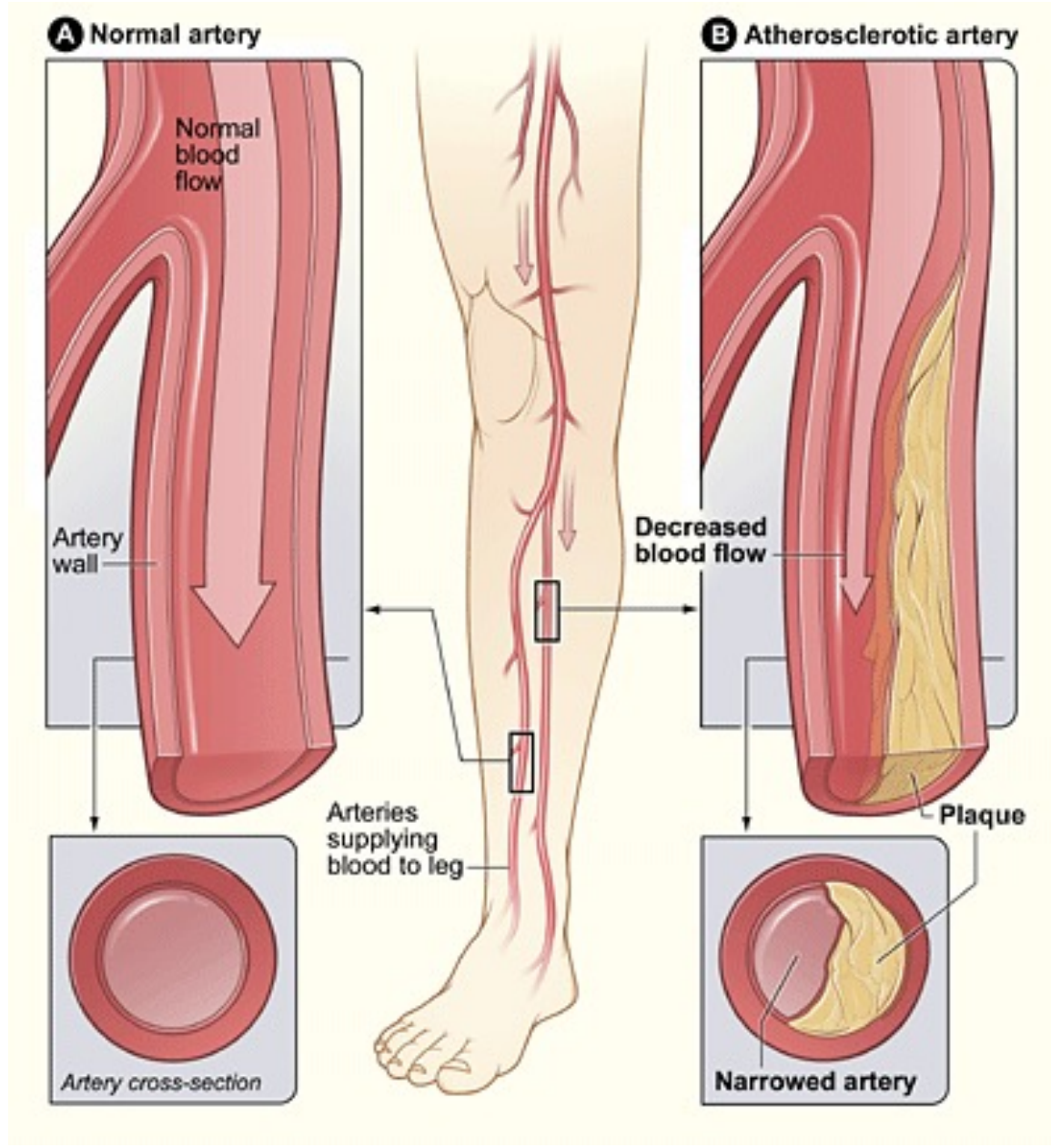
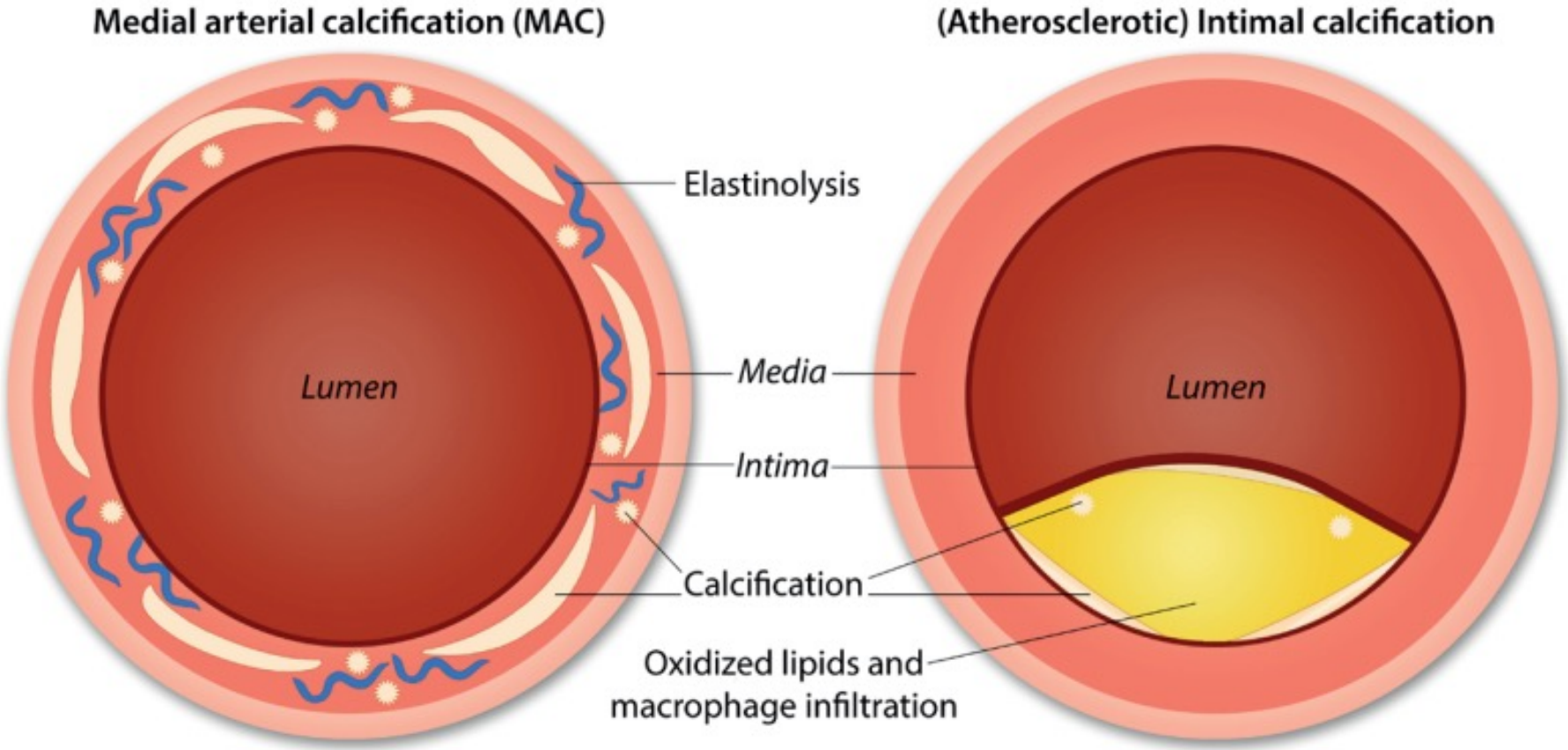
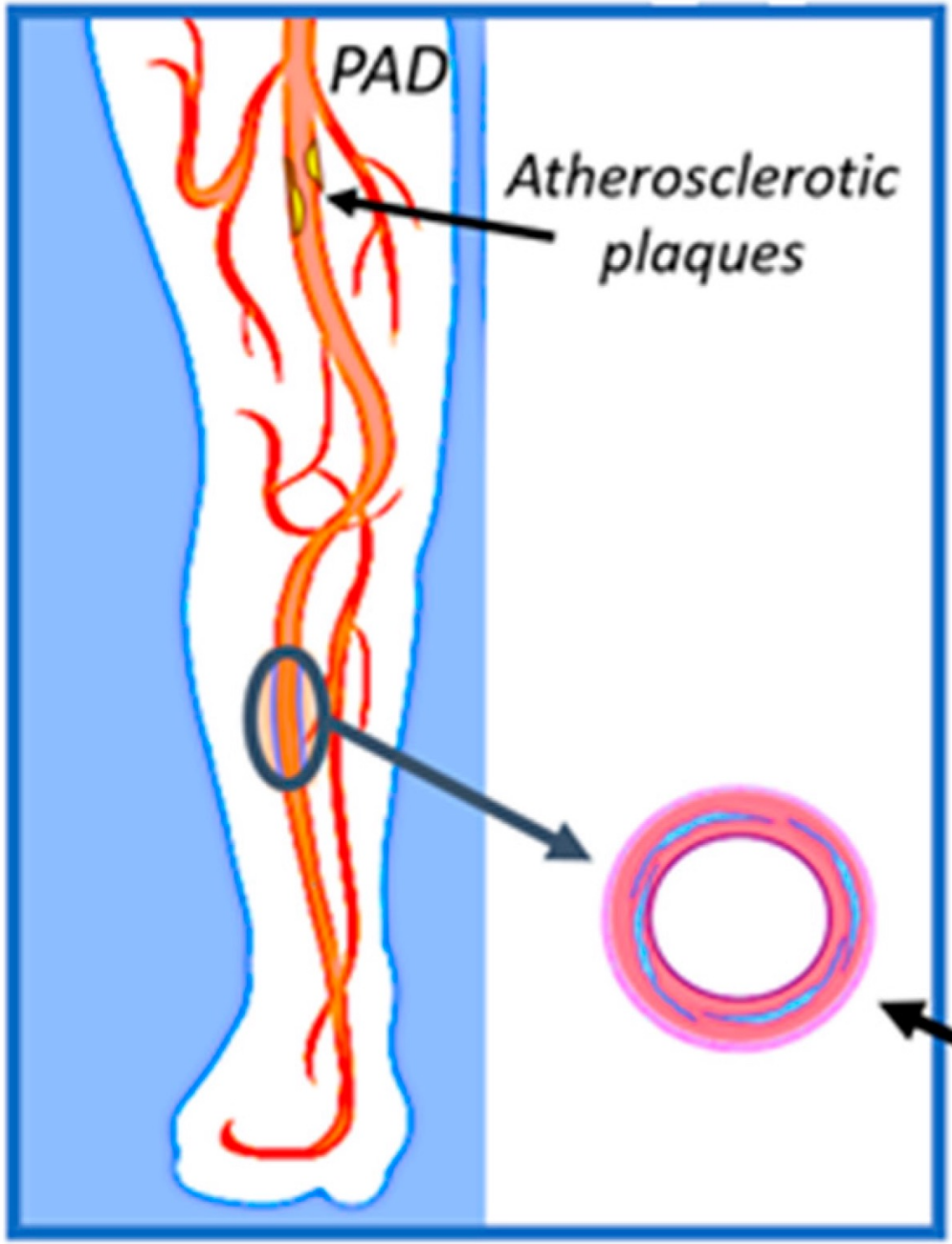

A Normal artery
Normal blood flow
Artery wall
Artery cross-section
Arteries supplying blood to leg
B Atherosclerotic artery
Decreased blood flow
Plaque
Narrowed artery

Atherosclerosis vs Non-atherosclerosis mediated:



Diabetes, chronic kidney failure, ageing ...



Changes in arterial wall:

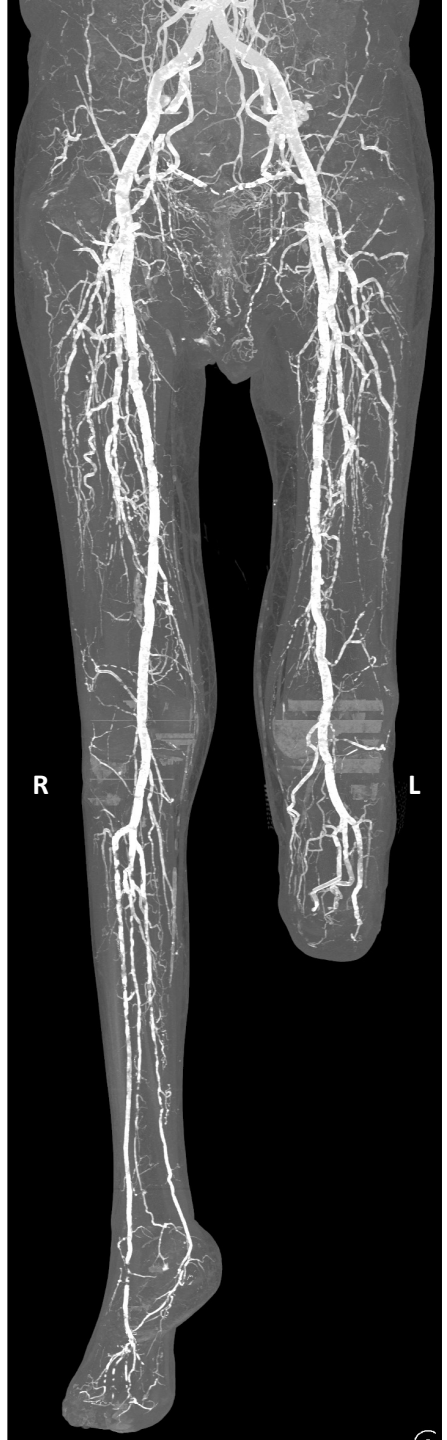
- inflammatory (TNF-α, IL-1β, SASP,..) -
- metabolic (hyperphosphatemia, hyperglycemia, AGEs,..)
- coagulation (vitamin K-dependent proteins,..)

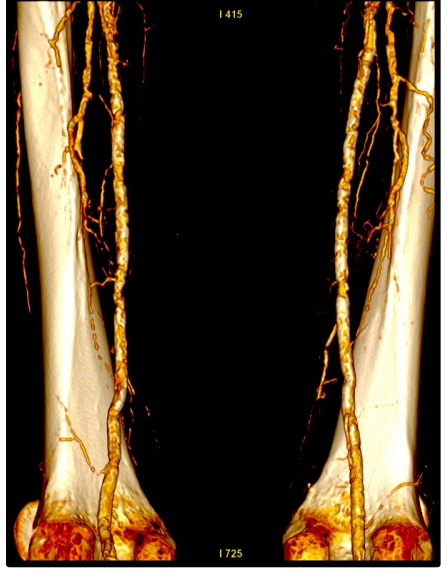
↓

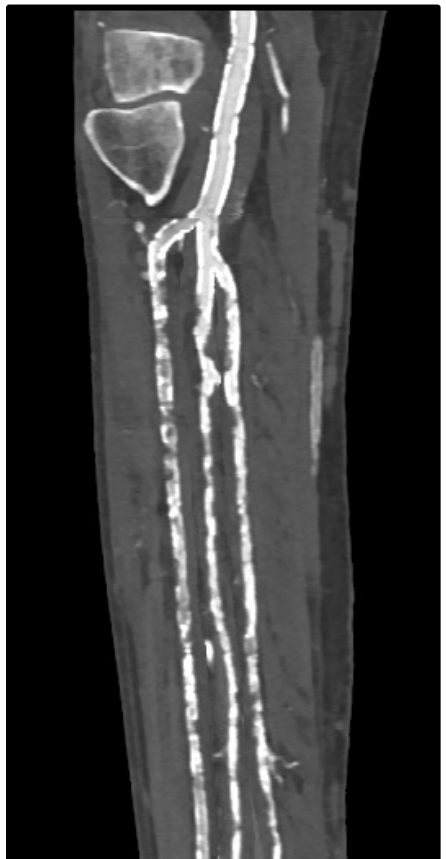
Osteogenic switch of VSMCs

↓

Medial arterial calcification

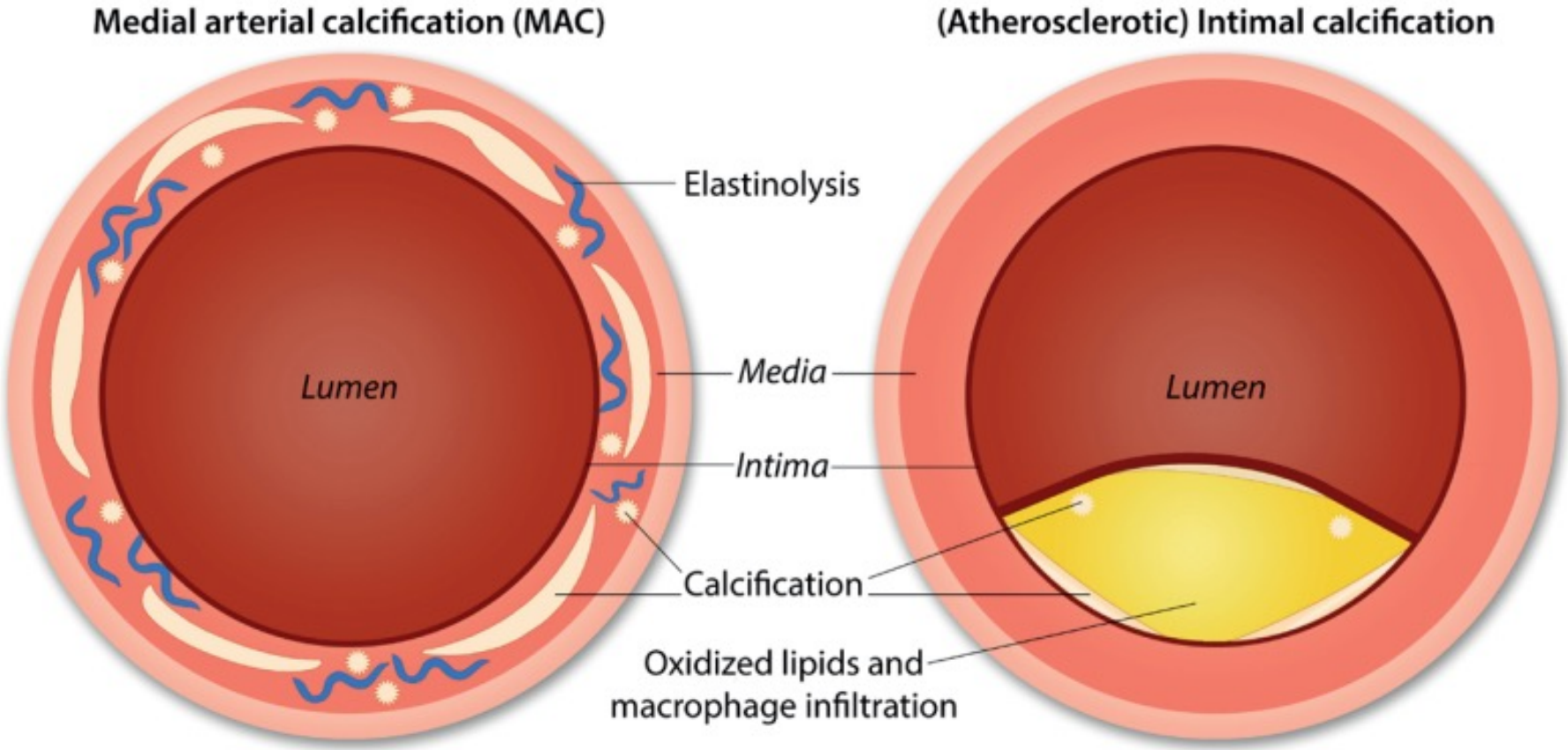






Alsaigh, T., *NEJM*, 2023.

Atherosclerosis vs Non-atherosclerosis mediated:



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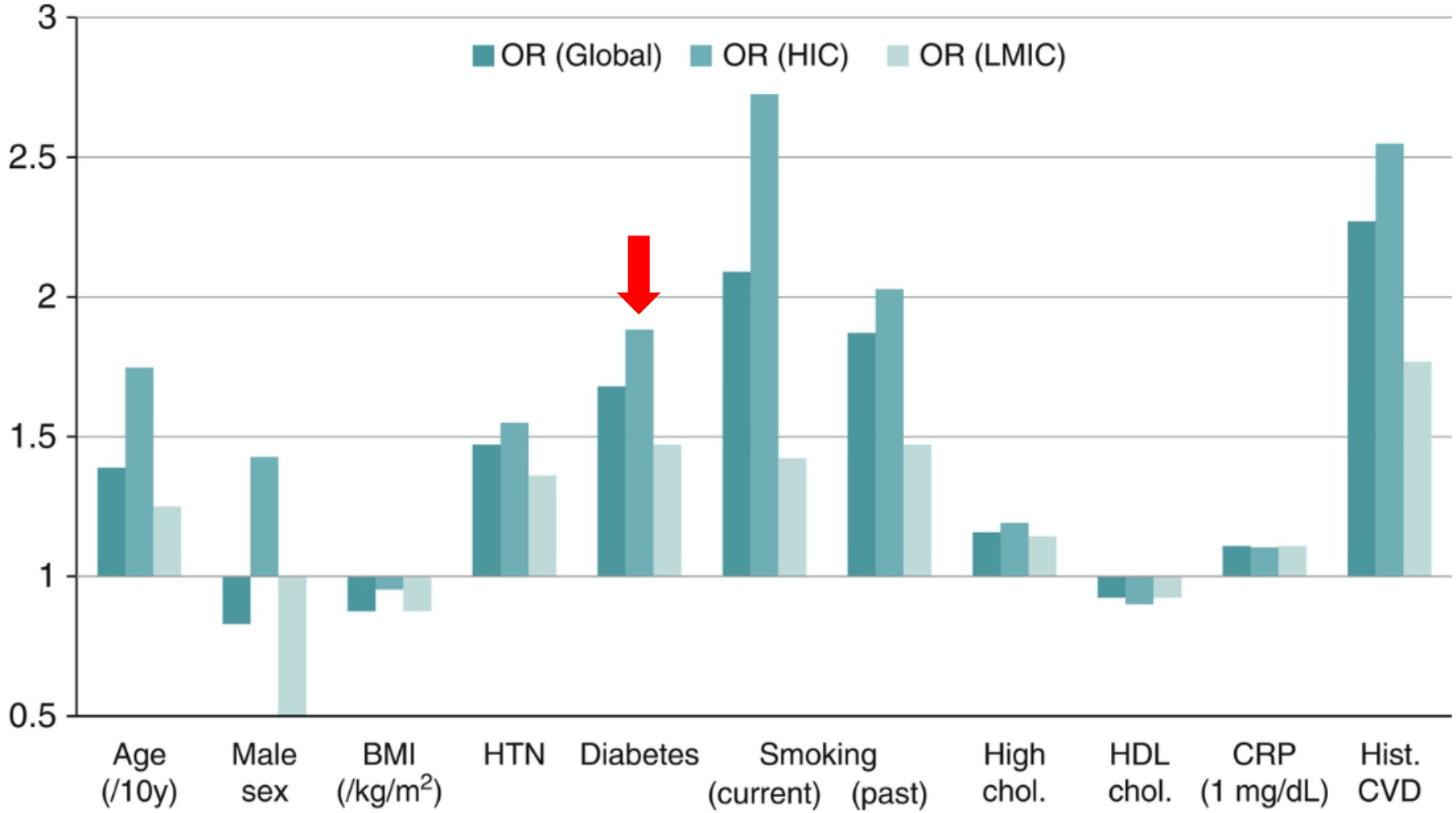
Epidemiology

- **PAD affects ~200M people worldwide (*NEJM*, 2016);**
- PAD is poorly recognized based on PARTNERS trial[1,2]:
  - Only 49% of the primary care physicians treating patients with a prior diagnosis of PAD were actually aware of it, despite documentation in medical records.
  - PAD is very common (prevalence: 29%) in high-risk individuals (>70 years without additional risk factors, or 50–69 years with a history of cigarette smoking or diabetes).
  - PAD patients are generally less intensively managed compared with CAD patients[3].

- **~10% of pts >55yo seeking care in the VA Healthcare System have PAD[4].**

[1]Shu, J, et al. *Atherosclerosis*. 2018
[2]Hirsch, AT, et al. *JAMA*. 2001
[3]Hiatt, WR, et al. *NEJM*. 2017
[4]Klarin, D, et al. *Nat Med*. 2019



Fowkes, FG., et al. *Lancet*. 2013.

Adjusted expenditures	History of PAD (weighted n = 640,098)	All U.S. adults (weighted n = 148,387,362)	*P* value
	Expenditure, USD (95% CI)	Expenditure, USD (95% CI)	
Inpatient	3834 (2209-5459)	1091 (1003-1179)	**.001**
Outpatient	1185 (591-1779)	498 (443-553)	**.02**
Office-based	2746 (1291-4201)	1068 (1029-1107)	**.02**
ED	343 (180-507)	205 (185-226)	.09
Medications	2662 (1905-3419)	1108 (1041-1176)	**<.001**
Other	1275 (301-2248)	444 (418-471)	.09
Total	11,553 (8137-14,968)	4219 (4064-4375)	**<.001**

Scully, RE, et al. *J Vasc Surg*. 2018

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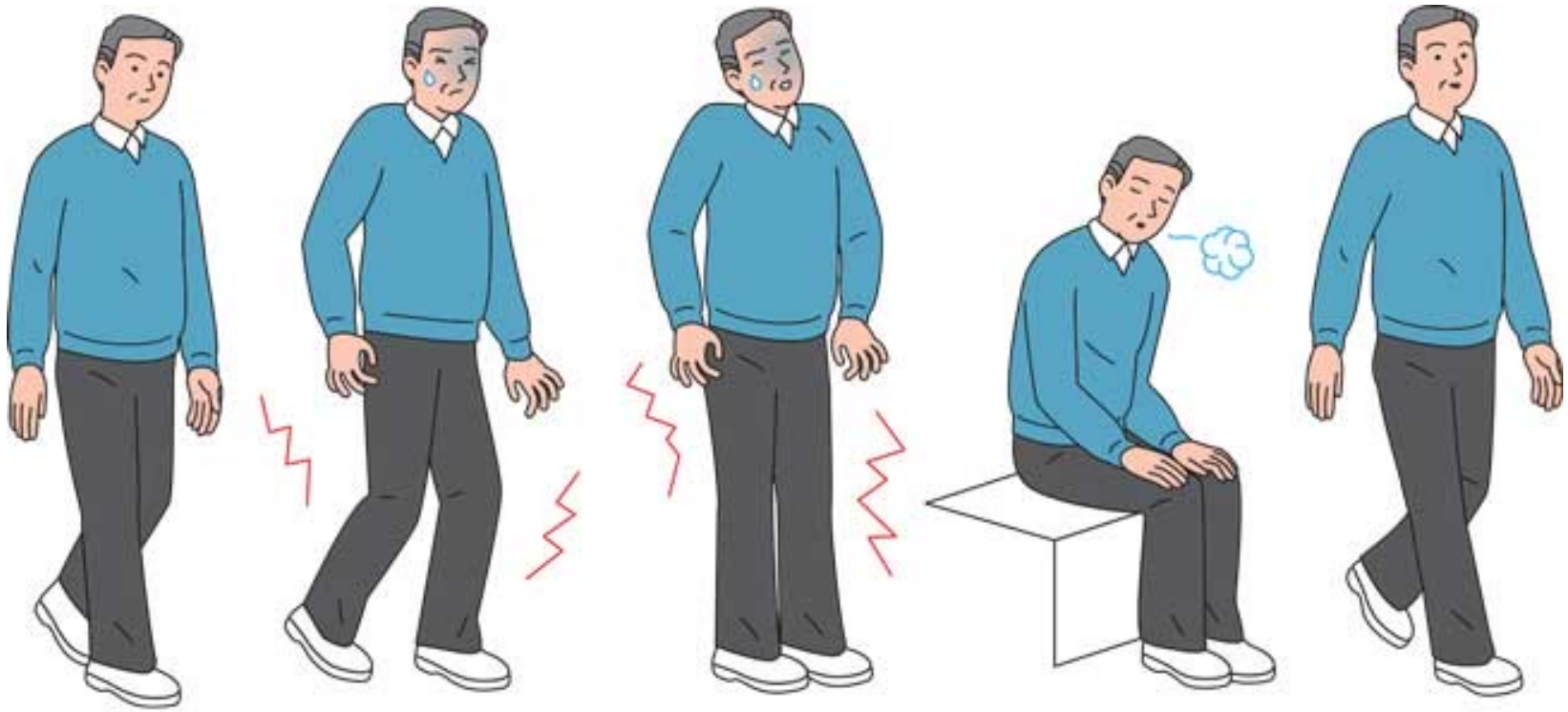
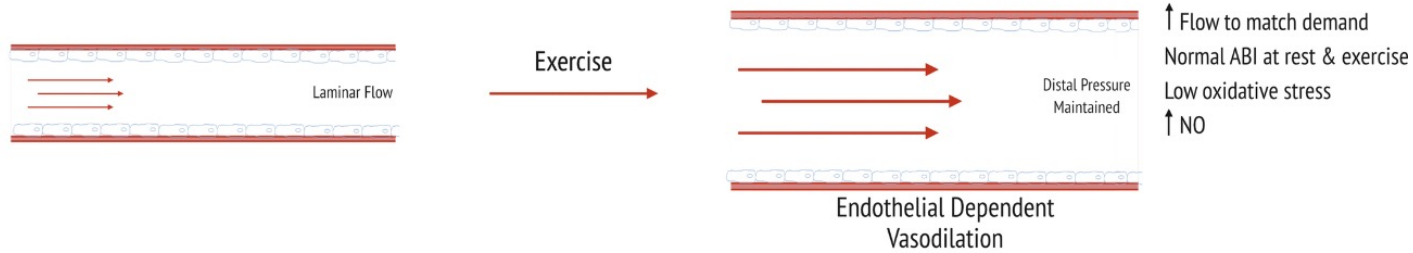
Clinical manifestations:

- Claudication



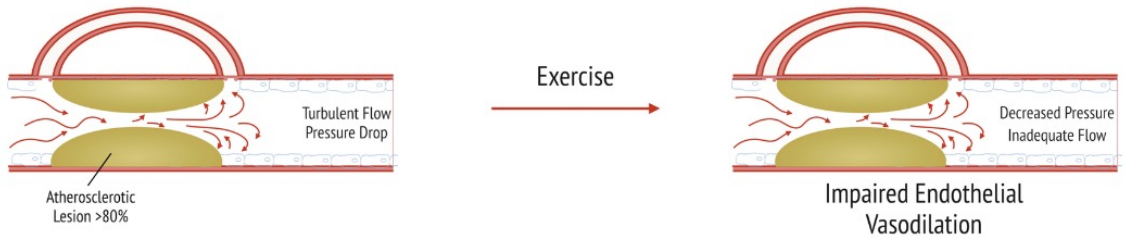
The first noticeable symptom of PAD may be intermittent claudication. This is leg discomfort, pain or cramping that develops with activity, is relieved with rest, and recurs upon resuming activity. The pain is most often noticed in the calf, but may also be felt in the buttocks or thighs.

Healthy Artery

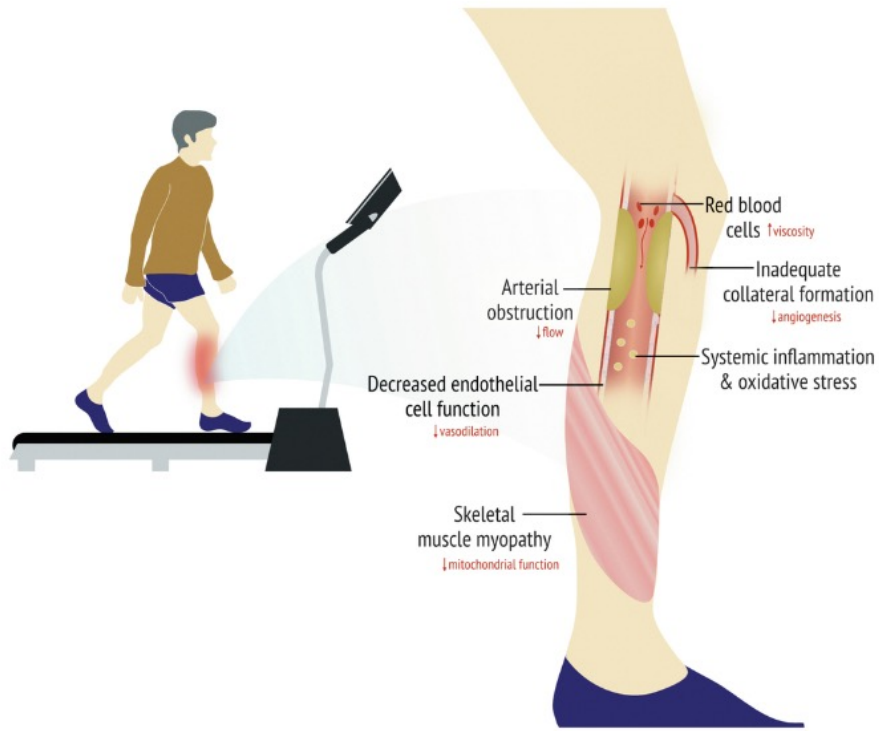


↑ Flow to match demand
Normal ABI at rest & exercise
Low oxidative stress
↑ NO

Artery in PAD



Abnormal ABI
Inadequate O_2 supply
↑ Oxidative stress
↑ Inflammation
↑ Thrombosis
↓ NO
Muscle ischemia



Nonatherosclerotic Causes of Exertional Leg Pain

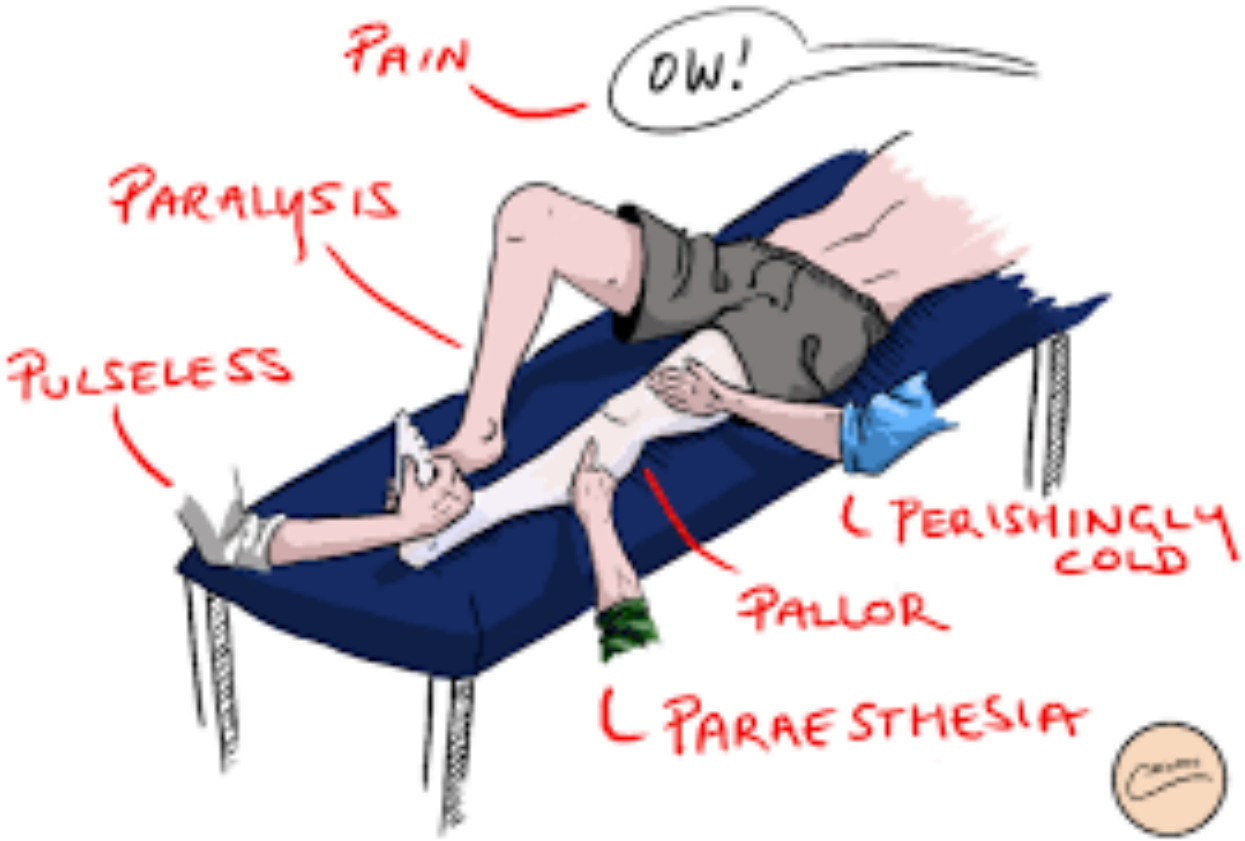
Nonatherosclerotic arterial disease
Atheroembolism
Vasculitis
Extravascular compression
Popliteal artery entrapment
Adventitial cysts
Fibromuscular dysplasia
Endofibrosis of the internal iliac artery
Venous claudication
Compartment syndrome
Lumbar radiculopathy
Spinal stenosis
Hip/knee arthritis
Myositis

Differential diagnoses of intermittent claudication:

Condition	Differentiation
Non-vascular	
Spinal stenosis	Relieved by position change, may have leg weakness
Osteoarthritis	Not quickly relieved by rest
Lumbar nerve root irritation	Straight leg raise test is positive
Vascular	
Venous claudication	History of deep vein thrombosis, pain relief on leg elevation, oedema, venous skin changes
Buerger's disease (thromboangiitis obliterans)	Young male smokers

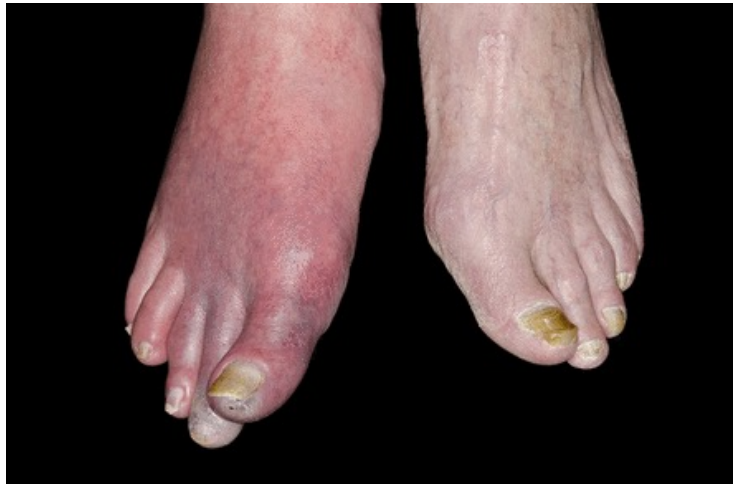
Clinical manifestations:

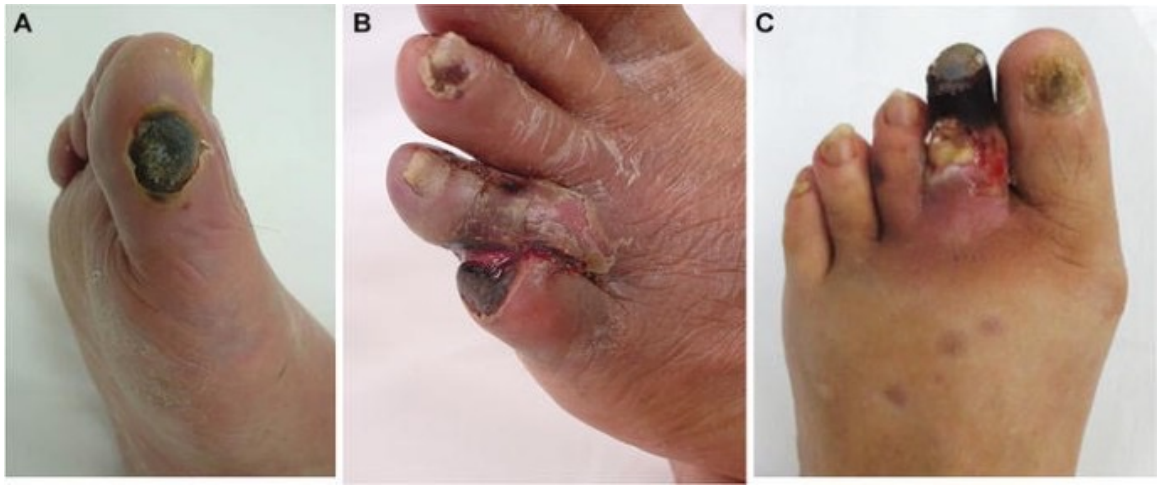
- Claudication
- Acute Limb Ischemia

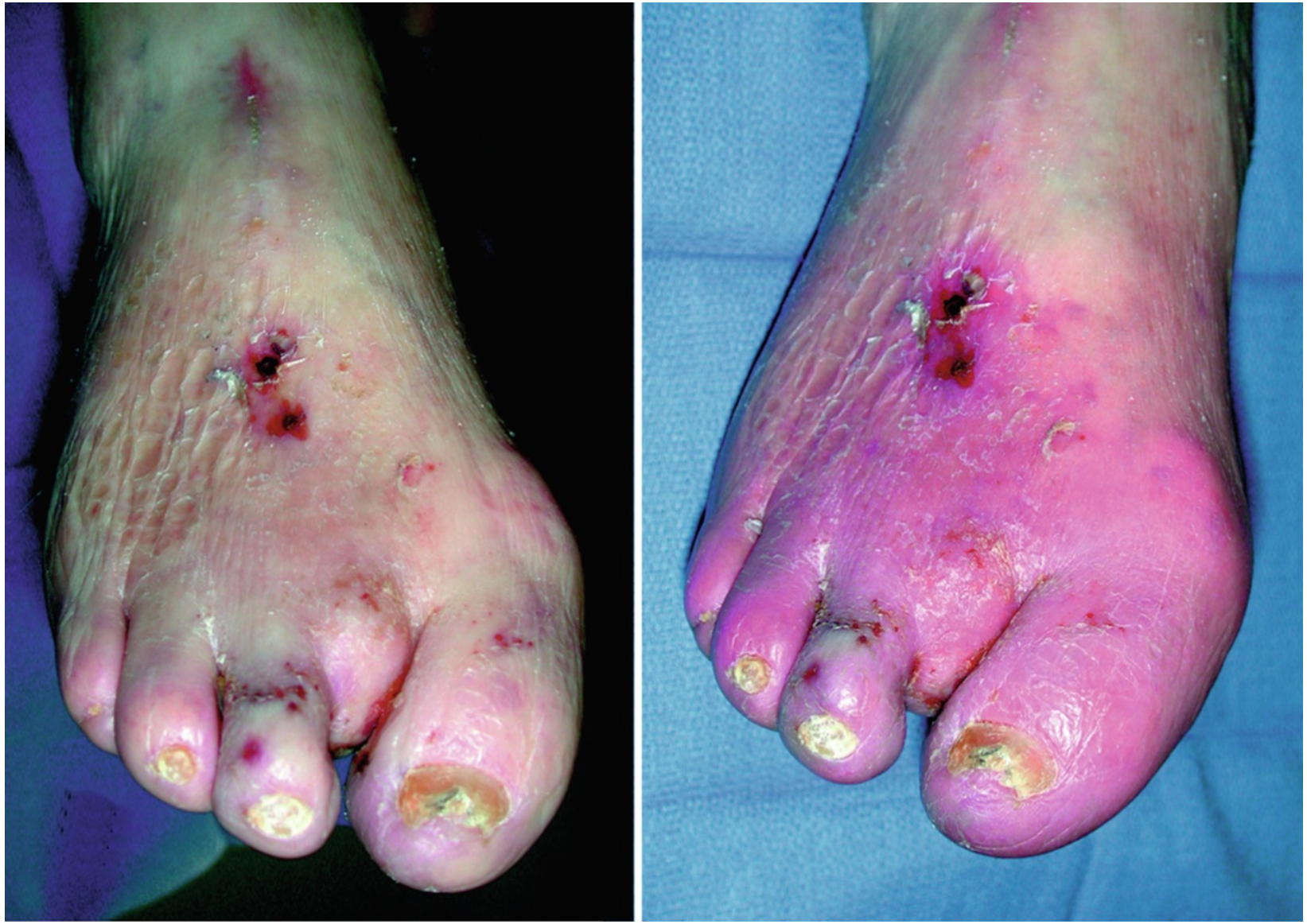


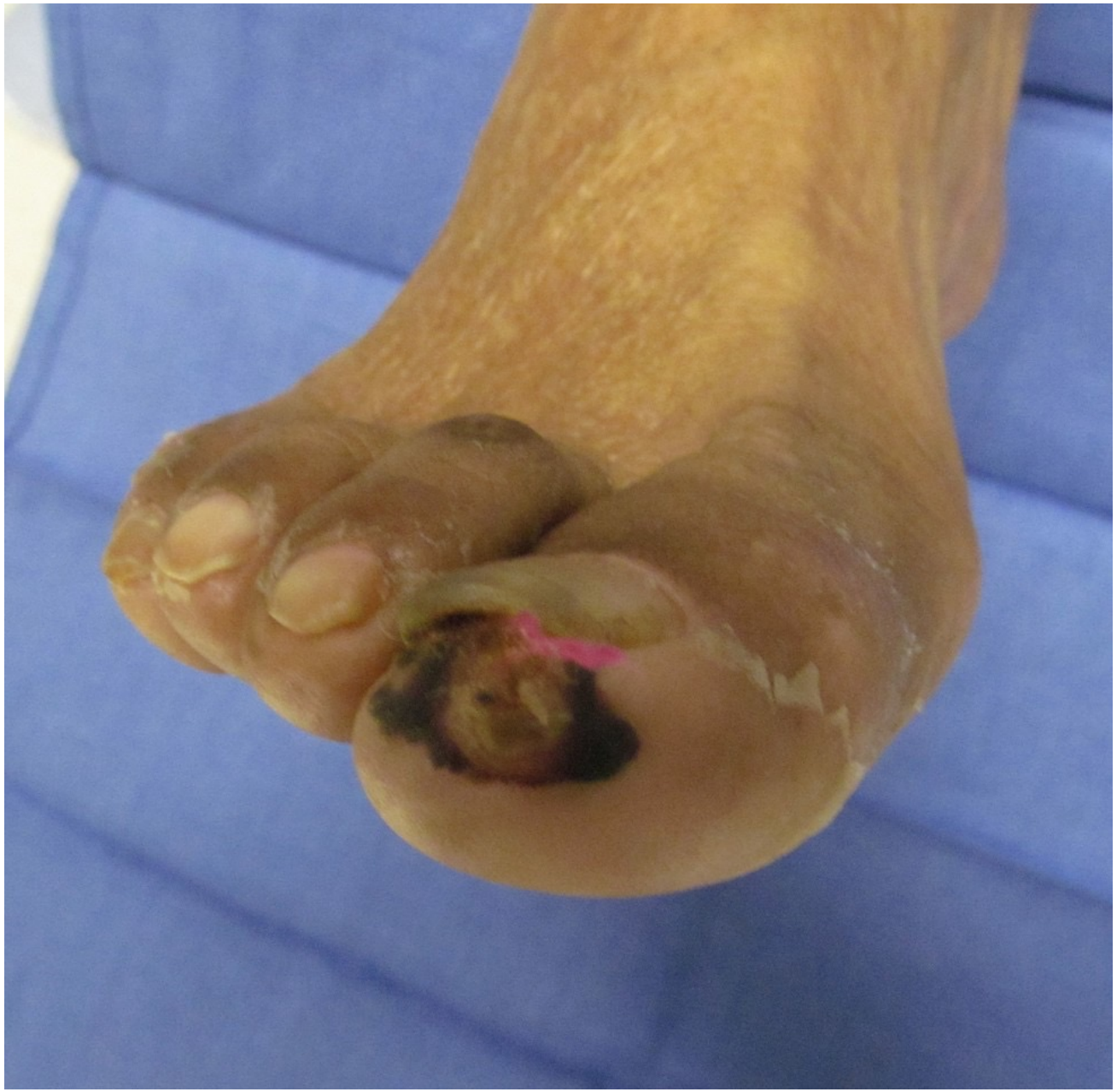
Clinical manifestations:

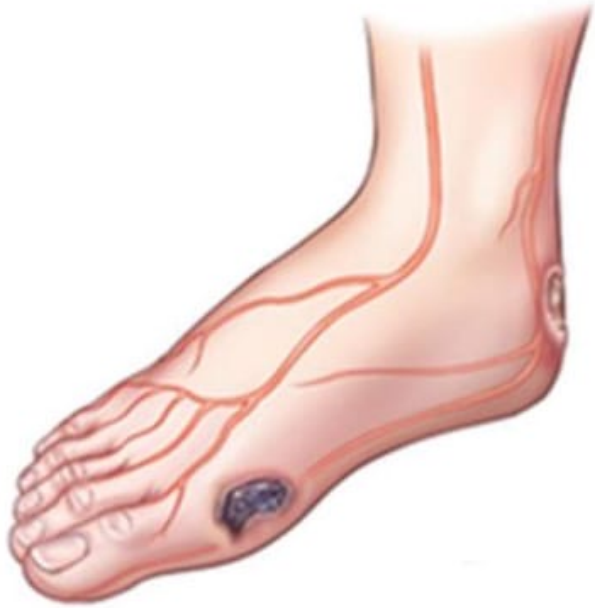
- Claudication
- Acute Limb Ischemia
- Chronic limb threatening ischemia

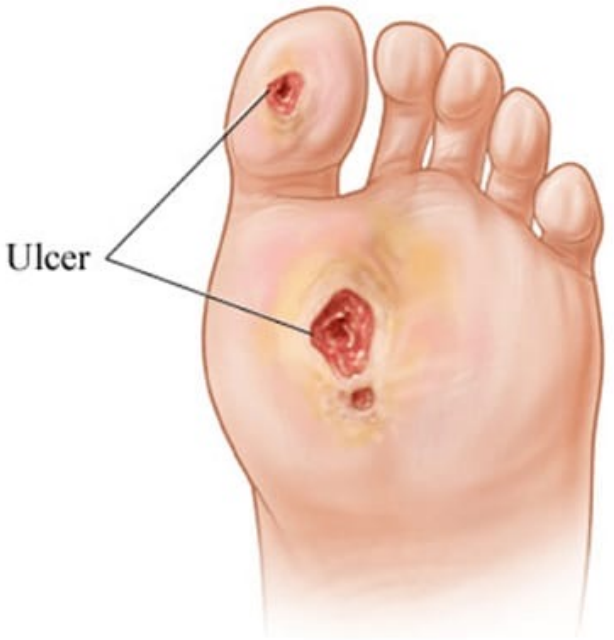











Ulcer

Chronic Limb Threatening Ischemia (CTLI)

- Most debilitating manifestation of PAD.
- Incidence is between 300 and 1000 persons per million per year.
- In patients with critical limb ischemia the one-year risk of limb amputation is 30% and five-year all-cause mortality is 50%[1].

About **50% of patients with critical limb ischaemia** (CLI), the advanced stage of PAD associated with lower-extremity amputation and significant mortality, also have diabetes and they fare worse than non-diabetics.

[1]Norgren, et al. *Int Angiol*. 2007

Non-invasive laboratory testing:

- Ankle-Brachial Index (US Lower Extremity ART Physiologic Complete)
- Toe-Brachial Index
- Segmental pressures with pulse volume recordings and waveform analysis (US Lower Extremity ART Physiologic Complete)
- Arterial duplex ultrasound (US Duplex Low EXTR ART Complete)
- CT Angiogram w/runoff

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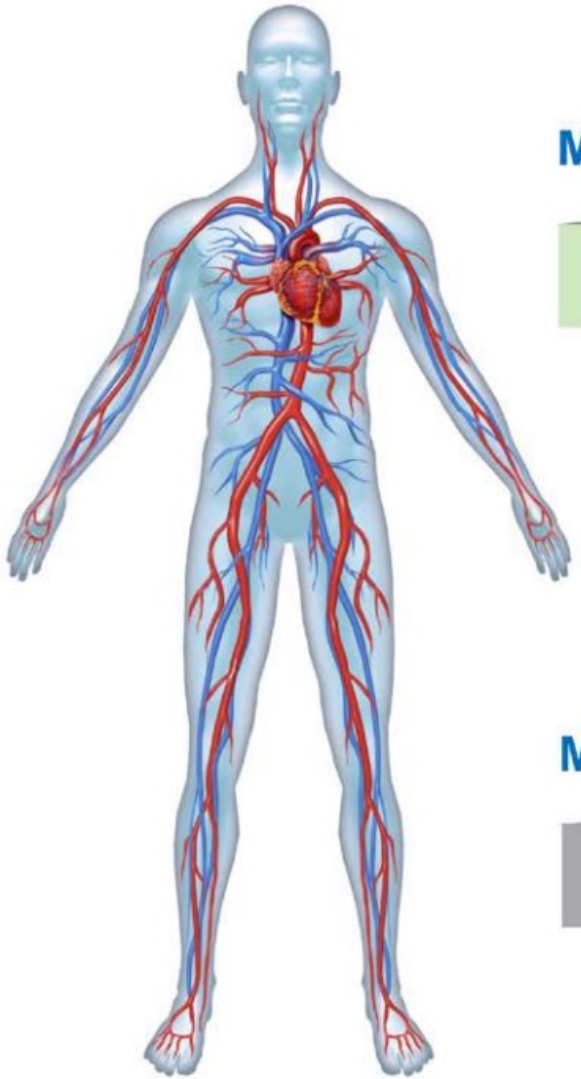
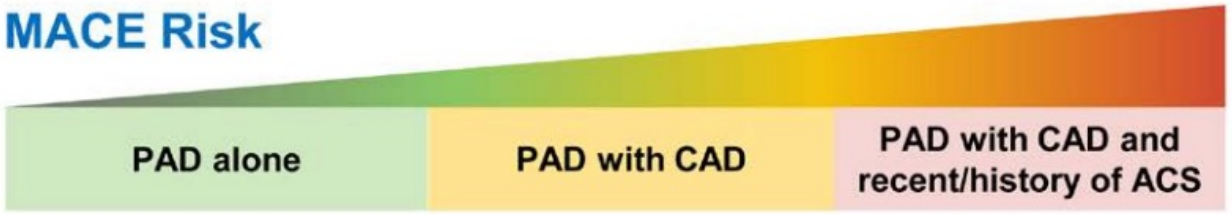
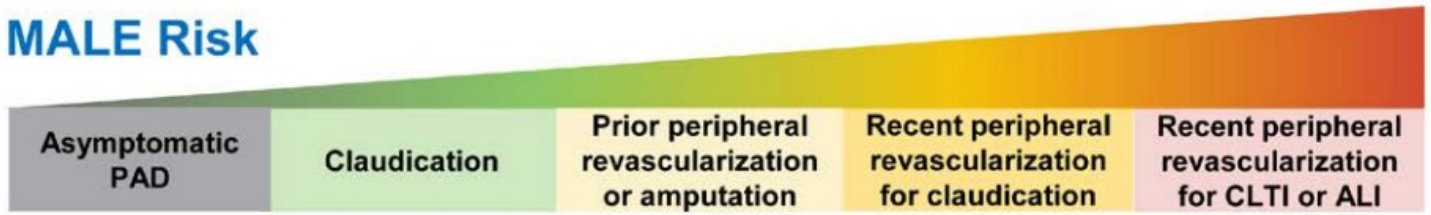
Management:




MACE Risk
PAD alone
PAD with CAD
PAD with CAD and recent/history of ACS


MALE Risk
Asymptomatic PAD
Claudication
Prior peripheral revascularization or amputation
Recent peripheral revascularization for claudication
Recent peripheral revascularization for CLTI or ALI

Management:

- Exercise

Exercise:

- A meta-analysis of 32 randomized trials involving 1,835 patients with PAD showed that exercise therapy led to a significant improvement in maximum walking distance (mean 82 m; 95% CI 72–92 m).
- Exercise therapy is recommended for all patients without CLTI before revascularization is considered.
- Treadmill or other walking-based exercise programs, involving 30–50 min sessions three times per week for at least 12 weeks.

Management:

- Exercise
- Smoking cessation
  - Counseling, nicotine patches, Buproprion, Varenicline (Chantix)

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- Blood pressure Lowering

Table 3 Clinical events in the different ranges of ABI for patients randomized to ramipril and placebo respectively (percentage incidence). Relative risk with ramipril treatment and 95% confidence intervals are given below percentages

Clinical event[a]	No clinical PAD						Clinical PAD (*n*=1725)		*P*-value for trend	
	ABI >0.9 (*n*=5231)		0.9–0.6 (*n*=1391)		<0.6 (*n*=727)					
	Ramipril	Placebo	Ramipril	Placebo	Ramipril	Placebo	Ramipril	Placebo	Unadjusted	Adjusted[b]
Primary outcome (cardiovascular mortality, MI, stroke)	12.6 0.83 (0.71, 0.96)	14.9	15.7 0.72 (0.56, 0.92)	21.6	16.4 0.77 (0.55, 1.09)	22.0	20.1 0.75 (0.61, 0.92)	25.8	0.45	0.53
MI	9.3 0.83 (0.70, 0.99)	11.0	12.3 0.81 (0.60, 1.09)	15.2	11.2 0.73 (0.48, 1.11)	15.5	12.3 0.75 (0.58, 0.98)	16.1	0.48	0.56
Stroke	2.9 0.72 (0.53, 0.98)	4.1	2.6 0.44 (0.26, 0.77)	6.0	5.4 0.99 (0.52, 1.89)	6.4	6.2 0.72 (0.50, 1.05)	8.3	0.76	0.75
Cardiovascular mortality	4.9 0.83 (0.65, 1.05)	5.7	6.3 0.62 (0.42, 0.90)	10.8	8.2 0.76 (0.46, 1.25)	10.4	10.4 0.75 (0.56, 0.99)	13.6	0.69	0.79
All cause death	8.9 0.99 (0.83, 1.20)	8.8	9.6 0.58 (0.42, 0.79)	15.9	13.2 0.81 (0.55, 1.19)	16.2	16.7 0.85 (0.68, 1.07)	19.4	0.37	0.39
Revascularization	15.6 0.87 (0.76, 0.99)	18.0	15.5 0.82 (0.64, 1.07)	18.8	14.2 0.91 (0.61, 1.37)	13.6	25.2 0.89 (0.74, 1.09)	27.7	0.81	0.78
Diabetic complications	14.4 0.89 (0.70, 1.13)	16.5	15.4 0.80 (0.53, 1.21)	17.0	17.4 0.83 (0.50, 1.39)	20.4	22.1 0.87 (0.62, 1.21)	26.7	0.85	0.82
Hospitalizations for CHF	2.7 1.13 (0.80, 1.60)	2.4	2.7 0.69 (0.38, 1.23)	4.1	4.2 0.66 (0.34, 1.28)	6.1	5.0 0.81 (0.53, 1.24)	6.6	0.21	0.22

P-values are for trend of effect on ramipril on each of the outcomes with PAD category. Primary outcome=cardiovascular mortality, MI, stroke., MI=Myocardial infarction, CHF=Congestive heart failure.

[a] In those with an ABI ≤0.9 and no clinical PAD the results in the primary outcome is RR 0.73 (95% CI=0.60–0.90).
[b] After adjustment for all baseline variables (in Table 1) which are significantly different.

Eur Heart J, 2004.

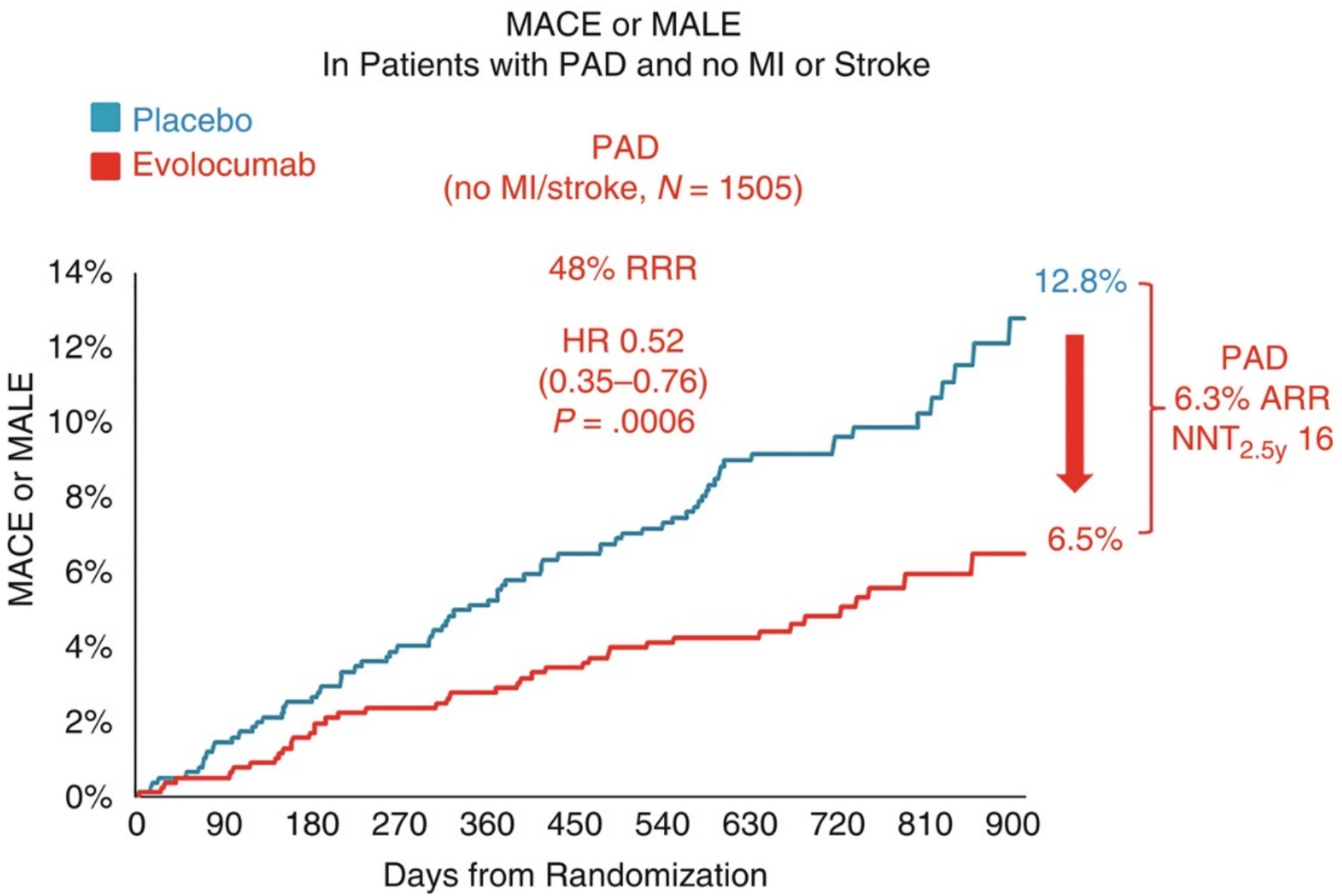
Table 2. Primary and Secondary Outcomes and Renal Outcomes.*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per year*	*no. of patients (%)*	*% per year*		
All participants	**(N=4678)**		**(N=4683)**			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005
Death from any cause	155 (3.3)	1.03	210 (4.5)	1.40	0.73 (0.60–0.90)	0.003
Primary outcome or death	332 (7.1)	2.25	423 (9.0)	2.90	0.78 (0.67–0.90)	<0.001
Participants with CKD at baseline	**(N=1330)**		**(N=1316)**			
Composite renal outcome‡	14 (1.1)	0.33	15 (1.1)	0.36	0.89 (0.42–1.87)	0.76
≥50% reduction in estimated GFR§	10 (0.8)	0.23	11 (0.8)	0.26	0.87 (0.36–2.07)	0.75
Long-term dialysis	6 (0.5)	0.14	10 (0.8)	0.24	0.57 (0.19–1.54)	0.27
Kidney transplantation	0		0			
Incident albuminuria¶	49/526 (9.3)	3.02	59/500 (11.8)	3.90	0.72 (0.48–1.07)	0.11
Participants without CKD at baseline‖	**(N=3332)**		**(N=3345)**			
≥30% reduction in estimated GFR to <60 ml/min/1.73 m^2§	127 (3.8)	1.21	37 (1.1)	0.35	3.49 (2.44–5.10)	<0.001
Incident albuminuria¶	110/1769 (6.2)	2.00	135/1831 (7.4)	2.41	0.81 (0.63–1.04)	0.10

NEJM, 2015.

Management:

- Exercise
- Smoking cessation
  - Counseling, nicotine patches, Buproprion, Varenicline (Chantix)
- Blood pressure Lowering
- Lipid-lowering therapy
  - UK Heart Protection Study → 40mg simvastatin reduced incidence of MACE in PAD pts (RR 0.78, 95% CI 0.71–0.85).



Bonaca, M., et al. *Circulation*. 2018

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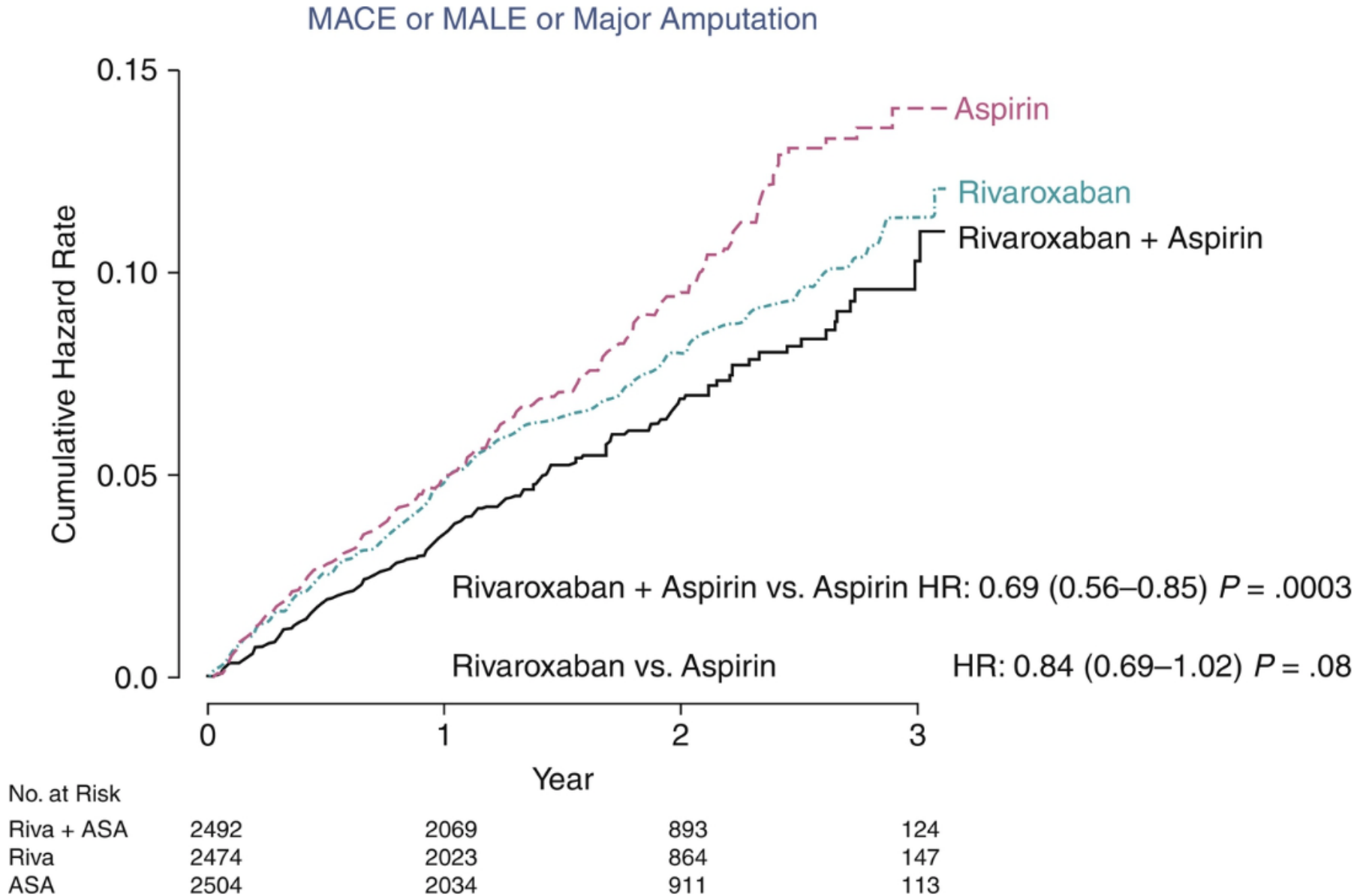
- Antiplatelet/antithrombotic therapy



Anand, SS, et al. *Lancet*. 2018.

LETTERS
https://doi.org/10.1038/s41591-019-0492-5
nature medicine

Genome-wide association study of peripheral artery disease in the Million Veteran Program

Derek Klarin[1,2,3,4], Julie Lynch[5,6,7], Krishna Aragam[2,3], Mark Chaffin[3], Themistocles L. Assimes[8,9], Jie Huang[10], Kyung Min Lee[5,7,11], Qing Shao[7], Jennifer E. Huffman[10], Pradeep Natarajan[1,2,12], Shipra Arya[8,13], Aeron Small[14,15], Yan V. Sun[16,17,18], Marijana Vujkovic[14,19], Matthew S. Freiberg[20,21], Lu Wang[19], Jinbo Chen[19], Danish Saleheen[14,19], Jennifer S. Lee[9,10], Donald R. Miller[22,23], Peter Reaven[24], Patrick R. Alba[5,25], Olga V. Patterson[5,25], Scott L. DuVall[5,25], William E. Boden[1,10], Joshua A. Beckman[26], J. Michael Gaziano[1,27], John Concato[15,28,34], Daniel J. Rader[29], Kelly Cho[1], Kyong-Mi Chang[14,29], Peter W. F. Wilson[16,30], Christopher J. O'Donnell[1,31], Sekar Kathiresan[2,3], VA Million Veteran Program[32], Philip S. Tsao[8,9,35] and Scott M. Damrauer[14,33,35*]

Table 1 | PAD risk loci discovered in the MVP biobank and replicated in the UK Biobank

Chr:Pos	rsid	EA	NEA	EAF	Overall OR[a]	Overall 95% CI[a]	Overall *P*[a]	Annotation	Gene/Locus[b]
1:109817192	rs7528419	A	G	0.772	1.07	1.05–1.09	2.54×10^{-11}	3′ UTR variant	*CELSR2/SORT1*
1:169519049	rs6025	T	C	0.026	1.2	1.14–1.26	1.63×10^{-12}	Missense variant (Factor V Leiden)	*F5* ←
6:160985526	rs118039278	A	G	0.068	1.26	1.22–1.30	1.57×10^{-43}	Intron variant	*LPA* ←
6:31065071	rs3130968	T	C	0.144	1.07	1.05–1.10	3.16×10^{-10}	Regulatory region variant	*(HLA-B)*
7:19049388	rs2107595	A	G	0.187	1.08	1.05–1.10	2.49×10^{-11}	Regulatory region variant	*(HDAC9)*
7:22786532	rs4722172	G	A	0.202	1.08	1.05–1.10	3.65×10^{-11}	Intergenic variant	*(IL6)*
8:19819217	rs322	A	C	0.706	1.06	1.04–1.07	2.53×10^{-9}	Intron variant	*LPL*
9:136149229	rs505922	C	T	0.334	1.06	1.04–1.07	7.10×10^{-11}	Intron variant	*ABO*
9:22103183	rs1537372	T	G	0.421	1.12	1.10–1.14	4.32×10^{-39}	Intron variant	*CDKN2B-AS1*/9p21
10:114758349	rs7903146	T	C	0.293	1.06	1.04–1.08	3.76×10^{-11}	Intron variant	*TCF7L2*
11:102710471	rs566125	T	C	0.127	1.08	1.05–1.11	4.37×10^{-9}	Intron variant	*MMP3*
11:46342834	rs7476	C	A	0.364	1.06	1.04–1.08	8.33×10^{-10}	3′ UTR variant	*CREB3L1*
12:112871372	rs11066301	G	A	0.413	1.06	1.04–1.08	2.96×10^{-11}	Intron variant	*PTPN11*
12:79951566	rs4842266	G	A	0.388	1.06	1.04–1.08	1.01×10^{-9}	Upstream gene variant	*RP11-359M6.3*
13:110828891	rs1975514	C	T	0.357	1.05	1.04–1.07	8.32×10^{-10}	Intron variant	*COL4A1*
14:70501364	rs55784307	A	C	0.183	1.06	1.04–1.09	2.93×10^{-8}	Downstream gene variant	*SMOC1*
15:78915864	rs10851907	A	G	0.41	1.06	1.05–1.08	1.49×10^{-13}	Upstream gene variant	*CHRNA3*
17:66089393	rs62084752	C	G	0.216	1.07	1.05–1.09	1.58×10^{-10}	Upstream gene variant	*LOC732538*
19:11191729	rs138294113	C	T	0.879	1.09	1.06–1.11	1.20×10^{-10}	Intergenic variant	*(LDLR)* ←

[a]Overall OR, 95% CI and *P* (two-sided) represent logistic regression statistics following meta-analysis of MVP and UK Biobank (total $N=36{,}424$ PAD cases and 601,044 controls). [b]Genes for variants that are outside the transcript boundary of a protein-coding gene are shown with nearest candidate gene in parentheses (for example, *(LDLR)*). Chr, chromosome; Pos, position; rsid, RefSNP identification number; EA, effect allele; NEA, non effect allele; EAF, effect allele frequency.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban in Peripheral Artery Disease after Revascularization

Marc P. Bonaca, M.D., M.P.H., Rupert M. Bauersachs, M.D., Sonia S. Anand, M.D., E. Sebastian Debus, M.D., Ph.D., Mark R. Nehler, M.D., Manesh R. Patel, M.D., Fabrizio Fanelli, M.D., Warren H. Capell, M.D., Lihong Diao, M.D., Nicole Jaeger, M.S., Connie N. Hess, M.D., M.H.S., Akos F. Pap, M.Sc., John M. Kittelson, Ph.D., Ivan Gudz, M.D., Ph.D., Lajos Mátyás, M.D., Dainis K. Krievins, M.D., Rafael Diaz, M.D., Marianne Brodmann, M.D., Eva Muehlhofer, M.D., Lloyd P. Haskell, M.D., Scott D. Berkowitz, M.D., and William R. Hiatt, M.D.

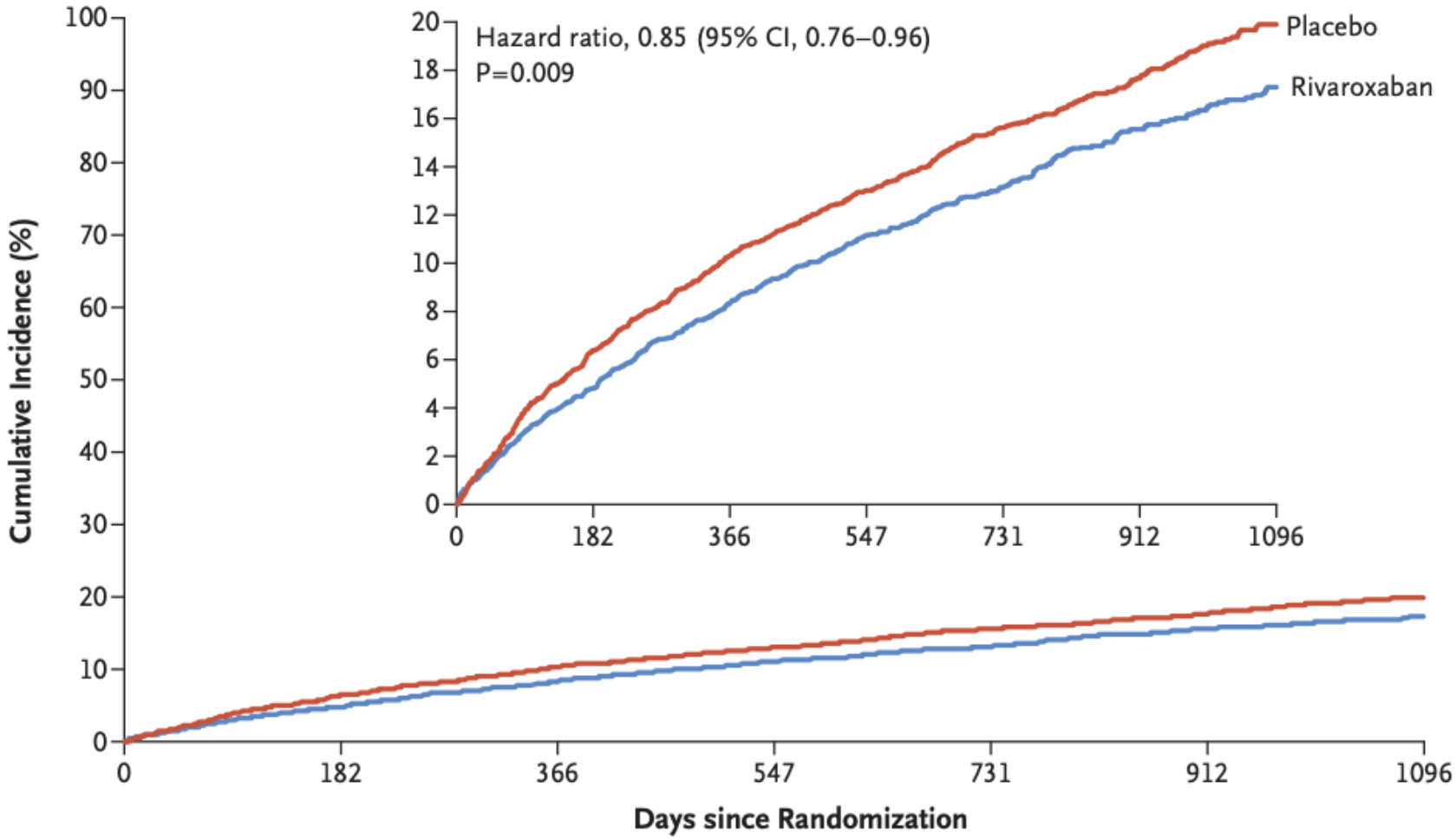


Figure 2. Kaplan–Meier Analysis of the Primary Composite Efficacy Outcome.

Management:

- Exercise
- Smoking cessation
  - Counseling, nicotine patches, Buproprion, Varenicline (Chantix)
- Blood pressure Lowering
- Lipid-lowering therapy
  - UK Heart Protection Study → 40mg simvastatin reduced incidence of MACE in PAD pts (RR 0.78, 95% CI 0.71–0.85).
- Antiplatelet/antithrombotic therapy
  - Aspirin + low dose rivaroxaban in PAD pts with stable CV disease or hx of revascularization.

Management:

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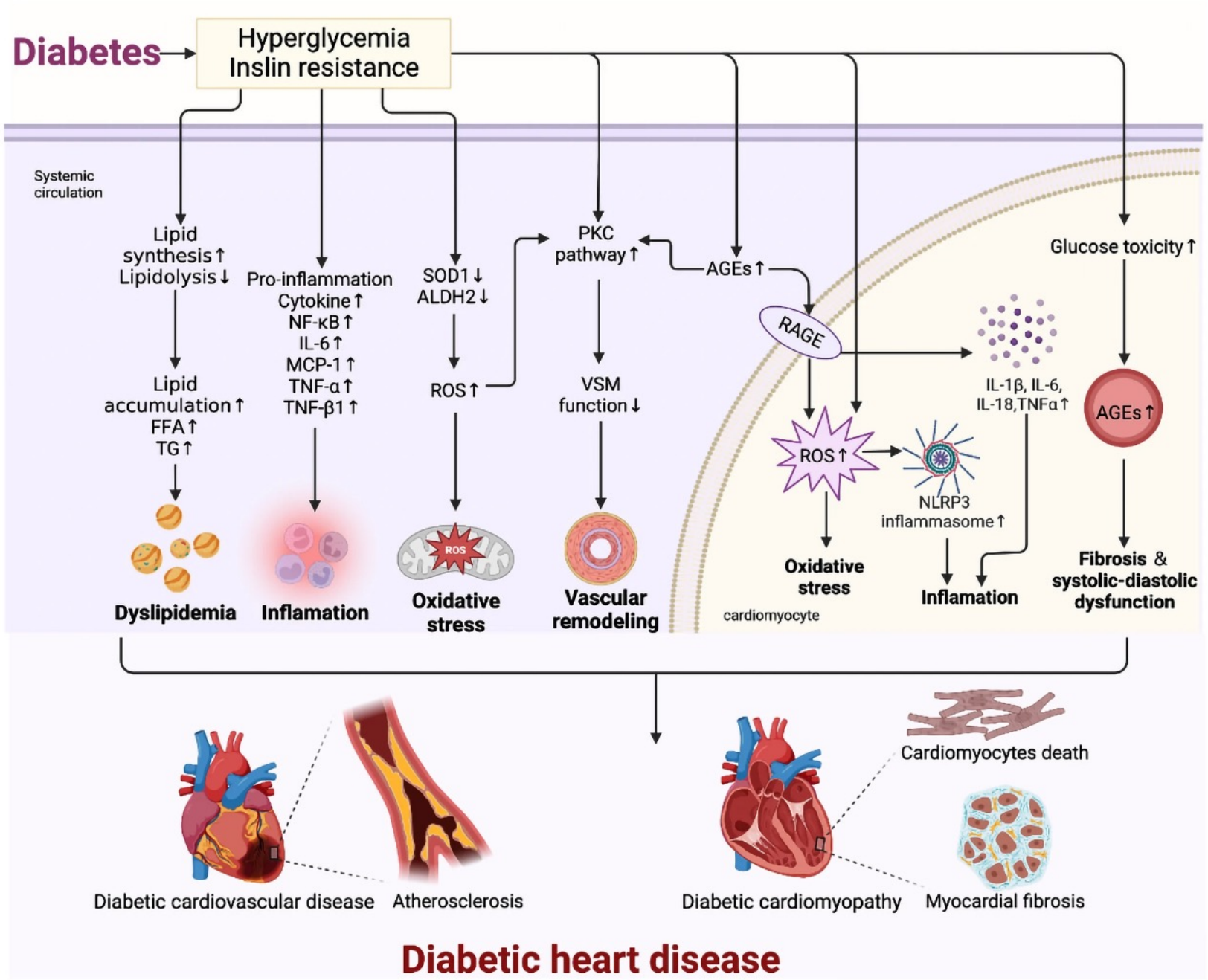
- Antiplatelet/antithrombotic therapy
  - Aspirin + low dose rivaroxaban in PAD pts with stable CV disease or hx of revascularization.
- Glucose-lowering therapies in Diabetics



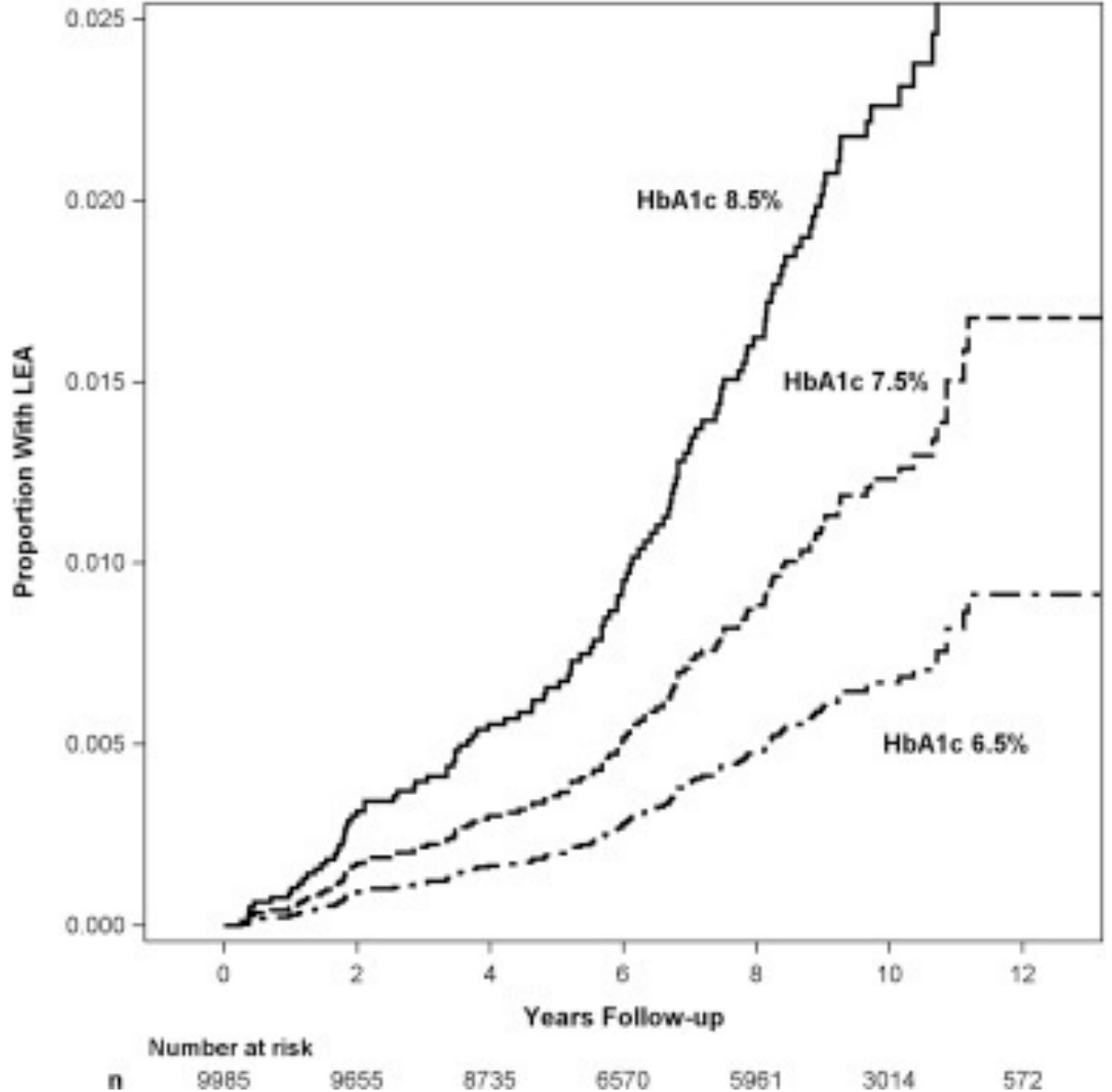
Li, Y, et al. *Sig Trans & Tar Ther*. 2023

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

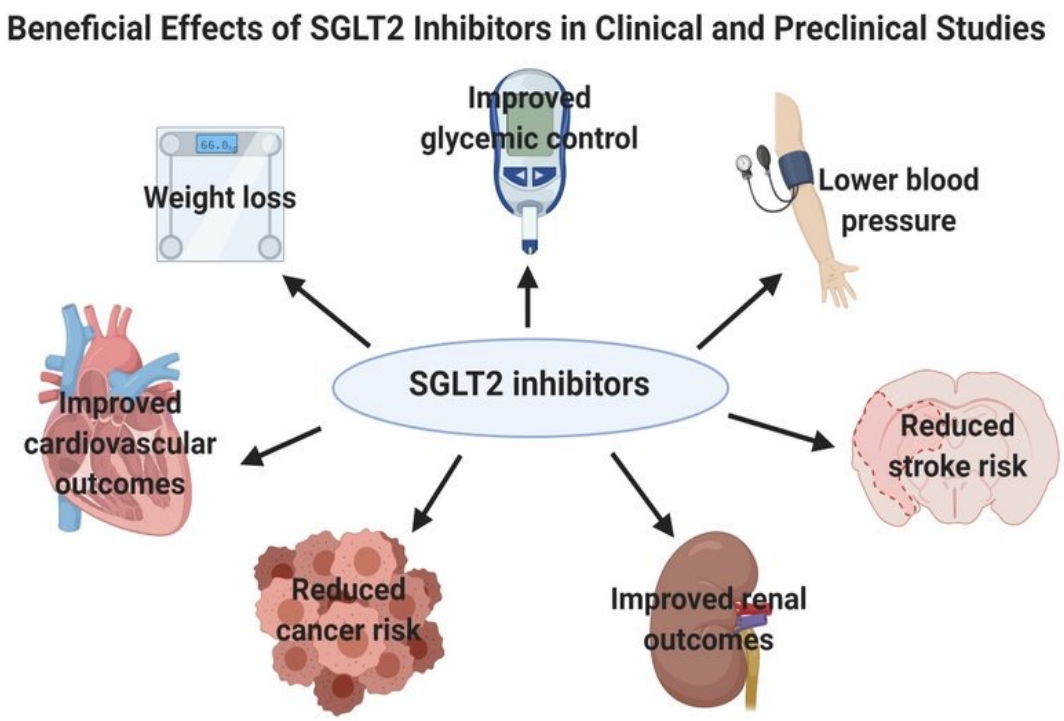
Effects of Intensive Glucose Lowering in Type 2 Diabetes

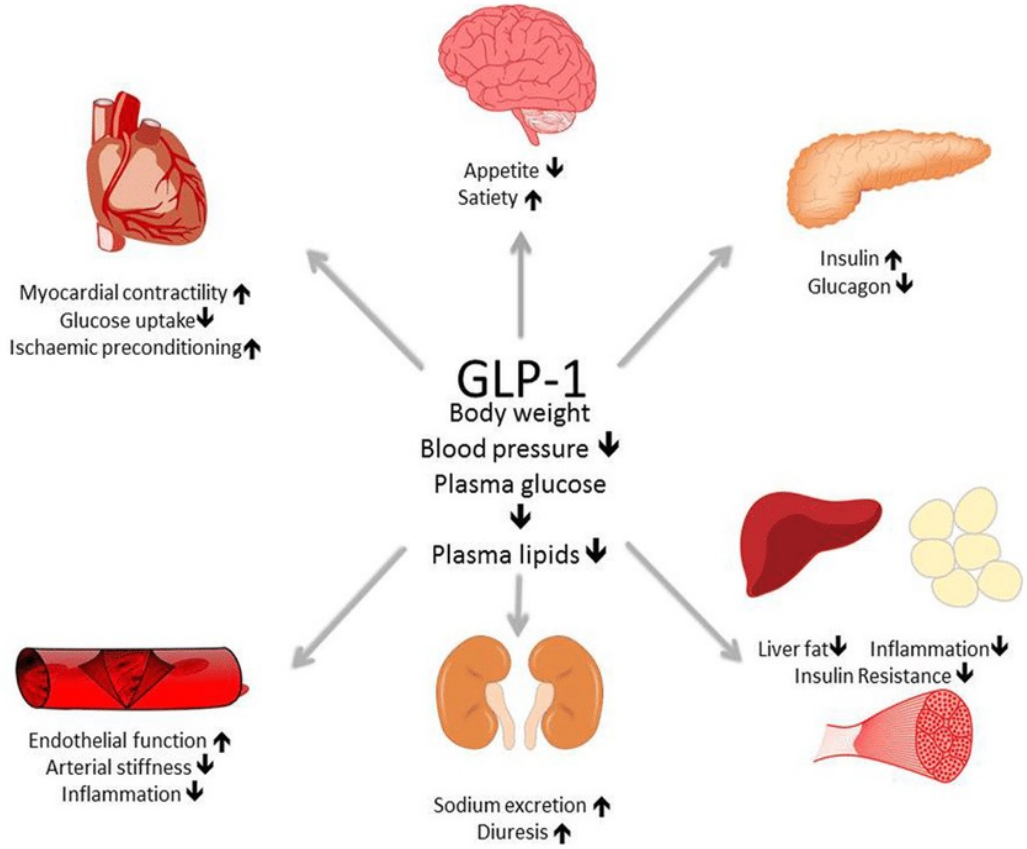
The Action to Control Cardiovascular Risk in Diabetes Study Group*



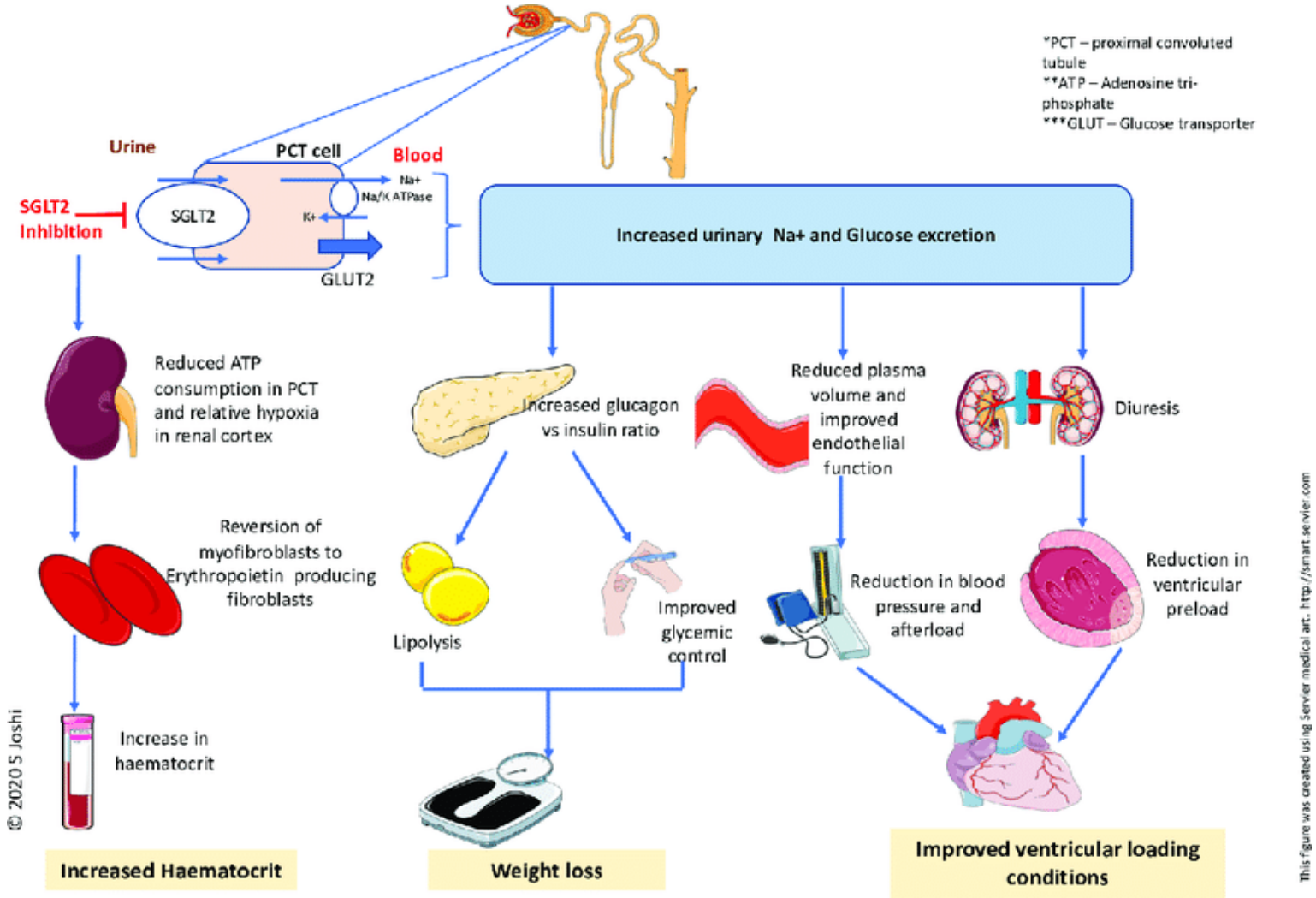
Goldman, M., et al. *J Am Coll Surg*. 2018

SGLT2i and GLP1-RA:





SGLT2i:


*PCT – proximal convoluted tubule
**ATP – Adenosine tri-phosphate
***GLUT – Glucose transporter
Urine
PCT cell
Blood
SGLT2 Inhibition
SGLT2
Na+
Na/K ATPase
K+
GLUT2
Increased urinary Na+ and Glucose excretion
Reduced ATP consumption in PCT and relative hypoxia in renal cortex
Increased glucagon vs insulin ratio
Reduced plasma volume and improved endothelial function
Diuresis
Reversion of myofibroblasts to Erythropoietin producing fibroblasts
Lipolysis
Improved glycemic control
Reduction in blood pressure and afterload
Reduction in ventricular preload
Increase in haematocrit
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Increased Haematocrit
Weight loss
Improved ventricular loading conditions
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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	4.4	0.10
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001
Severe hypersensitivity or cutaneous reaction	8.5	6.1	0.17
Hepatic injury	7.4	9.1	0.35
Renal-related (including acute kidney injury)	19.7	17.4	0.32

The NEW ENGLAND JOURNAL of MEDICINE

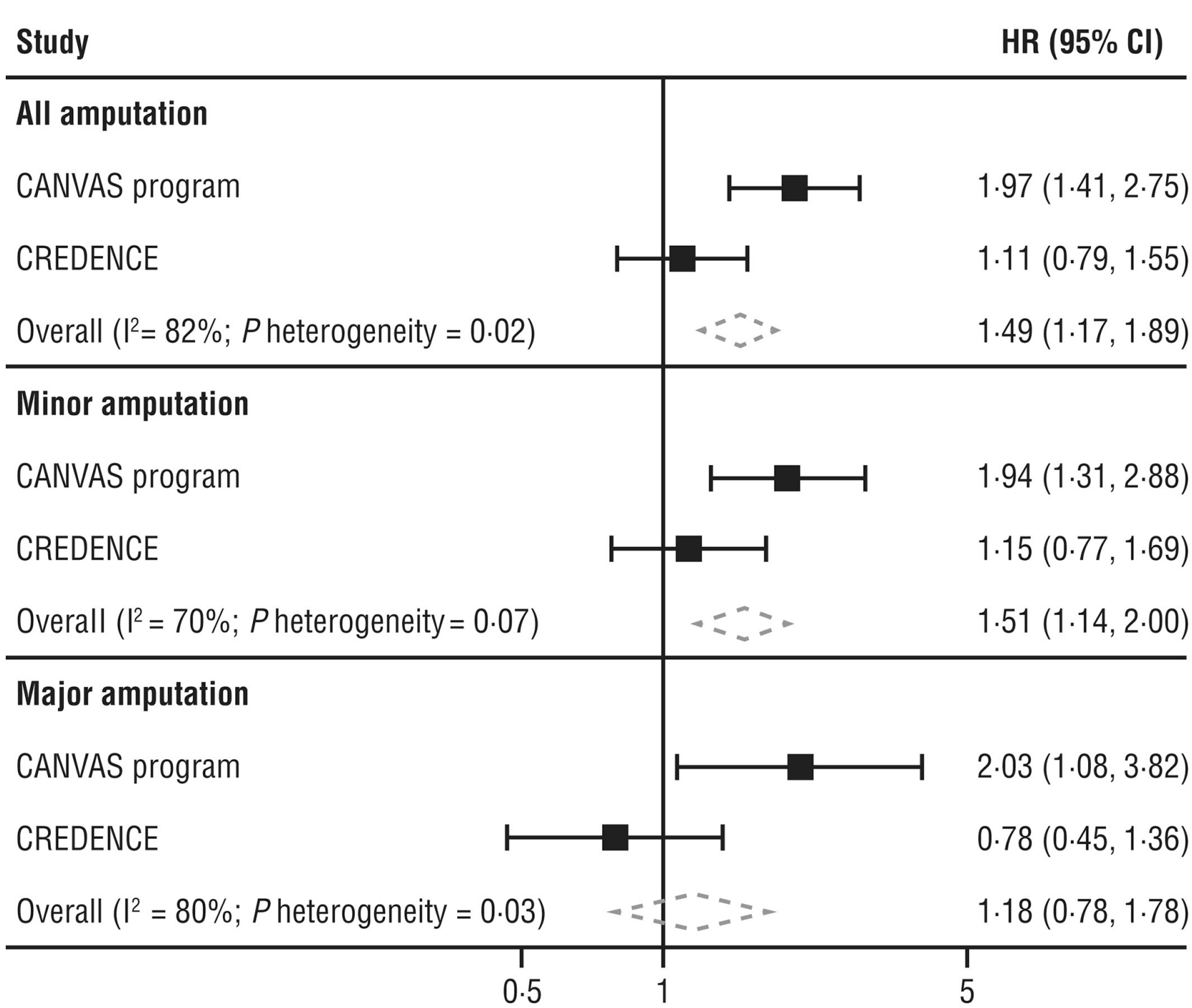
ESTABLISHED IN 1812 JUNE 13, 2019 VOL. 380 NO. 24

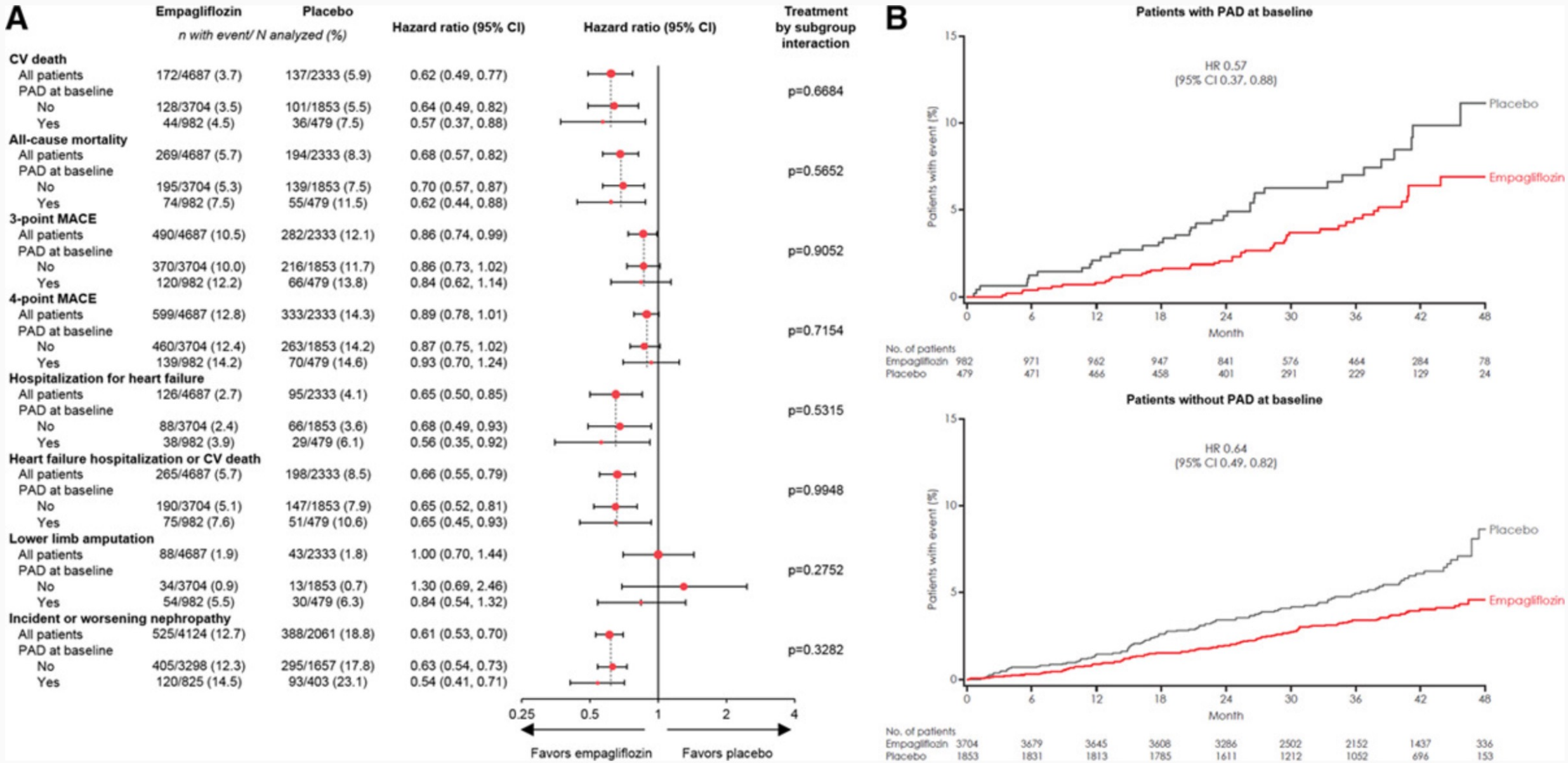
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Canagliflozin (N=2202)	Placebo (N=2199)	All Patients (N=4401)
Age — yr	62.9±9.2	63.2±9.2	63.0±9.2
Female sex — no. (%)	762 (34.6)	732 (33.3)	1494 (33.9)
Race or ethnic group — no. (%)†			
White	1487 (67.5)	1444 (65.7)	2931 (66.6)
Black	112 (5.1)	112 (5.1)	224 (5.1)
Asian	425 (19.3)	452 (20.6)	877 (19.9)
Other	178 (8.1)	191 (8.7)	369 (8.4)
Current smoker — no. (%)	341 (15.5)	298 (13.6)	639 (14.5)
Hypertension — no. (%)	2131 (96.8)	2129 (96.8)	4260 (96.8)
Heart failure — no. (%)	329 (14.9)	323 (14.7)	652 (14.8)
Duration of diabetes — yr	15.5±8.7	16.0±8.6	15.8±8.6
Cardiovascular disease — no. (%)	1113 (50.5)	1107 (50.3)	2220 (50.4)
Amputation — no. (%)	119 (5.4)	115 (5.2)	234 (5.3)
Body-mass index‡	31.4±6.2	31.3±6.2	31.3±6.2
Blood pressure — mm Hg			
Systolic	139.8±15.6	140.2±15.6	140.0±15.6
Diastolic	78.2±9.4	78.4±9.4	78.3±9.4
Glycated hemoglobin — %	8.3±1.3	8.3±1.3	8.3±1.3
Estimated GFR — ml/min/1.73 m^2§	56.3±18.2	56.0±18.3	56.2±18.2
Median urinary albumin-to-creatinine ratio (IQR)¶	923 (459–1794)	931 (473–1868)	927 (463–1833)

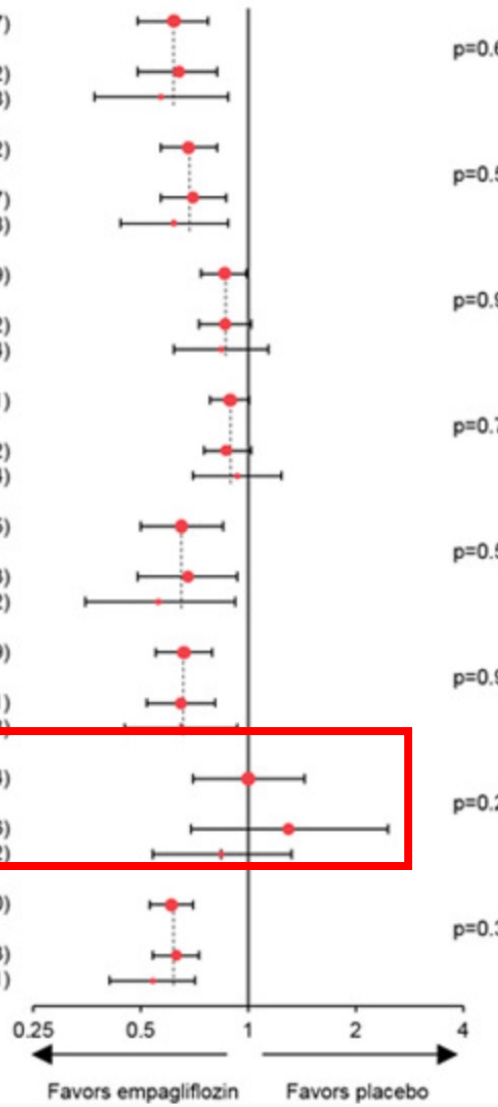

Study
HR (95% CI)
All amputation
CANVAS program
1·97 (1·41, 2·75)
CREDENCE
1·11 (0·79, 1·55)
Overall (I²= 82%; P heterogeneity = 0·02)
1·49 (1·17, 1·89)
Minor amputation
CANVAS program
1·94 (1·31, 2·88)
CREDENCE
1·15 (0·77, 1·69)
Overall (I² = 70%; P heterogeneity = 0·07)
1·51 (1·14, 2·00)
Major amputation
CANVAS program
2·03 (1·08, 3·82)
CREDENCE
0·78 (0·45, 1·36)
Overall (I² = 80%; P heterogeneity = 0·03)
1·18 (0·78, 1·78)
0·5
1
5



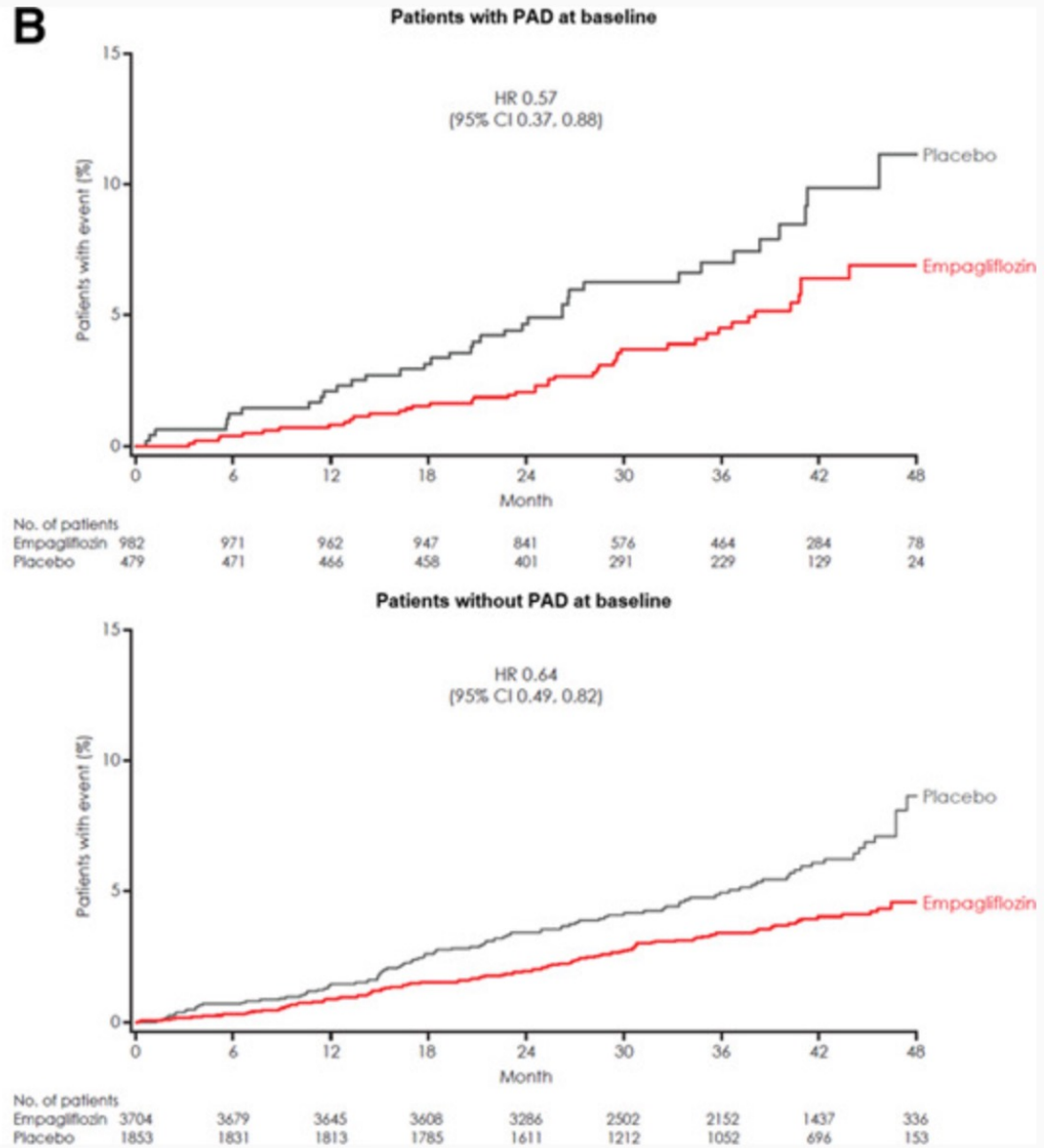
Verma, S. *Circulation*, 2017.

A

	Empagliflozin	Placebo	Hazard ratio (95% CI)	Treatment by subgroup interaction
	n with event/ N analyzed (%)			
CV death				
All patients	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)	
PAD at baseline				p=0.6684
No	128/3704 (3.5)	101/1853 (5.5)	0.64 (0.49, 0.82)	
Yes	44/982 (4.5)	36/479 (7.5)	0.57 (0.37, 0.88)	
All-cause mortality				
All patients	269/4687 (5.7)	194/2333 (8.3)	0.68 (0.57, 0.82)	
PAD at baseline				p=0.5652
No	195/3704 (5.3)	139/1853 (7.5)	0.70 (0.57, 0.87)	
Yes	74/982 (7.5)	55/479 (11.5)	0.62 (0.44, 0.88)	
3-point MACE				
All patients	490/4687 (10.5)	282/2333 (12.1)	0.86 (0.74, 0.99)	
PAD at baseline				p=0.9052
No	370/3704 (10.0)	216/1853 (11.7)	0.86 (0.73, 1.02)	
Yes	120/982 (12.2)	66/479 (13.8)	0.84 (0.62, 1.14)	
4-point MACE				
All patients	599/4687 (12.8)	333/2333 (14.3)	0.89 (0.78, 1.01)	
PAD at baseline				p=0.7154
No	460/3704 (12.4)	263/1853 (14.2)	0.87 (0.75, 1.02)	
Yes	139/982 (14.2)	70/479 (14.6)	0.93 (0.70, 1.24)	
Hospitalization for heart failure				
All patients	126/4687 (2.7)	95/2333 (4.1)	0.65 (0.50, 0.85)	
PAD at baseline				p=0.5315
No	88/3704 (2.4)	66/1853 (3.6)	0.68 (0.49, 0.93)	
Yes	38/982 (3.9)	29/479 (6.1)	0.56 (0.35, 0.92)	
Heart failure hospitalization or CV death				
All patients	265/4687 (5.7)	198/2333 (8.5)	0.66 (0.55, 0.79)	
PAD at baseline				p=0.9948
No	190/3704 (5.1)	147/1853 (7.9)	0.65 (0.52, 0.81)	
Yes	75/982 (7.6)	51/479 (10.6)	0.65 (0.45, 0.93)	
Lower limb amputation				
All patients	88/4687 (1.9)	43/2333 (1.8)	1.00 (0.70, 1.44)	
PAD at baseline				p=0.2752
No	34/3704 (0.9)	13/1853 (0.7)	1.30 (0.69, 2.46)	
Yes	54/982 (5.5)	30/479 (6.3)	0.84 (0.54, 1.32)	
Incident or worsening nephropathy				
All patients	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)	
PAD at baseline				p=0.3282
No	405/3298 (12.3)	295/1657 (17.8)	0.63 (0.54, 0.73)	
Yes	120/825 (14.5)	93/403 (23.1)	0.54 (0.41, 0.71)	

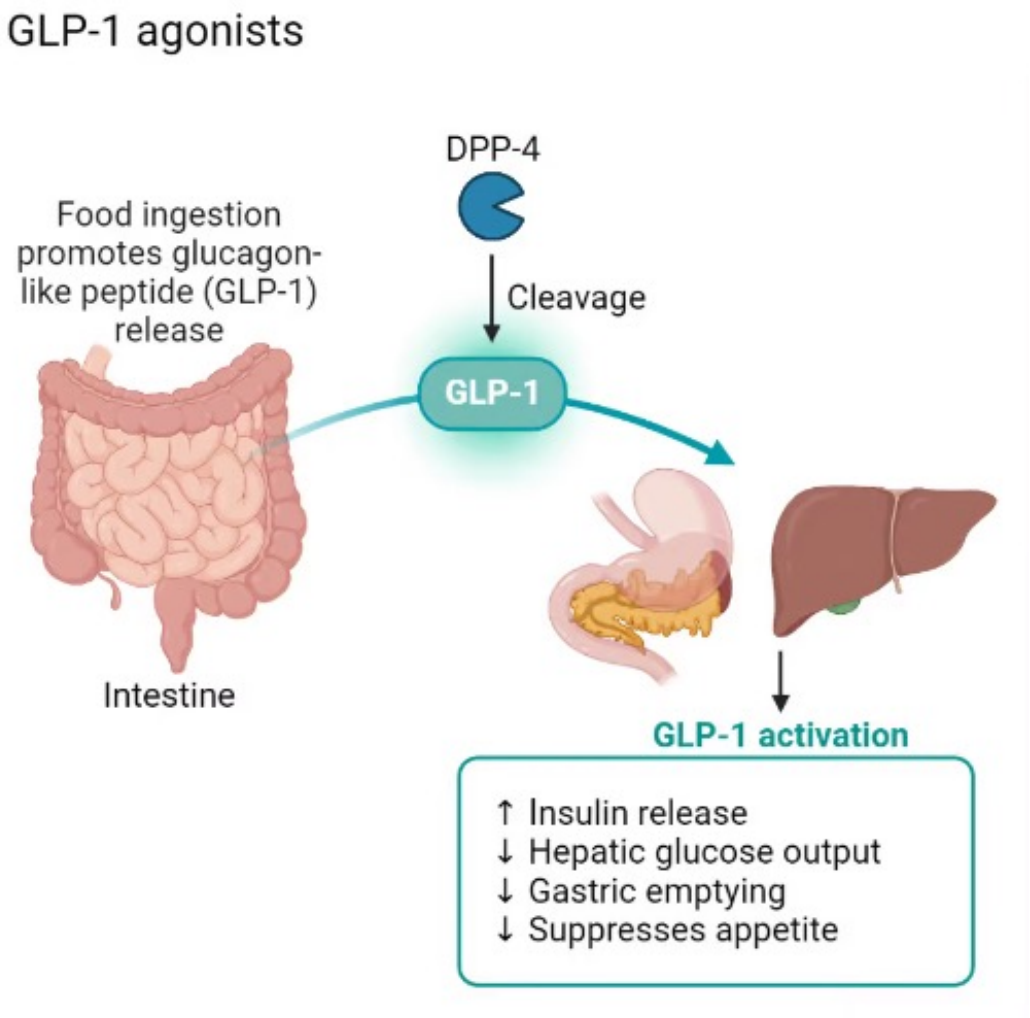


B



Verma, S. *Circulation*, 2017.

GLP1-RA:

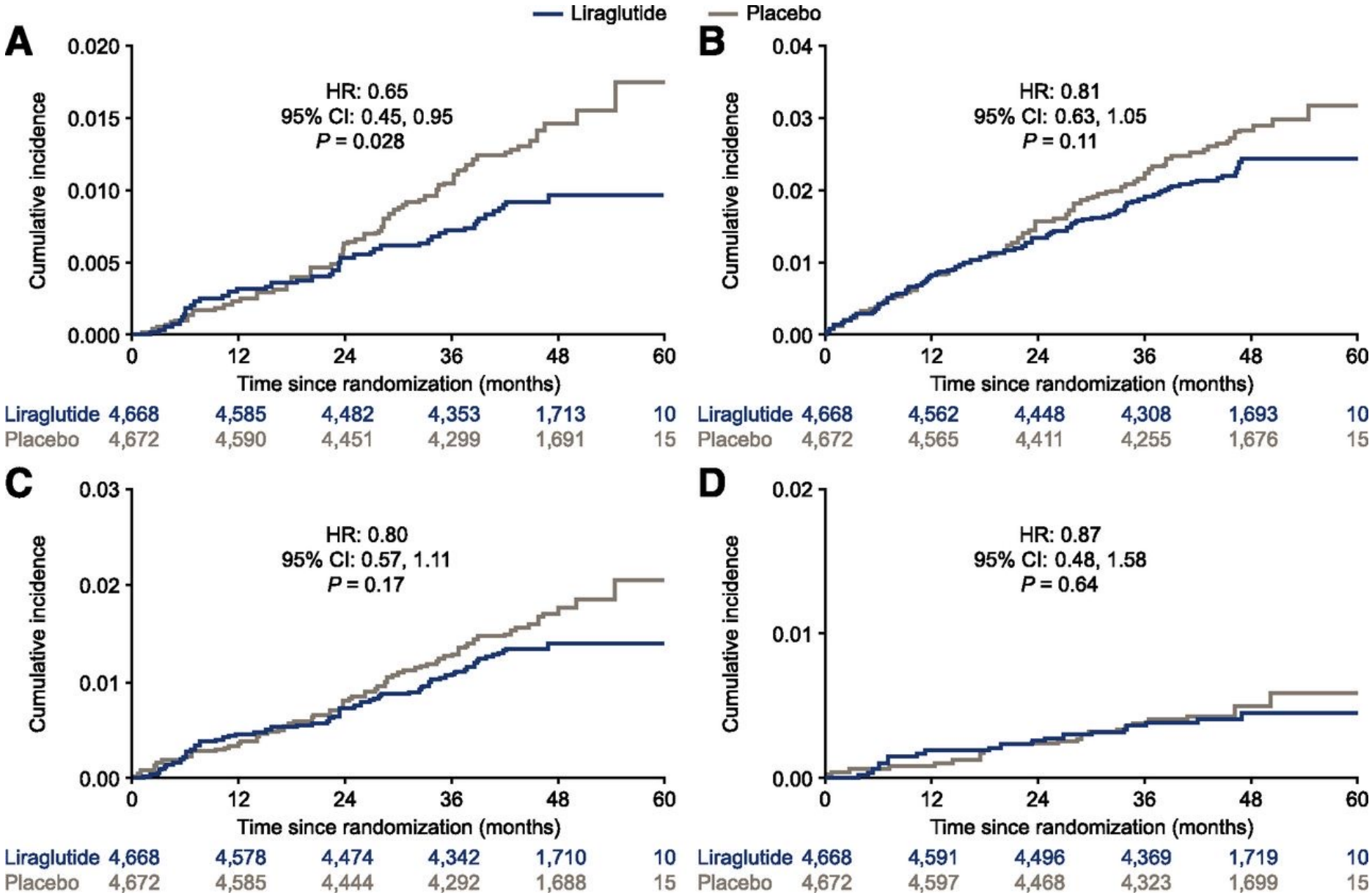

GLP-1 agonists
DPP-4
Food ingestion promotes glucagon-like peptide (GLP-1) release
Cleavage
GLP-1
Intestine
GLP-1 activation
↑ Insulin release
↓ Hepatic glucose output
↓ Gastric emptying
↓ Suppresses appetite

The NEW ENGLAND JOURNAL of MEDICINE

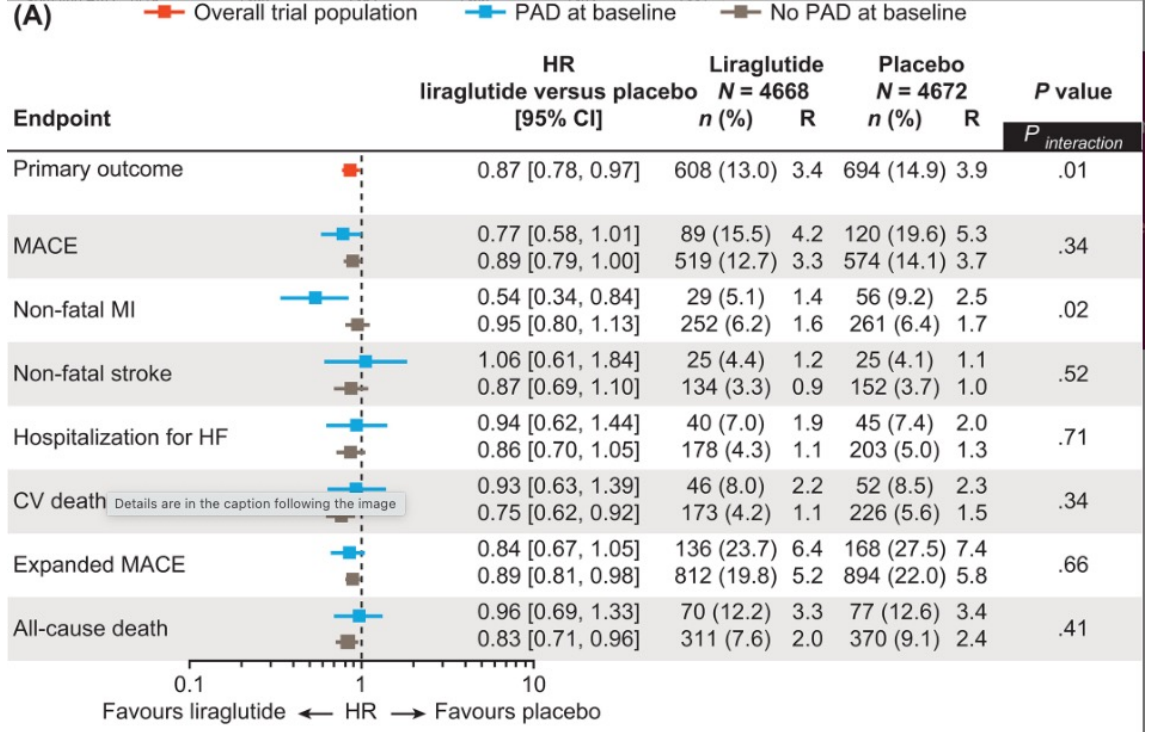
ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

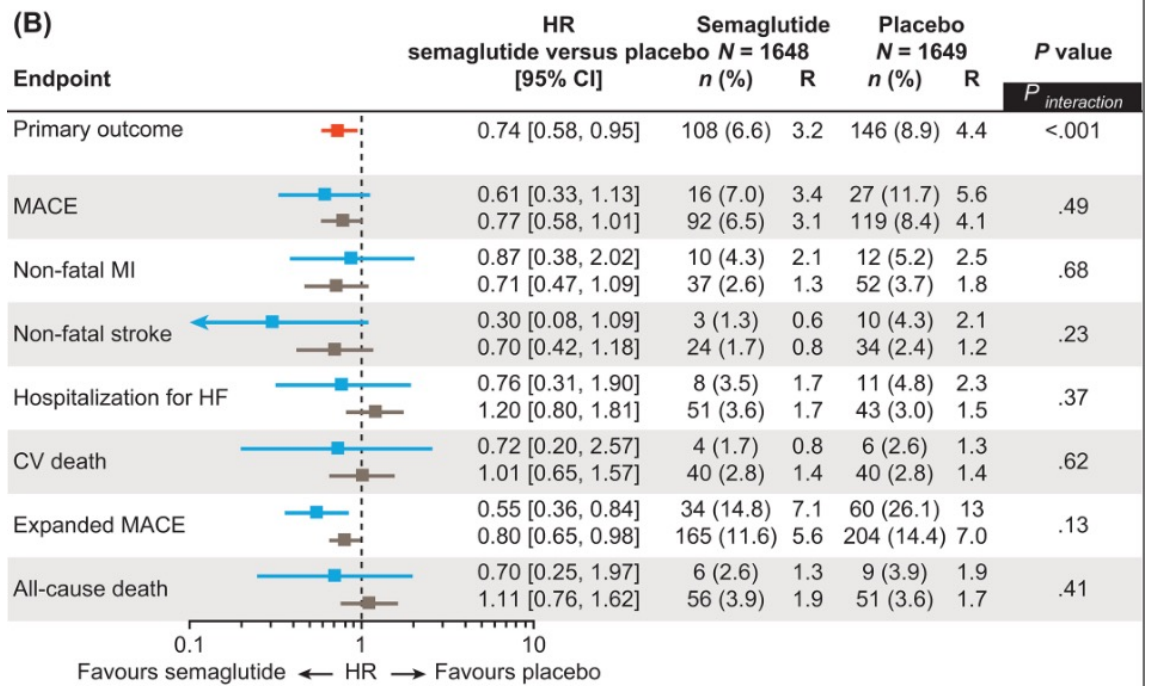
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

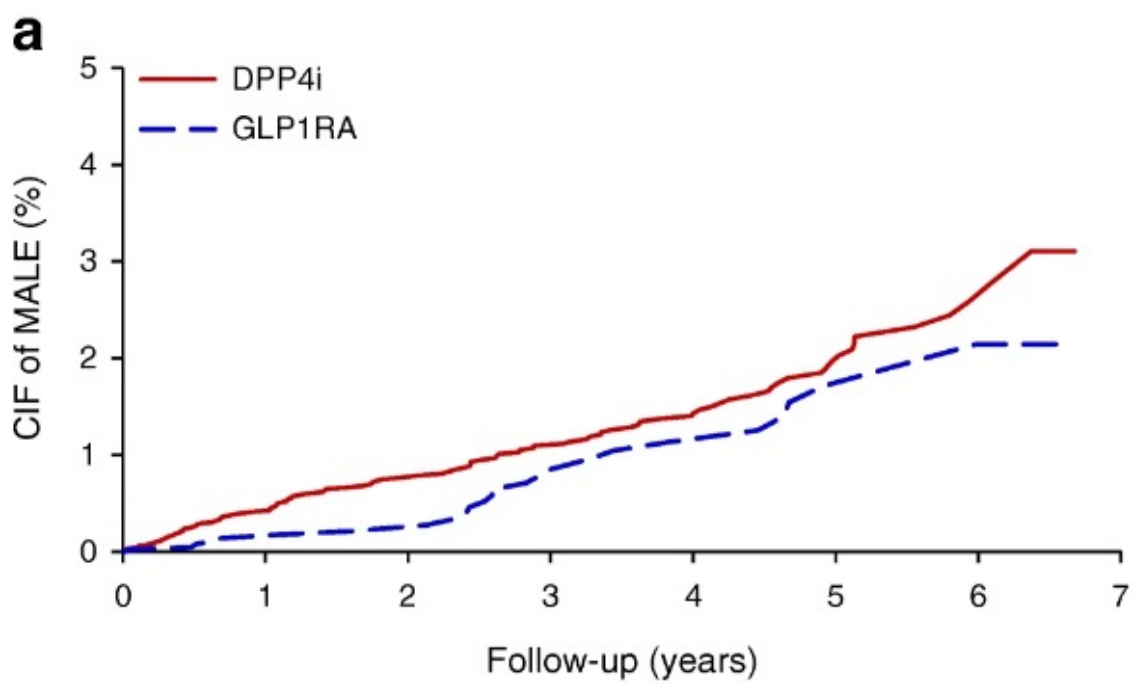
Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*



Dhatariya, K.. Et al. *Diabetes Care*. 2018

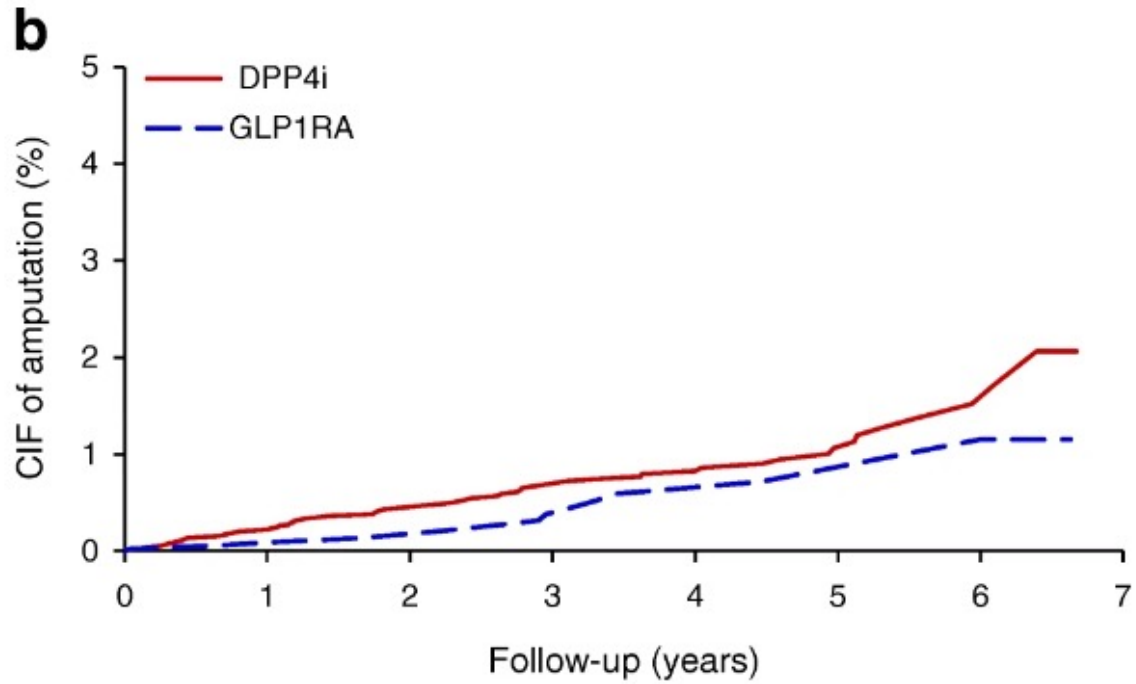

(A)
Overall trial population
PAD at baseline
No PAD at baseline
Endpoint
HR liraglutide versus placebo [95% CI]
Liraglutide N = 4668 n (%) R
Placebo N = 4672 n (%) R
P value P interaction
Primary outcome 0.87 [0.78, 0.97] 608 (13.0) 3.4 694 (14.9) 3.9 .01
MACE 0.77 [0.58, 1.01] 89 (15.5) 4.2 120 (19.6) 5.3
0.89 [0.79, 1.00] 519 (12.7) 3.3 574 (14.1) 3.7 .34
Non-fatal MI 0.54 [0.34, 0.84] 29 (5.1) 1.4 56 (9.2) 2.5
0.95 [0.80, 1.13] 252 (6.2) 1.6 261 (6.4) 1.7 .02
Non-fatal stroke 1.06 [0.61, 1.84] 25 (4.4) 1.2 25 (4.1) 1.1
0.87 [0.69, 1.10] 134 (3.3) 0.9 152 (3.7) 1.0 .52
Hospitalization for HF 0.94 [0.62, 1.44] 40 (7.0) 1.9 45 (7.4) 2.0
0.86 [0.70, 1.05] 178 (4.3) 1.1 203 (5.0) 1.3 .71
CV death 0.93 [0.63, 1.39] 46 (8.0) 2.2 52 (8.5) 2.3
0.75 [0.62, 0.92] 173 (4.2) 1.1 226 (5.6) 1.5 .34
Expanded MACE 0.84 [0.67, 1.05] 136 (23.7) 6.4 168 (27.5) 7.4
0.89 [0.81, 0.98] 812 (19.8) 5.2 894 (22.0) 5.8 .66
All-cause death 0.96 [0.69, 1.33] 70 (12.2) 3.3 77 (12.6) 3.4
0.83 [0.71, 0.96] 311 (7.6) 2.0 370 (9.1) 2.4 .41
Details are in the caption following the image
0.1
1
10
Favours liraglutide ← HR → Favours placebo


(B)
Endpoint
HR semaglutide versus placebo [95% CI]
Semaglutide N = 1648 n (%) R
Placebo N = 1649 n (%) R
P value P interaction
Primary outcome 0.74 [0.58, 0.95] 108 (6.6) 3.2 146 (8.9) 4.4 <.001
MACE 0.61 [0.33, 1.13] 16 (7.0) 3.4 27 (11.7) 5.6
0.77 [0.58, 1.01] 92 (6.5) 3.1 119 (8.4) 4.1 .49
Non-fatal MI 0.87 [0.38, 2.02] 10 (4.3) 2.1 12 (5.2) 2.5
0.71 [0.47, 1.09] 37 (2.6) 1.3 52 (3.7) 1.8 .68
Non-fatal stroke 0.30 [0.08, 1.09] 3 (1.3) 0.6 10 (4.3) 2.1
0.70 [0.42, 1.18] 24 (1.7) 0.8 34 (2.4) 1.2 .23
Hospitalization for HF 0.76 [0.31, 1.90] 8 (3.5) 1.7 11 (4.8) 2.3
1.20 [0.80, 1.81] 51 (3.6) 1.7 43 (3.0) 1.5 .37
CV death 0.72 [0.20, 2.57] 4 (1.7) 0.8 6 (2.6) 1.3
1.01 [0.65, 1.57] 40 (2.8) 1.4 40 (2.8) 1.4 .62
Expanded MACE 0.55 [0.36, 0.84] 34 (14.8) 7.1 60 (26.1) 13
0.80 [0.65, 0.98] 165 (11.6) 5.6 204 (14.4) 7.0 .13
All-cause death 0.70 [0.25, 1.97] 6 (2.6) 1.3 9 (3.9) 1.9
1.11 [0.76, 1.62] 56 (3.9) 1.9 51 (3.6) 1.7 .41
0.1
1
10
Favours semaglutide ← HR → Favours placebo



No. at risk:

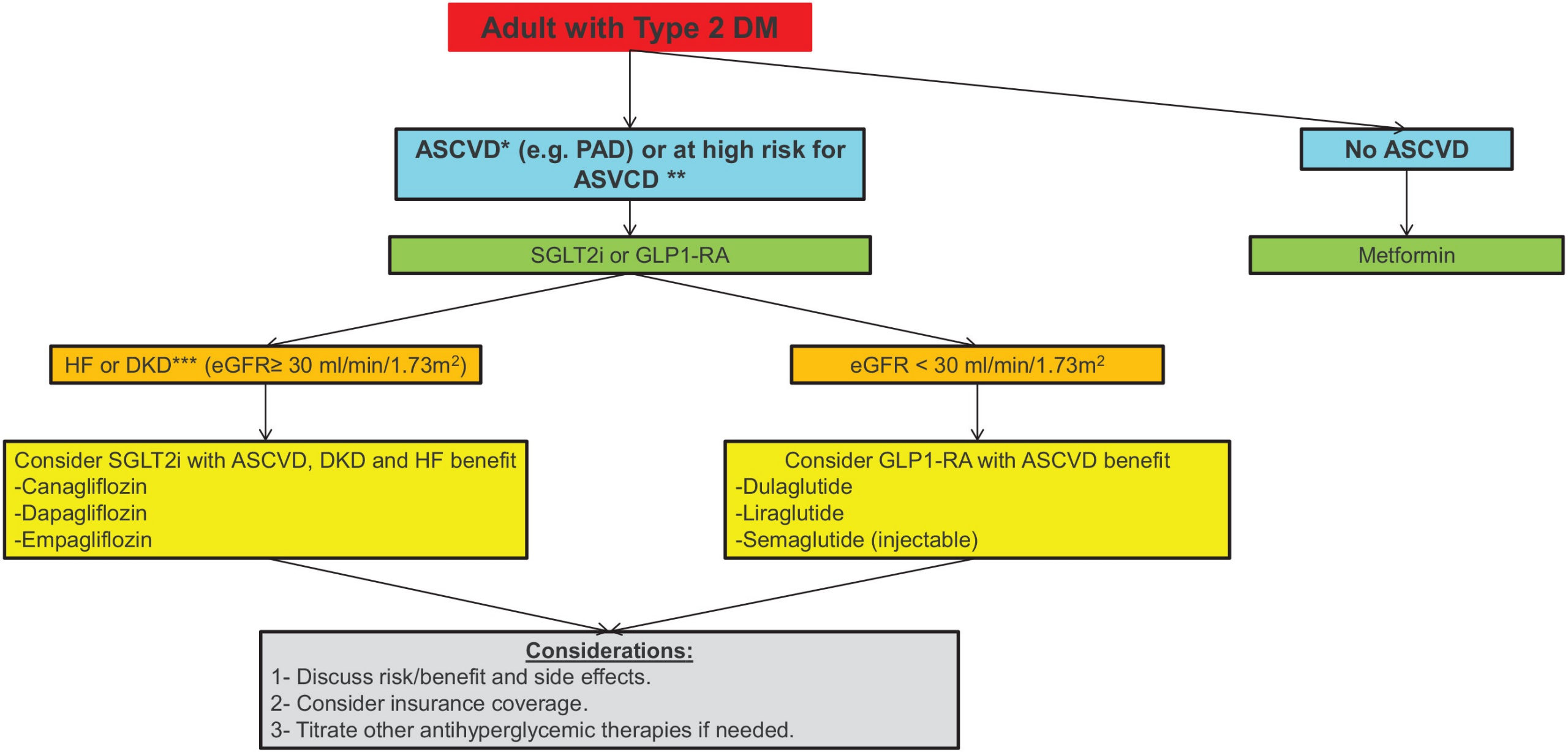
DPP4i	13,380	8611	5011	4340	2913	1496	543	0
GLP1RA	4460	2922	1748	1517	1041	536	207	0



No. at risk:

DPP4i	13,380	8625	5020	4351	2923	1505	545	0
GLP1RA	4460	2925	1748	1521	1045	538	208	0

Lin, D., et al. *Diabetologia*. 2021


Adult with Type 2 DM
ASCVD* (e.g. PAD) or at high risk for ASVCD **
No ASCVD
SGLT2i or GLP1-RA
Metformin
HF or DKD*** (eGFR≥ 30 ml/min/1.73m2)
eGFR < 30 ml/min/1.73m2
Consider SGLT2i with ASCVD, DKD and HF benefit
-Canagliflozin
-Dapagliflozin
-Empagliflozin
Consider GLP1-RA with ASCVD benefit
-Dulaglutide
-Liraglutide
-Semaglutide (injectable)
Considerations:
1- Discuss risk/benefit and side effects.
2- Consider insurance coverage.
3- Titrate other antihyperglycemic therapies if needed.

Summary

Thank You

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