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# Prevention and Management of Stroke in Patients with Diabetes

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PamTaubMD

# Disclosures

- Consultant to Sanofi, Novo-Nordisk, Novartis, Boehringer-Ingelheim, Amgen, Bayer, Medtronic, Edwards and Esperion
- Founder and Shareholder of Epirium Bio

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- Hillblom Network Grant (PI: Taub PR) (NCT05365529)
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Clinical Trial Leadership:

- US National Lead/Steering Committee Member for: Study of Inclisiran to Prevent Cardiovascular (CV) Events in Participants With Established Cardiovascular Disease (VICTORION-2P). (Sponsor: Novartis; NCT05030428)
- US National Lead/Steering Committee Member for: A Double-blind, Randomized, Placebo controlled, Multicenter Study Assessing the Impact of Olpasiran on Major Cardiovascular Events in Patients with Atherosclerotic Cardiovascular Disease and Elevated Lipoprotein (a). (Sponsor: Amgen)
- Executive Steering Committee for VICTORIAN-1P Trial (Sponsor: Novartis) and DREAM FAITH Trial (Sponsor: Bayer)

# Overview of Talk

- Overview of Stroke/TIA
- Incidence of Stroke in Patients with Diabetes
- Data on SLGT2 inhibitors and GLP-1 RA in Stroke
- Diabetes and Atrial Fibrillation
- Management of Carotid Stenosis and Cryptogenic Stroke
- Lipoprotein A and Stroke

neurocritical care society Neurocrit Care
DOI 10.1007/s12028-011-9535-6

ORIGINAL ARTICLE

# Elevated BNP is Associated with Vasospasm-Independent Cerebral Infarction Following Aneurysmal Subarachnoid Hemorrhage

**Pam R. Taub · Jeremy D. Fields · Alan H. B. Wu · Jacob C. Miss · Michael T. Lawton · Wade S. Smith · William L. Young · Jonathan G. Zaroff · Nerissa U. Ko**

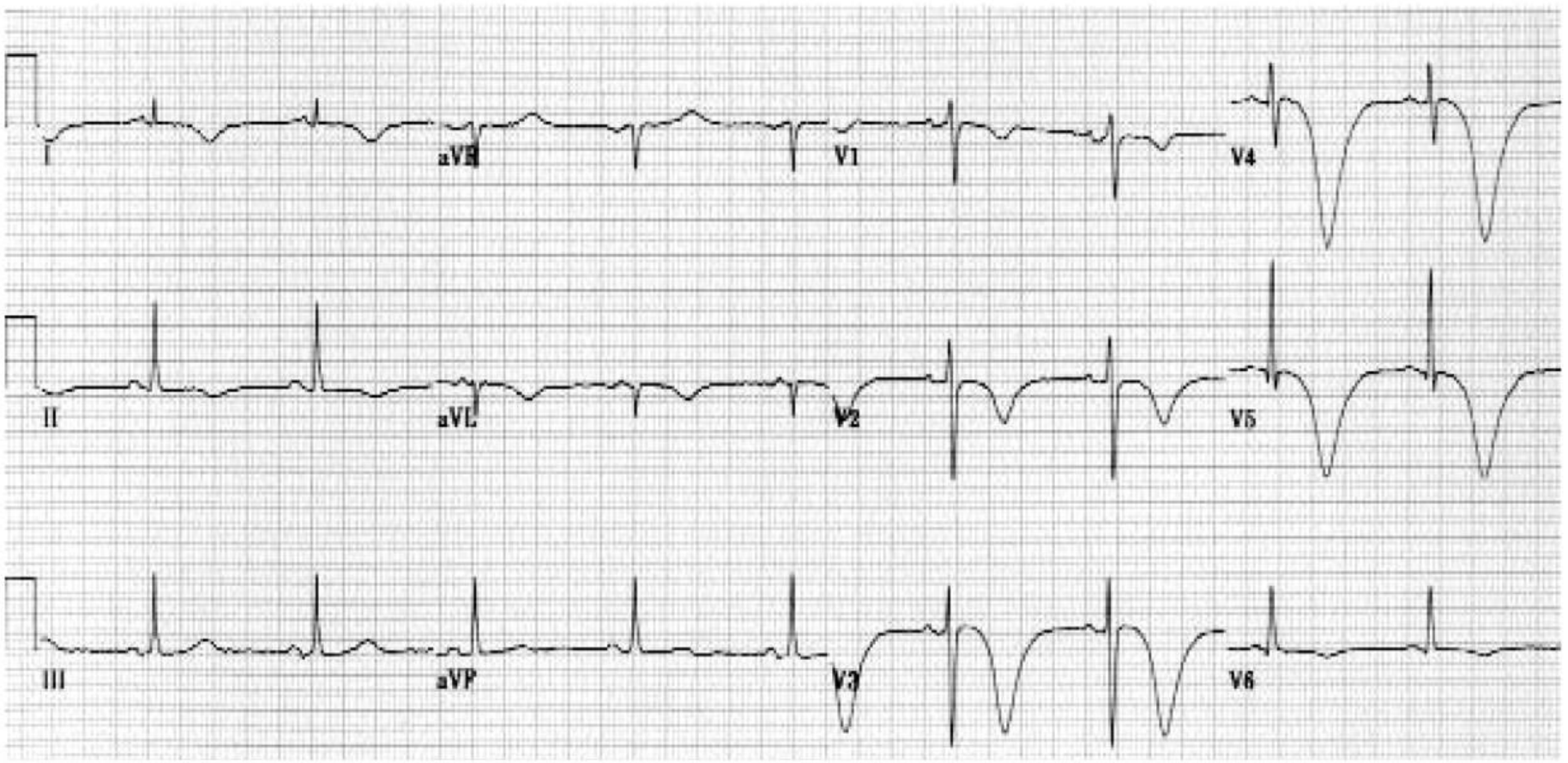


**Abstract**

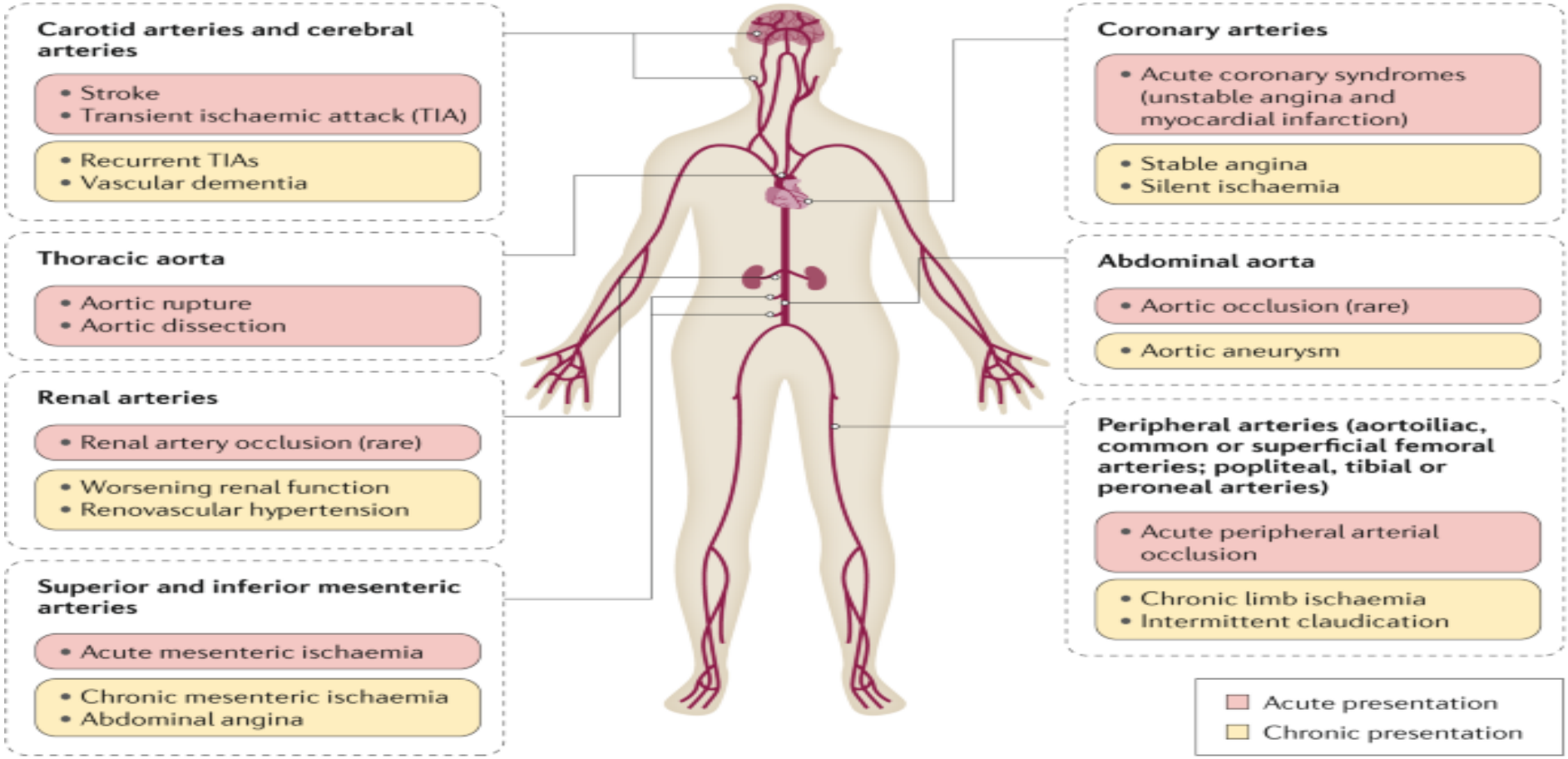
*Background* Elevated levels of B-type natriuretic peptide (BNP) have been associated with cardiac dysfunction and adverse neurological outcomes after subarachnoid hemorrhage (SAH). We sought to determine whether elevated levels of BNP are independently associated with radiographic cerebral infarction after SAH.

*Methods* Plasma BNP levels were measured after

# Cerebral T Waves



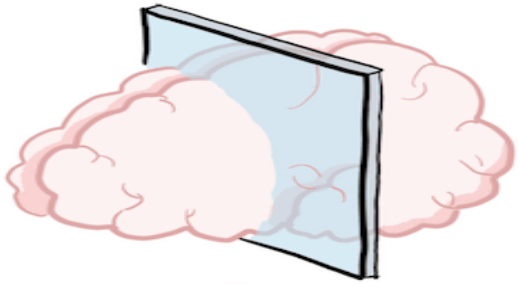
# Atherosclerosis is a Systemic Disease
# TIA/Stroke/Carotid Stenosis = ASCVD



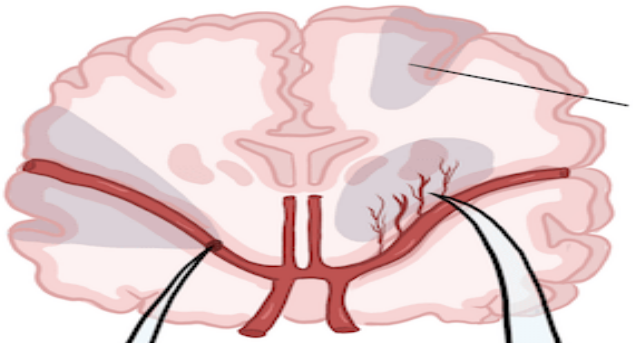

Libby, P *et al.* Atherosclerosis. *Nat Rev Dis Primers* **5,** 56 (2019)

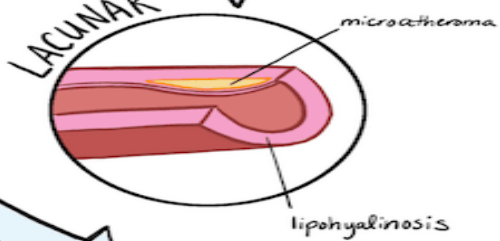
# TYPES OF STROKE

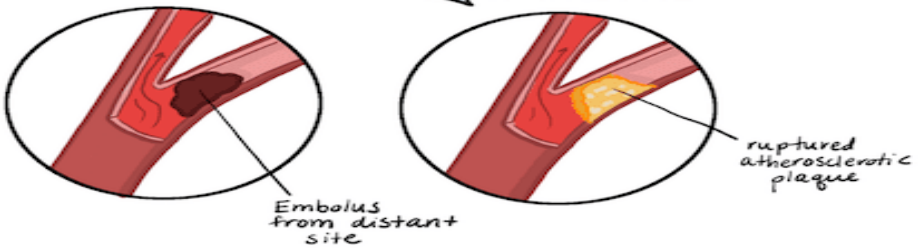
M. STEWART



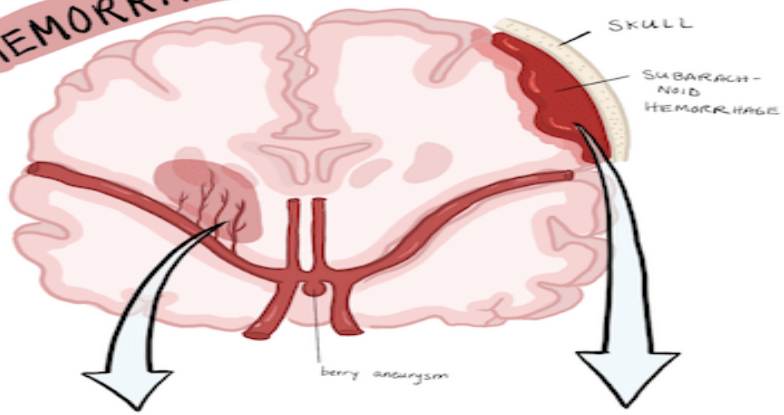
## ISCHEMIC

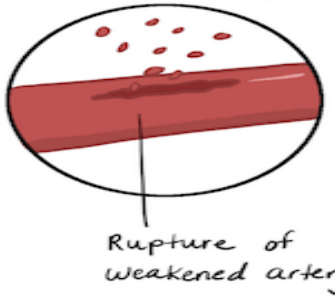


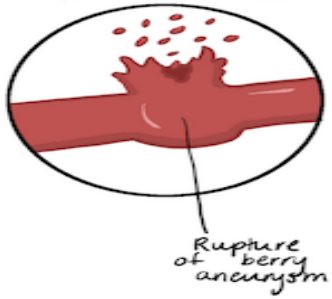




## HEMORRHAGIC




* WATERSHED STROKE

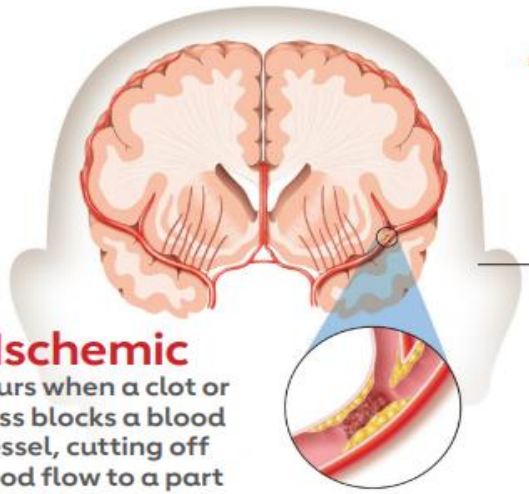
Terminal areas of blood supply are most affected by hypoperfusion. Seen in areas of blood supply overlap.

KNOWN

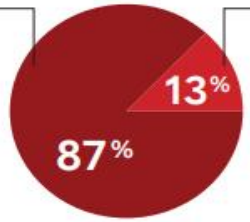
Each year **795,000** people in the U.S. have a stroke.[1]

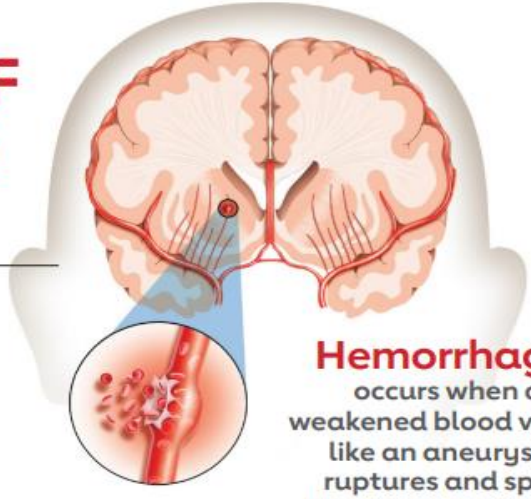
**STROKE IS** an interruption of blood flow to the brain. Without oxygen-rich blood, brain cells die.

# TYPES OF STROKE



**Ischemic**
occurs when a clot or mass blocks a blood vessel, cutting off blood flow to a part of the brain.[1]



**Hemorrhagic**
occurs when a weakened blood vessel, like an aneurysm, ruptures and spills blood into the brain.[1]

**ABOUT 1 in 3** ischemic strokes are classified as CRYPTOGENIC, meaning the CAUSE IS UNKNOWN.[2]

## FINDING THE CAUSE & SECONDARY STROKE RISK FACTORS

are important because it helps your doctor develop a plan personalized for you to prevent another stroke.

## POSSIBLE HIDDEN CAUSES

While some patients may continue to have the cause of their stroke unknown, a cause or secondary stroke risk factors may be revealed with further testing.

**Irregular heartbeat**
(Atrial Fibrillation)

AFib patients are at a **5X** greater risk for stroke.[1]

**Heart structure problem**
(such as Patent Foramen Ovale)

**Hardening of the arteries**
(Large Artery Atherosclerosis)

**Blood clotting disorder**
(Thrombophilia)

UNKNOWN

Viewpoint

February 11, 2022

# Time to Retire the Concept of *Transient Ischemic Attack*

J. Donald Easton, MD[1]; S. Claiborne Johnston, MD, PhD[2]

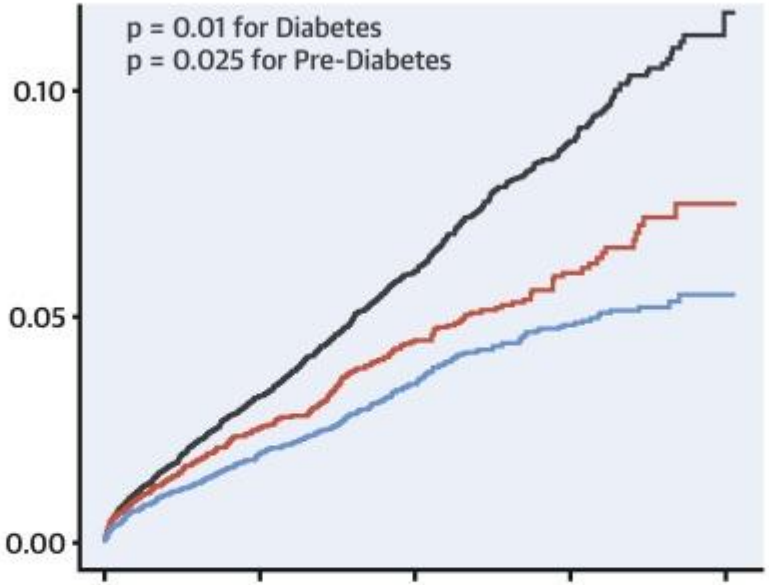
» Author Affiliations

*JAMA*. 2022;327(9):813-814. doi:10.1001/jama.2022.0300

*Transient ischemic attack (TIA)* has been a useful clinical term even though agreement on the diagnosis for individual cases has been far from perfect even among experts.[1] The utility of the diagnosis has waned with improvements in brain imaging and a deeper understanding of the natural history of acute cerebral ischemia. The current concept of TIA characterizes an ischemic episode in which symptoms are transient and not associated with brain injury. But recent evidence suggests that such episodes do not occur or are vanishingly rare and that brain injury almost always occurs during these events. Accordingly, it is time to reevaluate the conceptual soundness and utility of the term *TIA*.

# Increased Incidence of Stroke in Patients with Diabetes and Pre -Diabetes

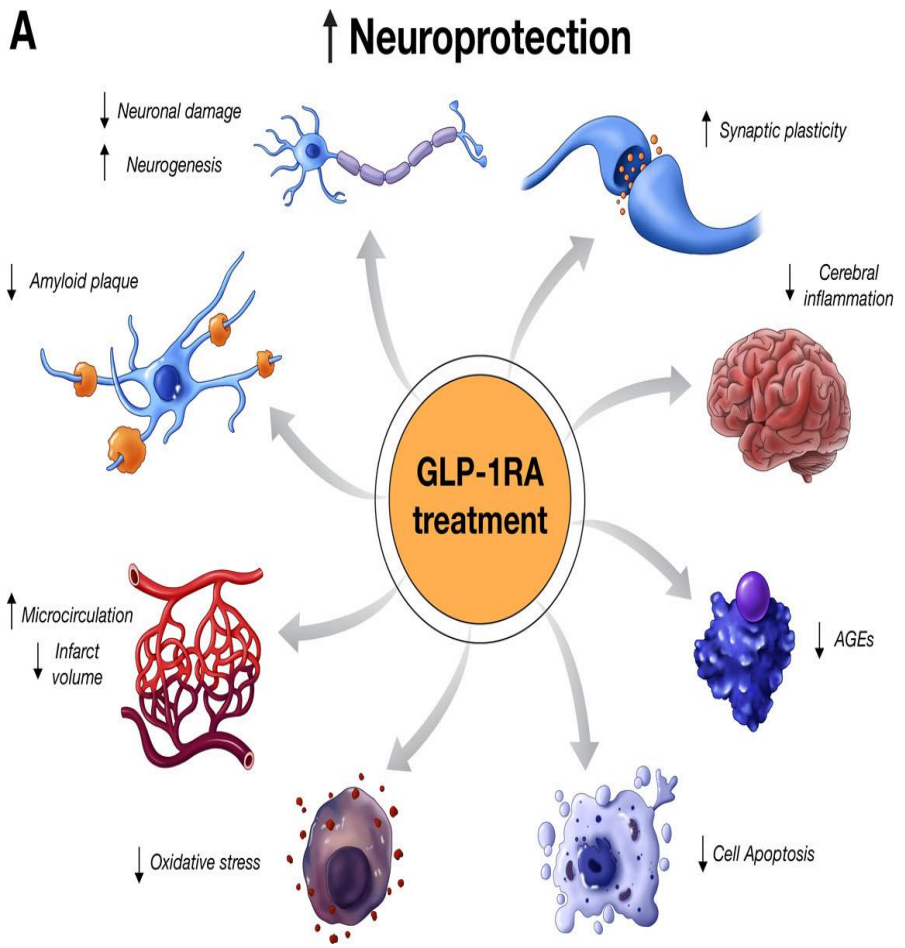
**CENTRAL ILLUSTRATION: Cumulative Incidence of Stroke Over Time Estimated by the Kaplan-Meier Method**

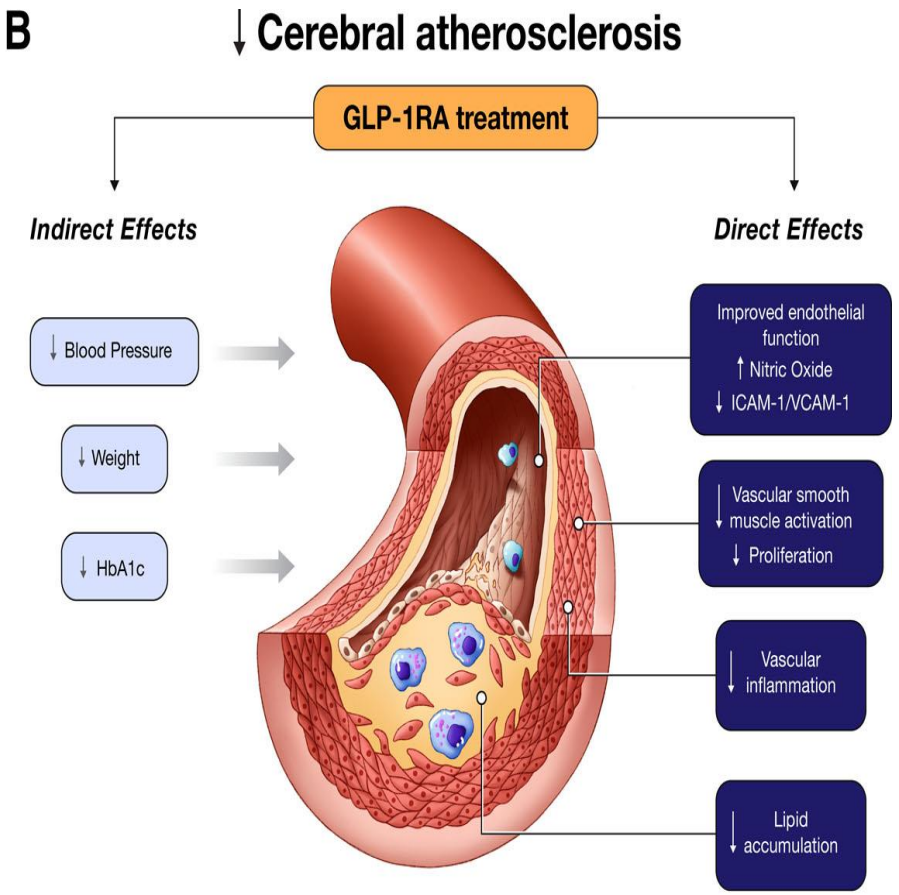



| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| Normoglycemics | 11,239 | 9,356 | 7,570 | 5,933 | 4,482 | 3,209 | 2,112 | 1,095 | 154 |
| Pre-Diabetes | 6,509 | 5,550 | 4,442 | 3,360 | 2,458 | 1,728 | 1,079 | 490 | 59 |
| Diabetes | 17,433 | 13,388 | 10,320 | 7,546 | 5,394 | 3,661 | 2,327 | 1,102 | 159 |

Kezerle, L. et al. J Am Coll Cardiol. 2021;77(7):875-84.

# Mechanisms Associated with Neuroprotection of GLP1-RA




https://www.ahajournals.org/cms/asset/41abe33a-1ab8-4b5d-a11f-e2d4a78b5d6e/strokeaha.121.038151.fig03.jpg

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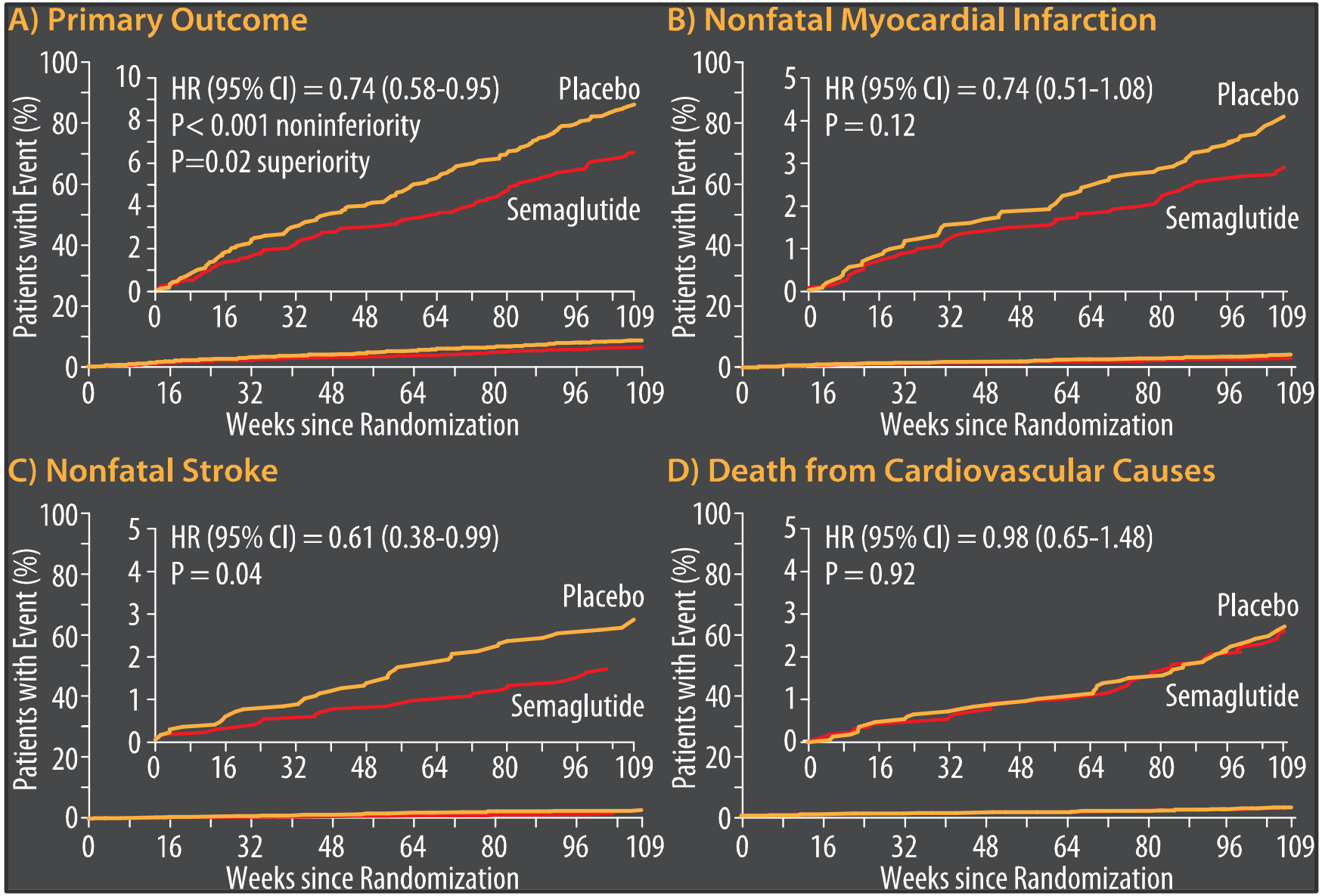
# SUSTAIN 6: CV Outcomes




Marso SP, et al. *N Engl J Med.* 2016;375:1834-1844

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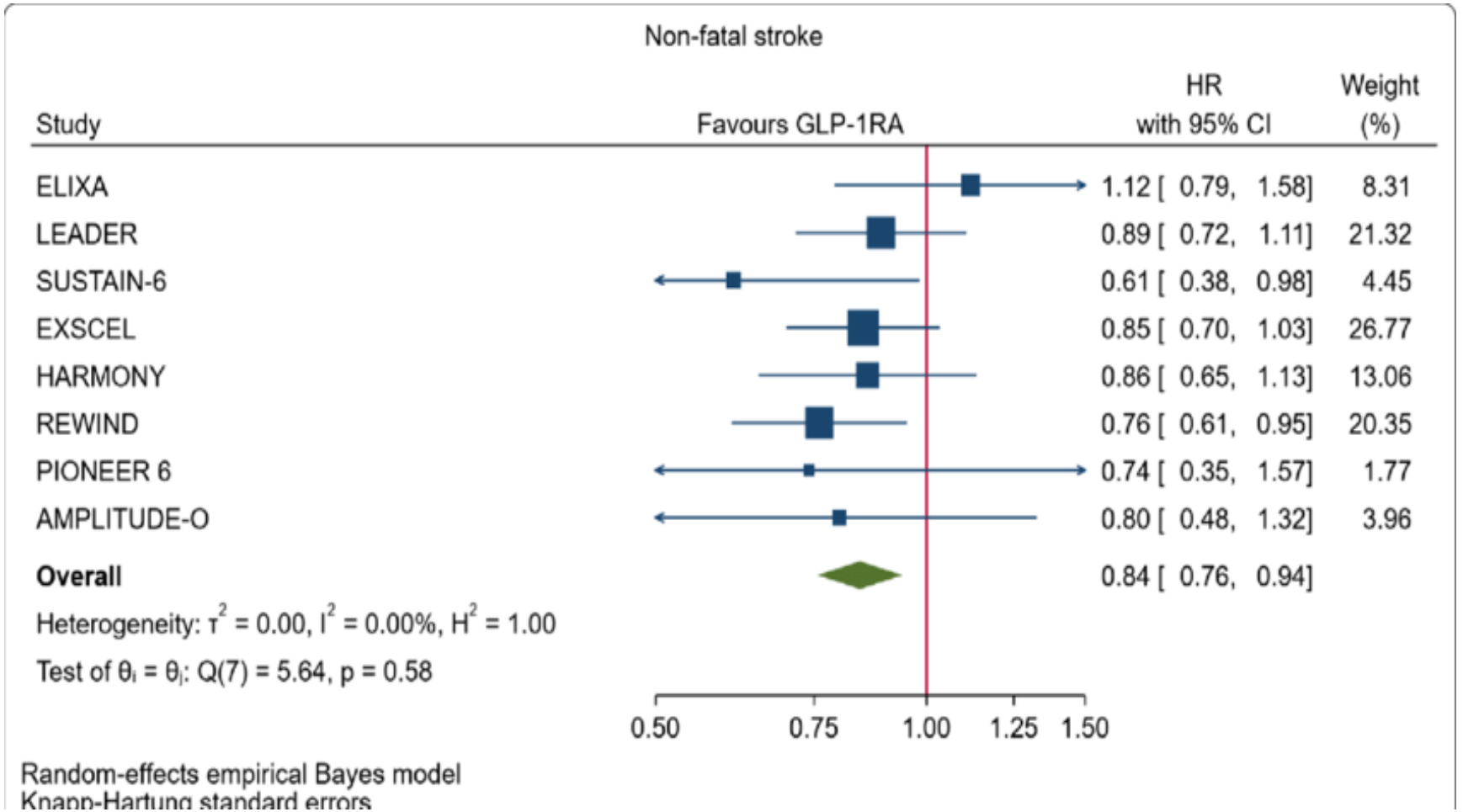
# GLP-1 RA and Non-Fatal Stroke




https://www.researchgate.net/publication/354607752/figure/fig3/AS:1068448209719297@1631749312192/Forest-plots-of-meta-analysis-of-the-eight-CVOTs-with-GLP-1RA-on-nonfatal-stroke.png

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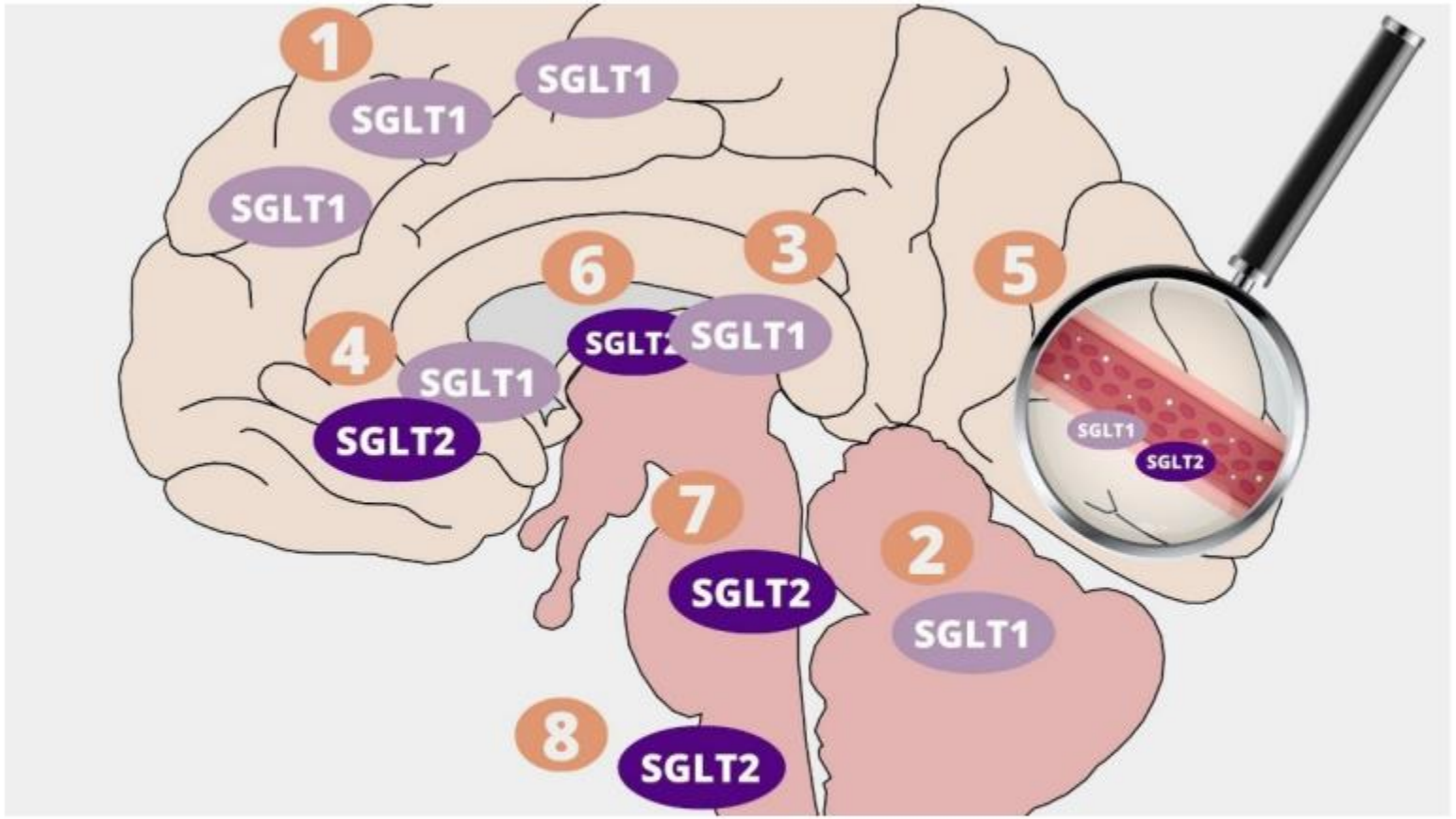
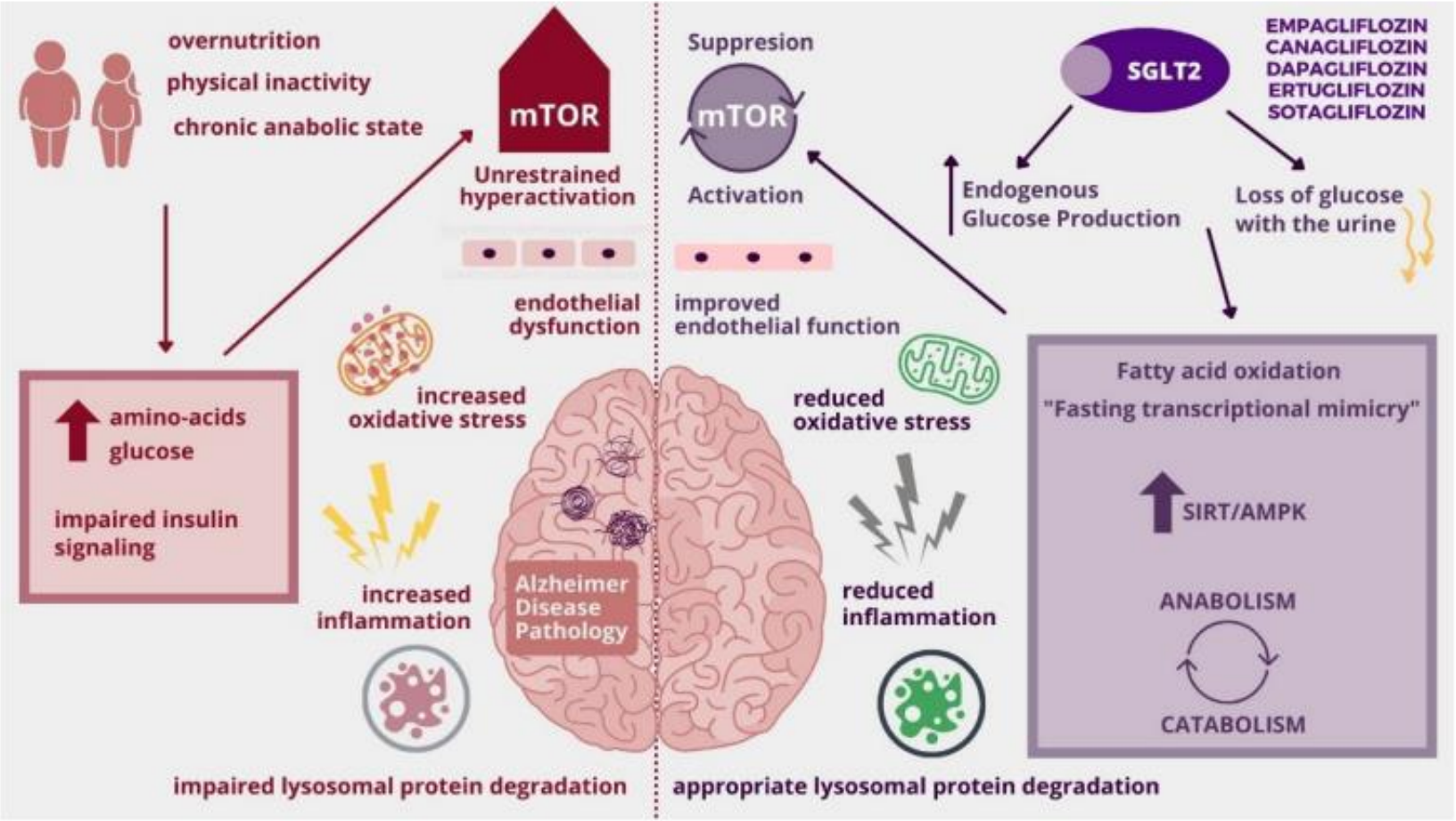



**Figure 1.** Distribution of SGLT1 and SGLT2 receptors in the Central Nervous System: 1. Pyramidal cells of brain cortex; 2. Purkinje cerebellum cells; 3. Hippocampus pyramidal and granular cells; 4. Hypothalamus; 5. Microvessels; 6. Amygdala; 7. Periaqueductal grey; 8. Dorsomedial medulla—nucleus of the solitary tract (NTS).

Molecules 2021, 26, 7213.

# Proposed Neuroprotective Mechanisms of SGLT2 Inhibitors




Molecules 2021, 26, 7213.

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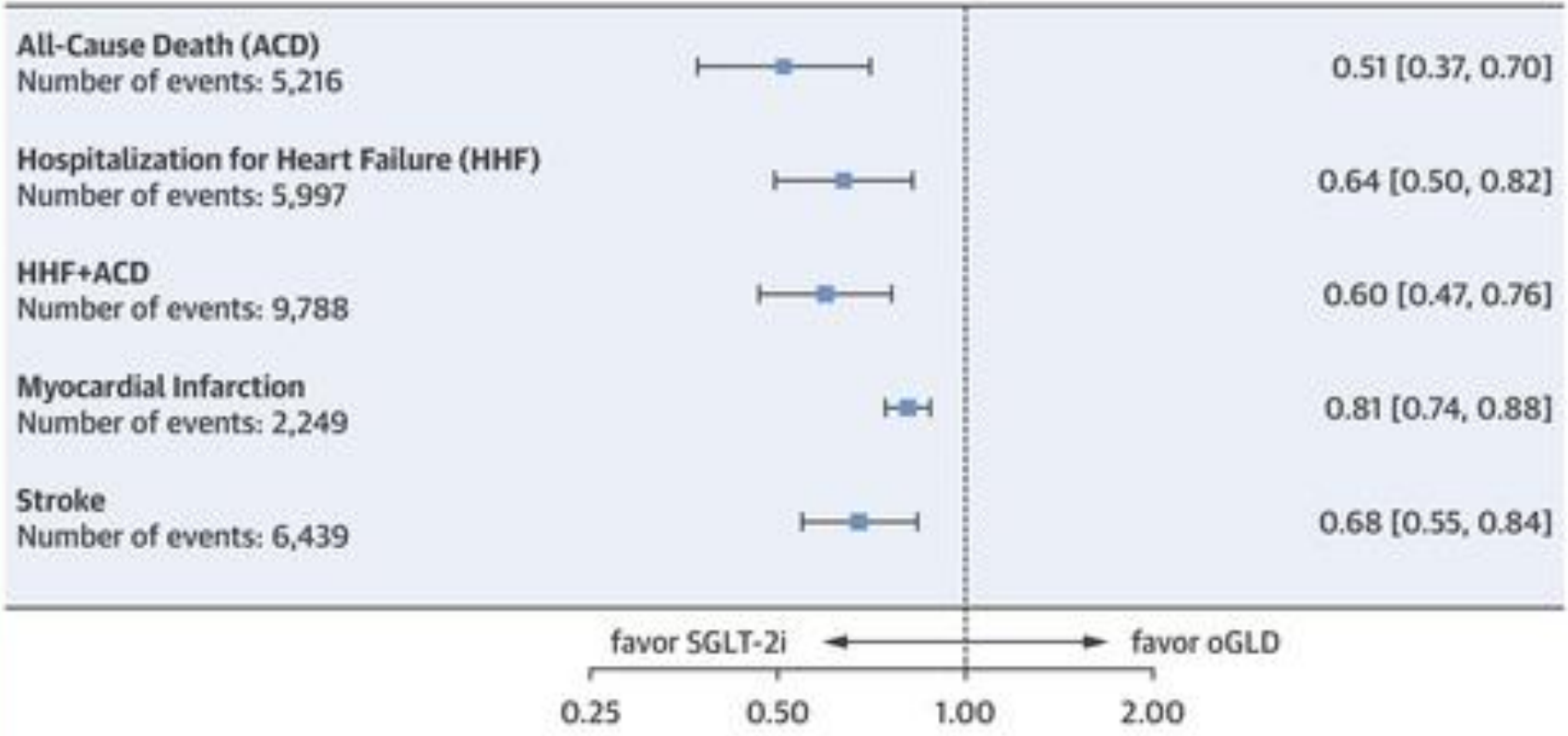
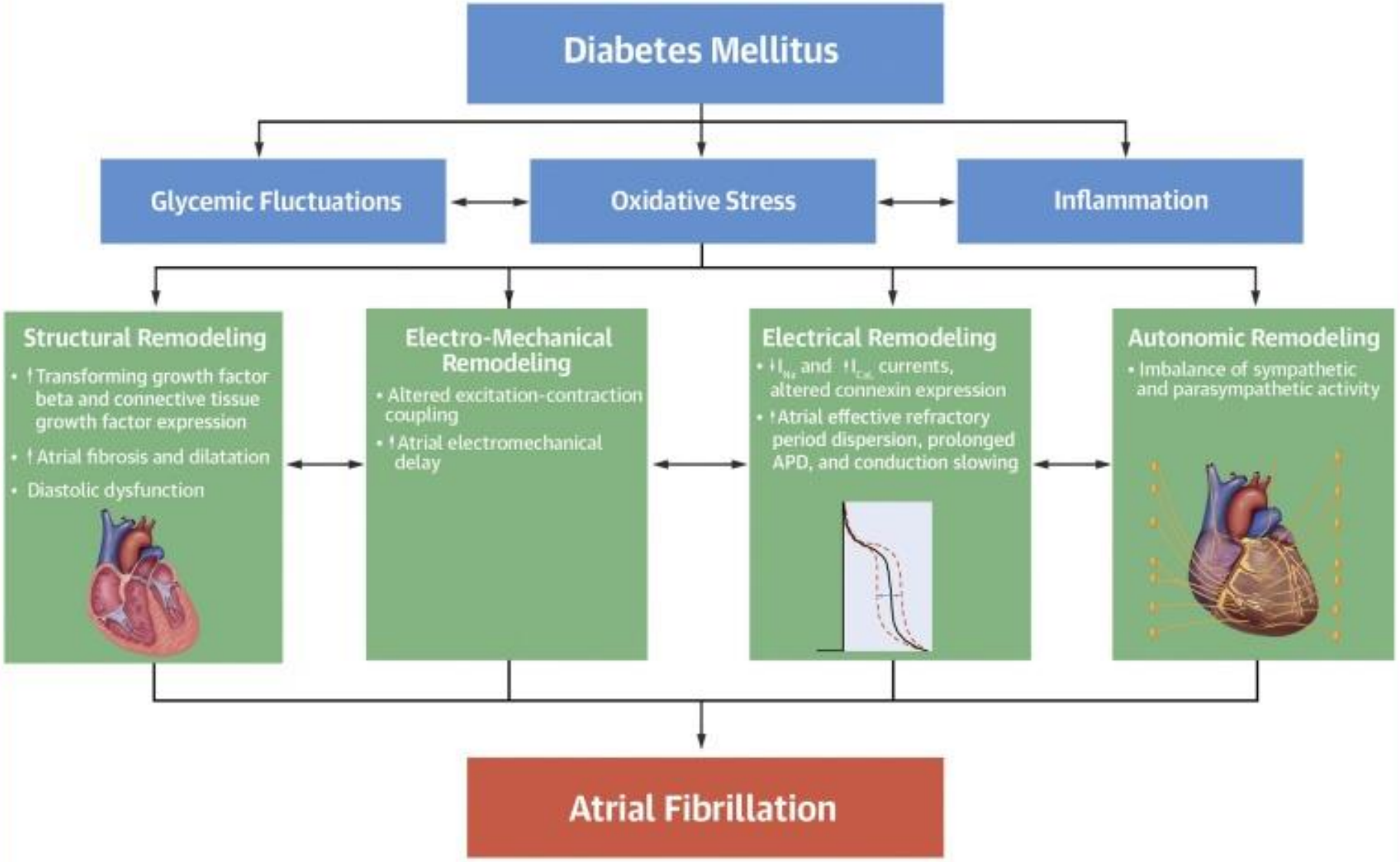
## CENTRAL ILLUSTRATION: Lower Cardiovascular Risk Associated With SGLT-2 Inhibitors




Kosiborod, M. et al. J Am Coll Cardiol. 2018;71(23):2628-39.

# CENTRAL ILLUSTRATION: Pathophysiology of Diabetes and Atrial Fibrillation

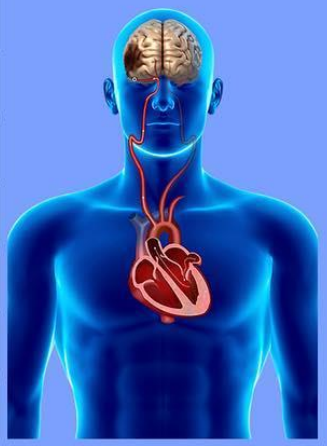



Wang, A. et al. J Am Coll Cardiol. 2019;74(8):1107–15.

# $CHA_2DS_2$ – VASc Score for Atrial Fibrillation Stroke Risk

| | |
|---|---|
| **C**HF | +1 |
| **H**ypertension | +1 |
| **A**ge ≥75 | +2 |
| **D**iabetes | +1 |
| **S**troke/TIA/VTE | +2 |
| **V**ascular Disease | +1 |
| **A**ge 65-74 | +1 |
| **S**ex (female) | +1 |

| Score | Risk of stroke | |
|---|---|---|
| 0 | 0.2% | Low |
| 1 | 0.6% | Moderate |
| 2 | 2.2% | High |
| 3 | 3.2% | |
| 4 | 4.8% | |
| 5 | 7.2% | |
| 6 | 9.7% | |
| 7 | 11.2% | |
| 8 | 10.8% | |
| 9 | 12.2% | |



1(male): oral anticoagulant should be considered

≥2: oral anticoagulant is recommended

The Art of Cardiology

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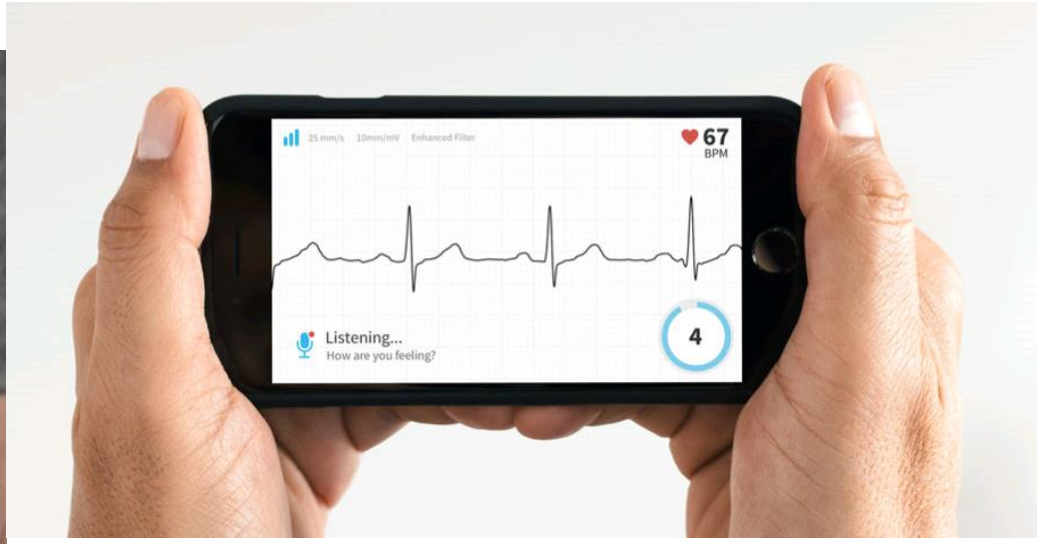
# Detection of Atrial Fibrillation Enhanced with Wearables



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# Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation

## The REHEARSE-AF Study

**CONCLUSIONS:** Screening with twice-weekly single-lead iECG with remote interpretation in ambulatory patients ≥65 years of age at increased risk of stroke is significantly more likely to identify incident AF than RC over a 12-month period. This approach is also highly acceptable to this group of patients, supporting further evaluation in an appropriately powered, event-driven clinical trial.

Study of 1001 patients with mean CHADS2vasc score of 3

*Circulation.* 2017;136:1784–1794. DOI: 10.1161/CIRCULATIONAHA.117.030583

# Implantable Loop Recorders (ILR)


45x7x4mm


62x19x8mm


56x19x8mm

# Clinical Use of ILR

- ILR allows for remote monitoring
- Helpful in diagnosing occult arrhythmias (such as atrial fibrilaltion in patient with cryptogenic stroke).
- Crystal AF study of 441 patients showed ILR was superior to conventional follow-up for detecting atrial fibrillation after cryptogenic stroke
  - By 12 months, atrial fibrillation had been detected in 12.4% of patients in the ILR group versus 2.0% of patients in the control group

Gladstone et al N Engl J Med 2014; 370:2467-2477

# Beneficial Left Atrial Remodeling seen with SGLT2 Inhibitors

| (A) Overall Effects | No.S | WMD | 95% CI | P value | $I^2$ (Q, df) |
|---|---|---|---|---|---|
| Left ventricular mass (g) | 6 | -6.319 | -10.850 - -1.789 | 0.006 | 69.8 (16.58,5) |
| Left ventricular mass index ($g/m^2$) | 7 | -2.372 | -4.940 - 0.196 | 0.070 | 67.2 (18.27,6) |
| Left ventricular ejection fractions (%) | 11 | 2.458 | 0.693 - 4.224 | 0.006 | 75.6 (40.95,10) |
| Left ventricular end-diastolic volume (mL) | 8 | -9.134 | -15.808 - -2.460 | 0.007 | 69.1 (22.65,7) |
| Left ventricular end-systolic volume (mL) | 7 | -8.440 | -15.093 - -1.787 | 0.013 | 82.7 (34.74,6) |
| Left ventricular end-systolic volume index ($mL/m^2$) | 4 | -3.675 | -7.837 - 0.486 | 0.083 | 53.6 (6.47,3) |
| Left ventricular end-diastolic volume index ($mL/m^2$) | 4 | -2.782 | -5.612 - 0.048 | 0.054 | 39.3 (4.95,3) |
| Left atrial volume index ($mL/m^2$) | 5 | -2.791 | -4.554 - -1.027 | 0.002 | 0 (1.19,4) |
| E/e' | 5 | -1.567 | -2.440 - -0.698 | <0.001 | 18.5 (4.91,4) |

| (B) From Randomised Clinical Trials | No.S | WMD | 95% CI | P value | $I^2$ (Q, df) |
|---|---|---|---|---|---|
| Left ventricular mass (g) | 5 | -7.726 | -13.185 - -2.268 | 0.006 | 74.9 (15.96,4) |
| Left ventricular mass index ($g/m^2$) | 6 | -1.616 | -3.651 - 0.420 | 0.120 | 53.2 (10.69,5) |
| Left ventricular ejection fractions (%) | 7 | 1.751 | -0.186 - 3.688 | 0.076 | 78.4 (27.74,6) |
| Left ventricular end-diastolic volume (mL) | 6 | -8.511 | -16.502 - -0.520 | 0.037 | 74.8 (19.82,5) |
| Left ventricular end-systolic volume (mL) | 6 | -7.868 | -14.966 - -0.770 | 0.030 | 84.8 (32.84,5) |
| Left ventricular end-systolic volume index ($mL/m^2$) | 4 | -3.675 | -7.837 - 0.486 | 0.083 | 53.6 (6.47,3) |
| Left ventricular end-diastolic volume index ($mL/m^2$) | 4 | -2.782 | -5.612 - 0.048 | 0.054 | 39.3 (4.95,3) |
| Left atrial volume index ($mL/m^2$) | 4 | -2.441 | -4.315 - -0.568 | 0.011 | 0 (0.02,3) |
| E/e' | 1 | -1.300 | -2.787 - 0.187 | 0.087 | 0 (0,0) |

| (C) From Cohort Studies | No.S | WMD | 95% CI | P value | $I^2$ (Q, df) | PI |
|---|---|---|---|---|---|---|
| Left ventricular mass (g) | 1 | -1.300 | -8.000 - 5.400 | 0.704 | 0 (0,0) | 0.145 |
| Left ventricular mass index ($g/m^2$) | 1 | -17.600 | -29.538 - -5.662 | 0.004 | 0 (0,0) | 0.010 |
| Left ventricular ejection fractions (%) | 4 | 4.407 | 0.894 - 7.921 | 0.014 | 54.0 (6.52,3) | 0.185 |
| Left ventricular end-diastolic volume (mL) | 2 | -12.949 | -21.961 - -3.937 | 0.005 | 0 (0.97,1) | 0.470 |
| Left ventricular end-systolic volume (mL) | 1 | -13.400 | -27.748 - 0.948 | 0.067 | 0 (0,0) | 0.498 |
| Left atrial volume index ($mL/m^2$) | 1 | -5.500 | -10.719 - -0.281 | 0.039 | 0 (0,0) | 0.280 |
| E/e' | 4 | -1.704 | -2.879 - -0.529 | 0.004 | 37.2 (4.77,3) | 0.676 |

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*J Clin Endocrinol Metab*, 2022; 107 (4): 1191–1203,

# Sodium-glucose cotransporter-2 inhibitors and the risk of incident atrial fibrillation in older adults with type 2 diabetes

**Elisabetta Patorno, MD, DrPH**
Associate Professor of Medicine, HMS

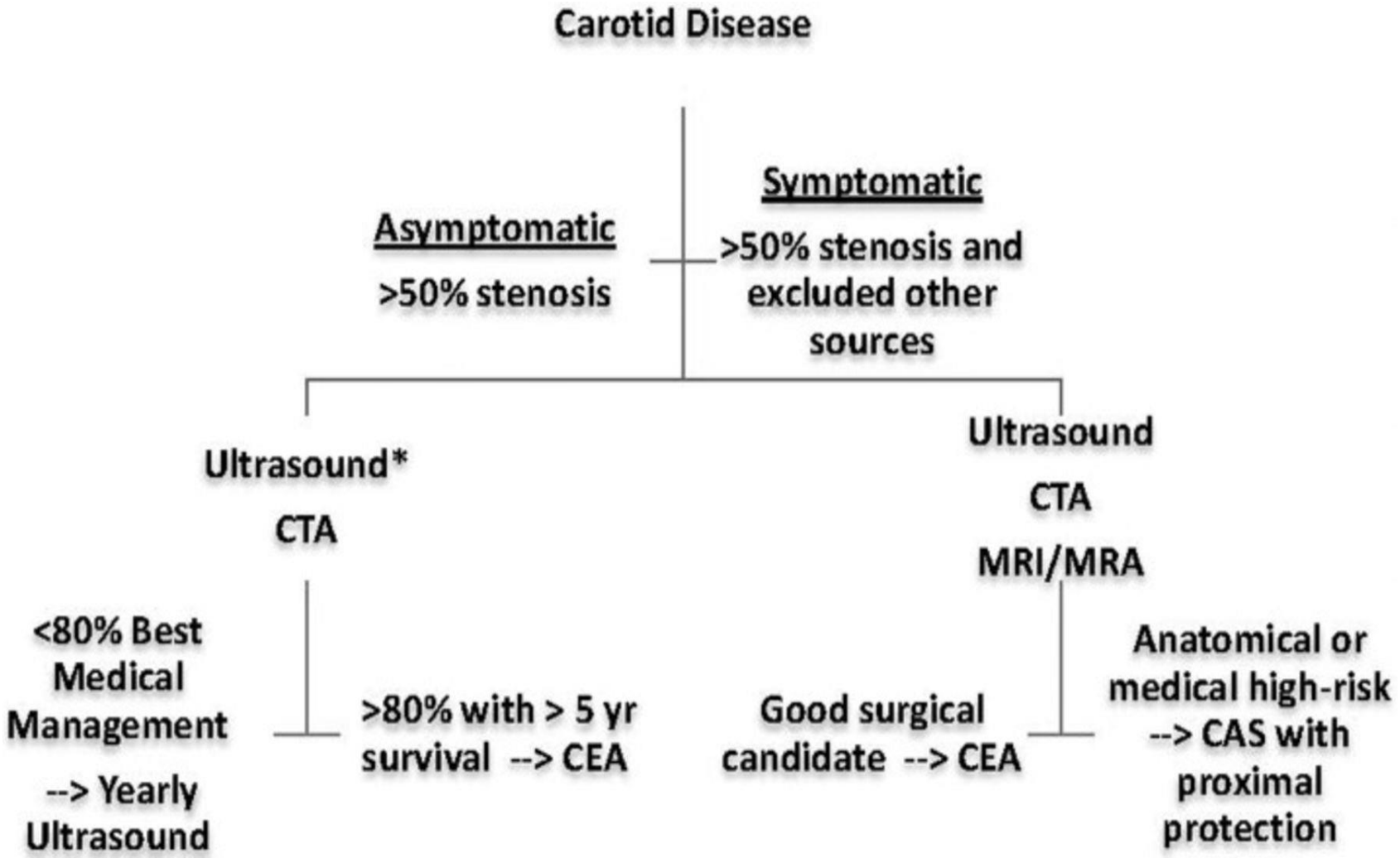
ADA Scientific Sessions, 2022

**Min Zhuo[1], Elvira D'Andrea[1], Julie M. Paik[1], Deborah J. Wexler[2], Brendan M. Everett[3], Robert J. Glynn[1], Seoyoung C. Kim[1], Elisabetta Patorno[1]**

1. Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Department of Medicine, Harvard Medical School, Boston, MA; 2. Diabetes Center, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; 3. Divisions of Cardiovascular and Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

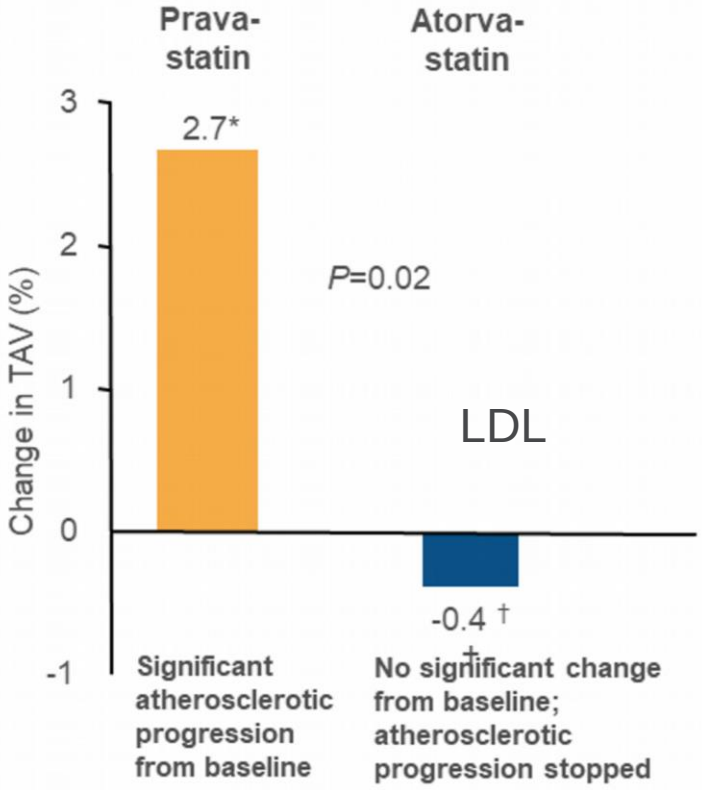
# Conclusions

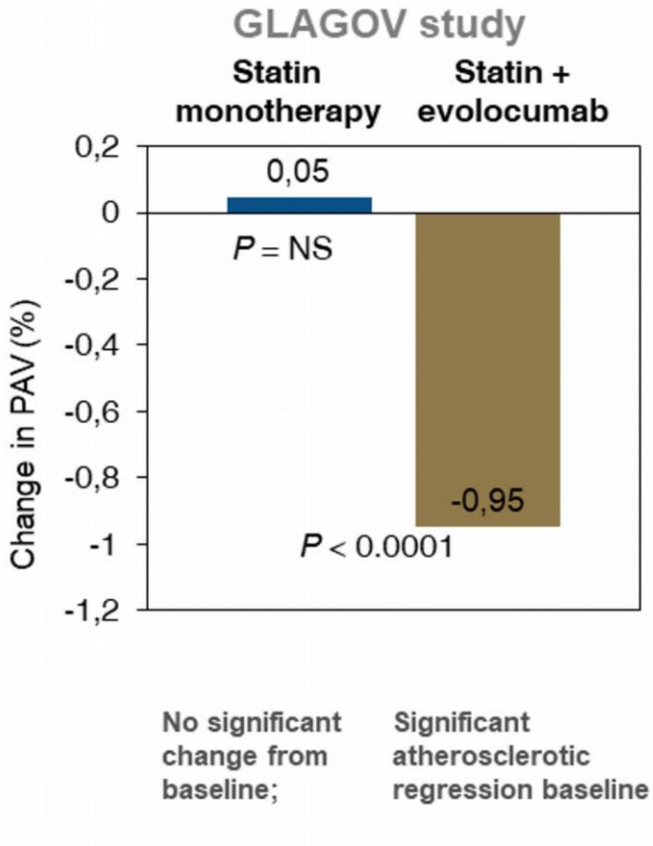
- In this large population-based cohort including more than 300,000 PS-matched older adults with T2D, the initiation of SGLT-2i, compared with DPP-4i or GLP-1RA, was associated with a 10-18% reduction in the risk of incident AF.
- Study findings were consistent across several outcome definitions of AF and did not appear to differ substantially across subgroups.
- Our data suggest that the initiation of SGLT-2i may be beneficial in older adults with T2D who are at risk of AF in clinical practice.
- These results may be helpful when weighing the potential risks and benefits of various glucose-lowering agents in older adults with T2D.


Carotid Disease
Asymptomatic
>50% stenosis
Symptomatic
>50% stenosis and excluded other sources
Ultrasound*
CTA
Ultrasound
CTA
MRI/MRA
<80% Best Medical Management
--> Yearly Ultrasound
>80% with > 5 yr survival --> CEA
Good surgical candidate --> CEA
Anatomical or medical high-risk --> CAS with proximal protection

# Plaque Stabilization versus Plaque Regression Depends on LDL Achieved

Reversal Study




**Aim for LDL of 36 or lower for plaque regression!**

LDL in pravastatin group: 110
LDL in atorvastatin group: 79

LDL in statin group: 93
LDL in statin+PCSK9i group: 36

Nissen SE et al. JAMA 2004;291:1091-80.
Nicholls SJ et al. JAMA 2016;316:2373-2384.

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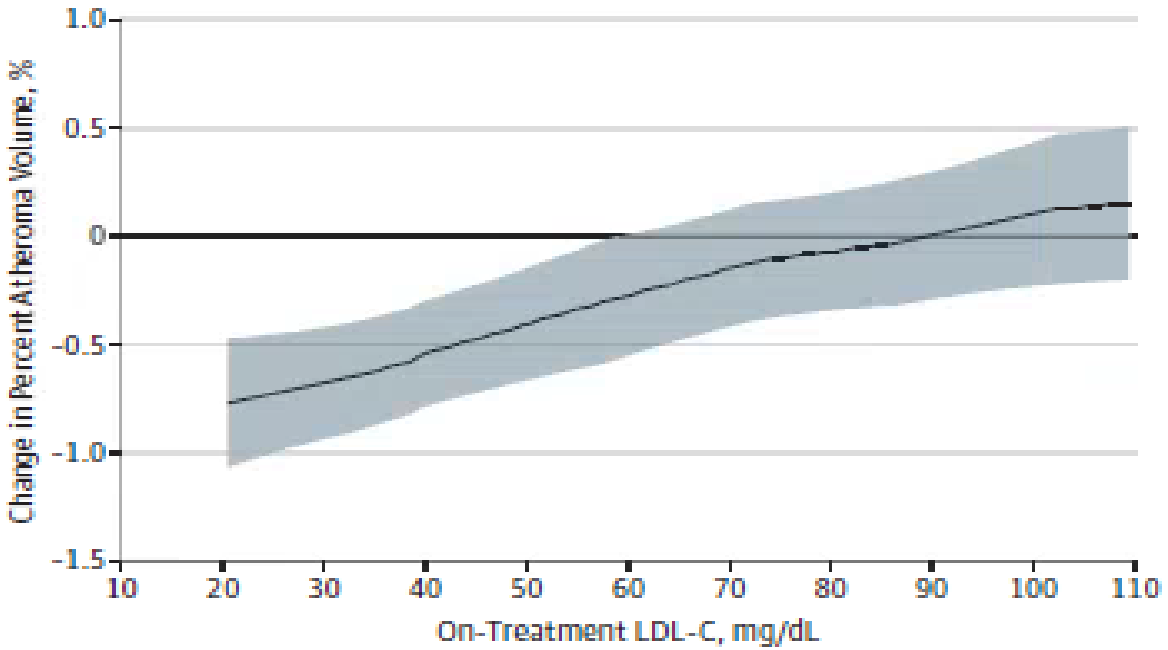
# GLAGOV Study: Benefit of LDL Lowering on Plaque Regression

**Figure 4. Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume**




Local regression (LOESS) curve illustrating the post hoc analysis of the association (with 95% confidence intervals) between achieved low-density lipoprotein cholesterol (LDL-C) levels and the change in percent atheroma volume in all patients undergoing serial IVUS evaluation. Curve truncated at 20 and 110 mg/dL owing to the small number of values outside that range. To convert LDL-C values to mmol/L, multiply by 0.0259.

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JAMA. 2016;316(22):2373-2384

# Real World Example of Glagov Study: Decrease in Carotid Artery Velocity and Reduction in Stenosis After PCSK9 Inhibitor

January 2020

FINDINGS:
Velocities reported in cm/s
RIGHT

| | PSV | EDV |
|---|---|---|
| Common carotid artery | 123 | 29 |
| Proximal internal carotid | 173 | 41 |
| Mid internal carotid | 215 | 29 |
| Distal internal carotid | 74 | 23 |
| External carotid | 165 | 13 |
| Vertebral artery | 54 | 13 |
| ICA CCA ratio | 1.7 | 1.0 |

LEFT

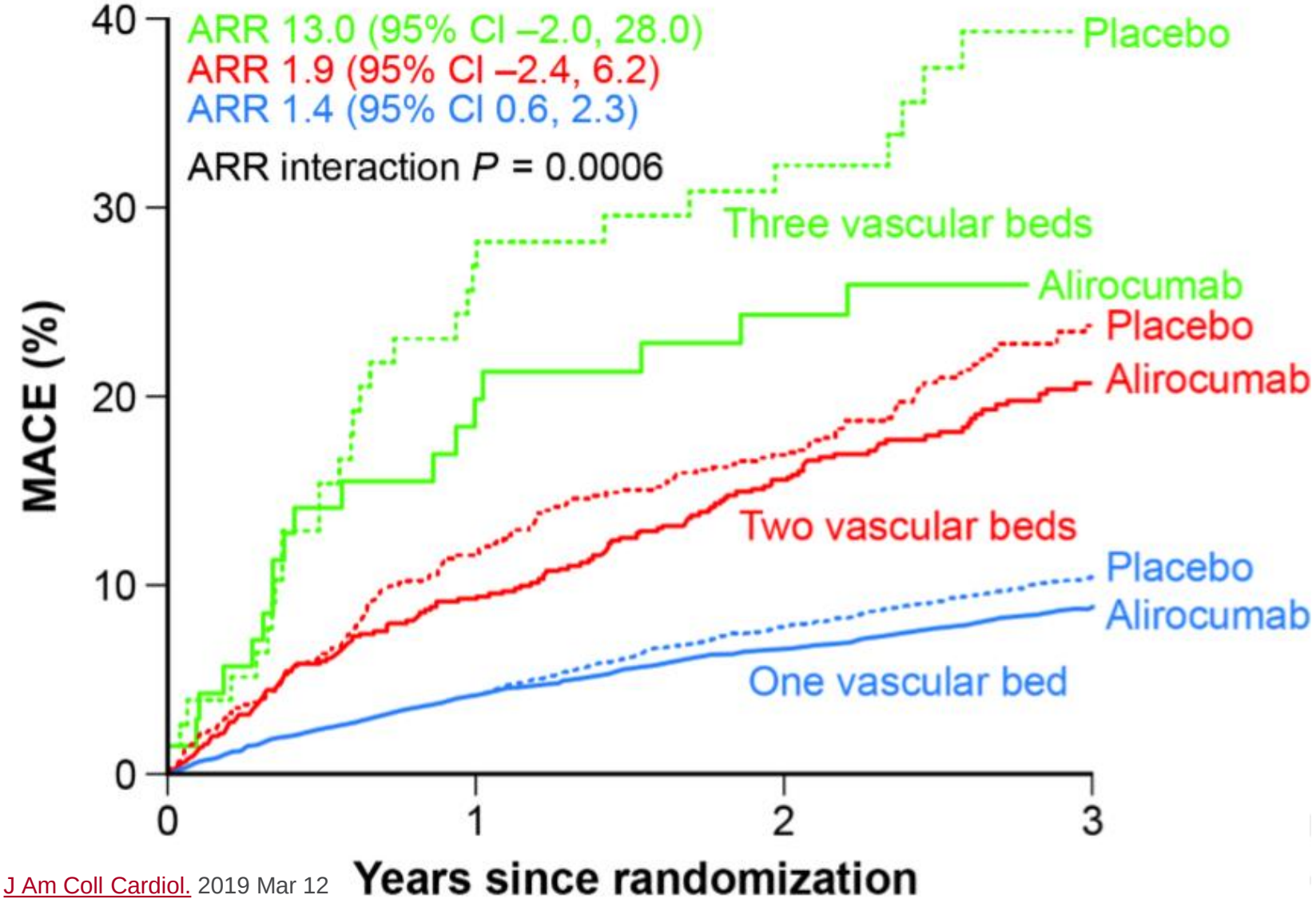
| | PSV | EDV |
|---|---|---|
| Common carotid artery | 112 | 25 |
| Proximal internal carotid | 52 | 10 |
| Mid internal carotid | 73 | 20 |
| Distal internal carotid | 67 | 28 |
| External carotid | 109 | 19 |
| Vertebral artery | 71 | 18 |
| ICA CCA ratio | 0.6 | 0.8 |

December 2021

| | PSV | EDV |
|---|---|---|
| | 70.1 | 17.1 |
| | 96.9 | 29.6 |
| | 135.5 | 18 |
| | 63.9 | 15.6 |
| | 107.3 | 16.7 |
| | 29.2 | 6.7 |
| | 1.9 | 1.1 |

| | PSV | EDV |
|---|---|---|
| | 77.1 | 14.5 |
| | 35 | 13 |
| | 65 | 20 |
| | 75.3 | 26.1 |
| | 61.7 | 10.1 |
| | 45.6 | 12 |
| | 1.0 | 1.8 |

# Absolute Risk Reduction PCSK9i stratified by number of Vascular Beds

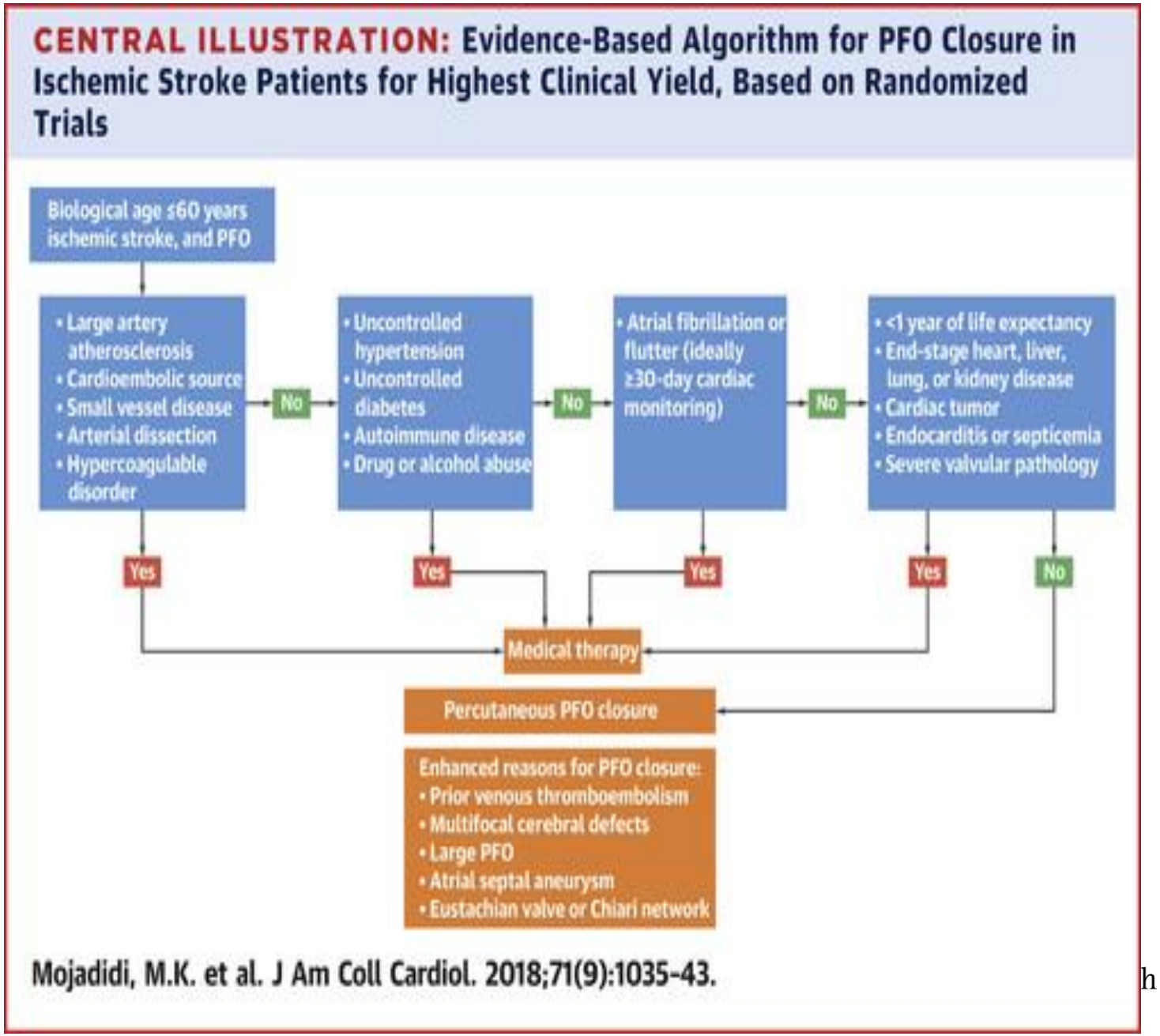



Jukema JW et al, J Am Coll Cardiol. 2019 Mar 12

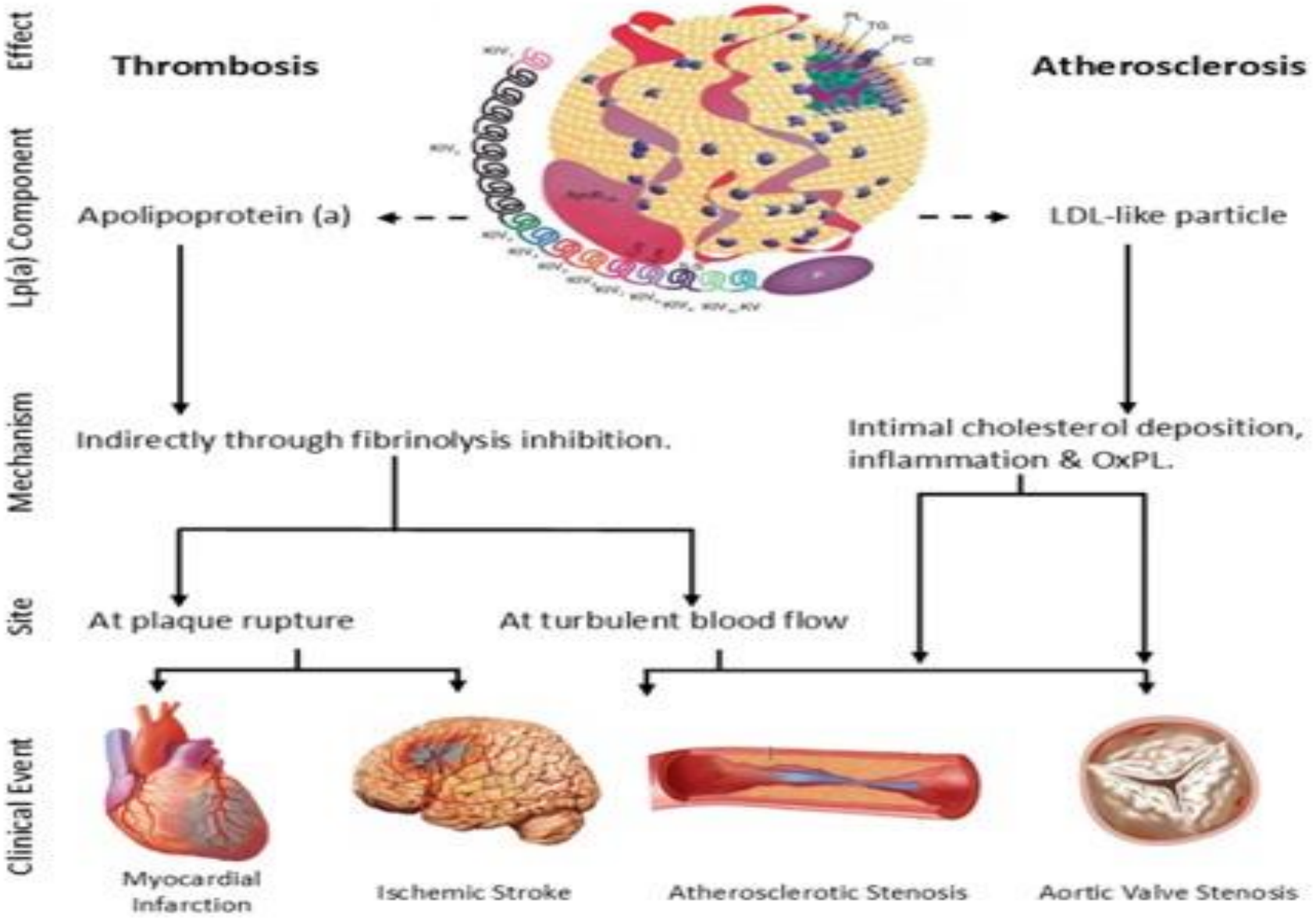
# When to Close a PFO?

25% of population has PFO

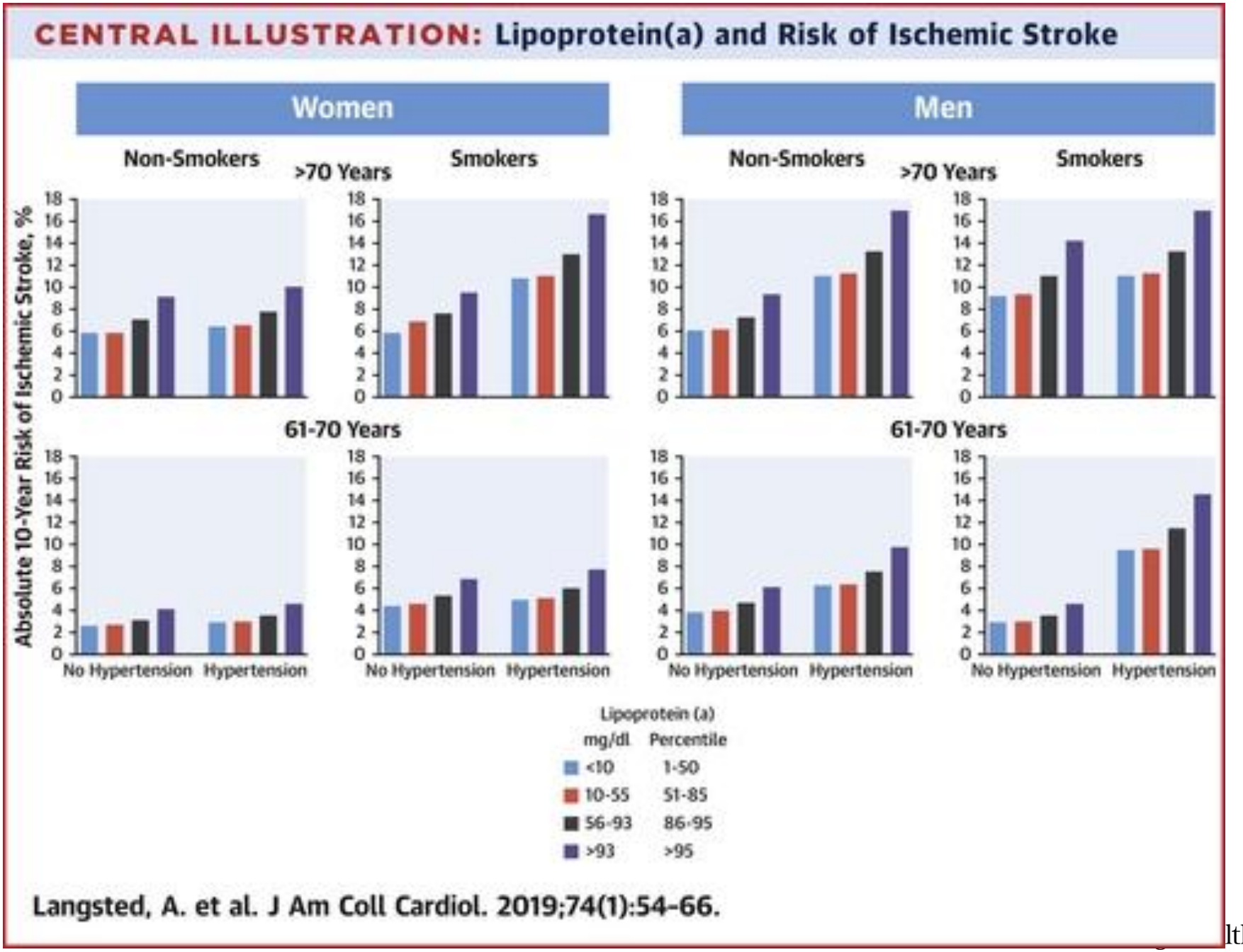
40-50% of patients with cryptogenic stoke have PFO



# Lipoprotein(a)




McNeal CJ, Peterson AL. Lipoprotein (a) in Youth. [Updated 2020 Feb 9]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.;


CENTRAL ILLUSTRATION: Lipoprotein(a) and Risk of Ischemic Stroke
Women
Men
Non-Smokers
>70 Years
Smokers
61-70 Years
Absolute 10-Year Risk of Ischemic Stroke, %
No Hypertension
Hypertension
Lipoprotein (a)
mg/dl
Percentile
<10
1-50
10-55
51-85
56-93
86-95
>93
>95
Langsted, A. et al. J Am Coll Cardiol. 2019;74(1):54-66.

# Don’t forget about Lp (a) in the hypercoagulable work up for Cryptogenic Stroke

## Hypercoagulable workup

- PT and PTT
- Protein C
- Protein S
- Antithrombin III activity
- Prothrombin gene mutations
- Factor V Leiden gene mutation
- Activated Protein C resistance
- Anticardiolipin antibodies (IgG and IgM)
- Beta2-glycoprotein I antibodies (IgG and IgM)
- Lupus anticoagulant tests
  - dilute Russell viper venom time
  - dilute activated PTT
  - hexagonal phospholipid
- Homocysteine
- Factor VIII activity
- D-dimer
- Lipoprotein (a)
- MTHFR

# Conclusions

- Use GLP-1RAs and SGLT2i in patients with diabetes to prevent stroke
- Possible role of GLP1-RA in the acute setting for neuroprotection
- Patients with TIA/Stroke need aggressive LDL lowering
- In patients with carotid stenosis target LDL levels<40 for plaque regression
- Check Lp(a) levels in patients with stroke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