SECONDARY STROKE PREVENTION

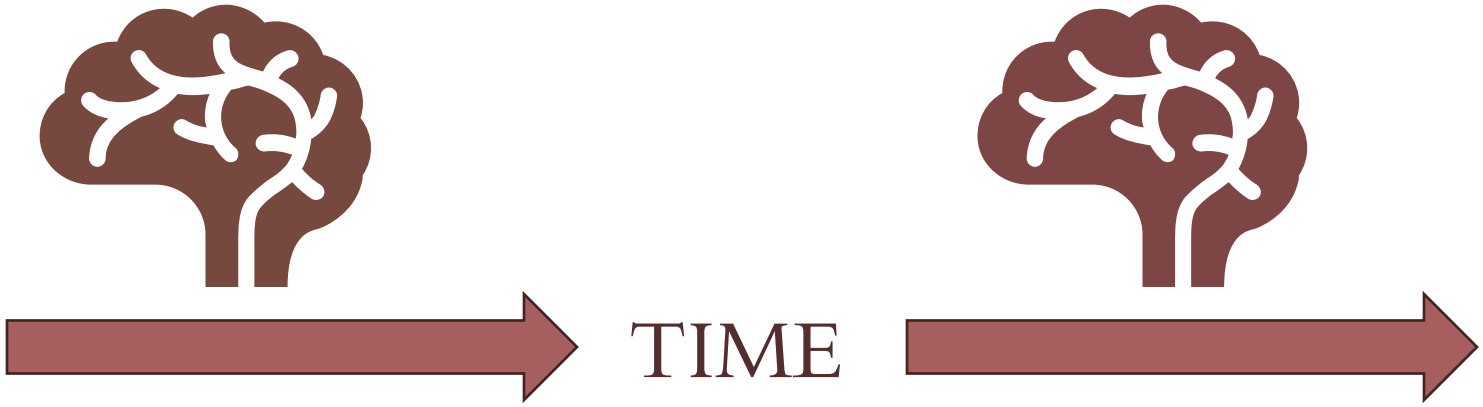
Walter N. Kernan, MD
Emeritus Professor of Medicine
Senior Research Scientist
Yale School of Medicine
May 2025

Disclosures

None

OUTLINE

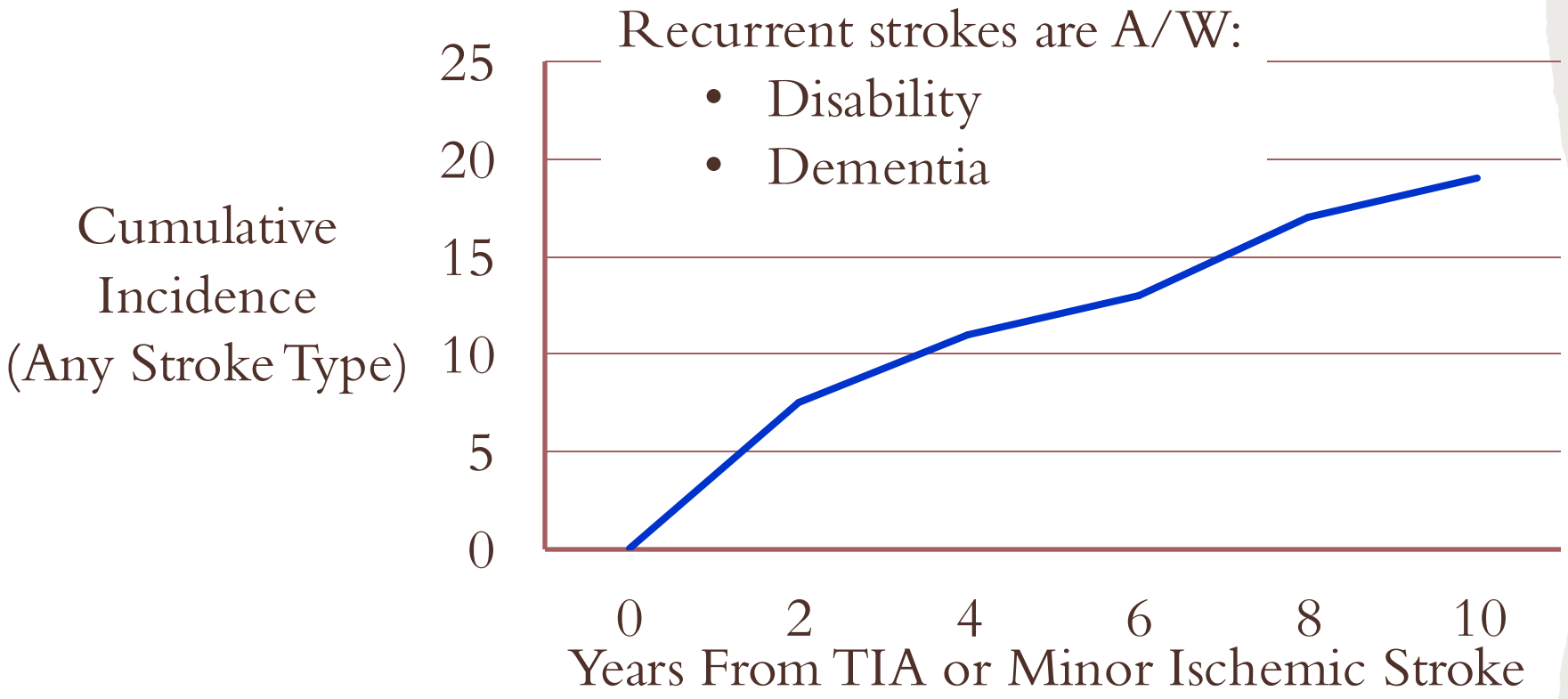
1. General concepts
2. Focus on secondary prevention
   Five specific treatments
3. The quality gap



A first stroke indicates vulnerable brain.

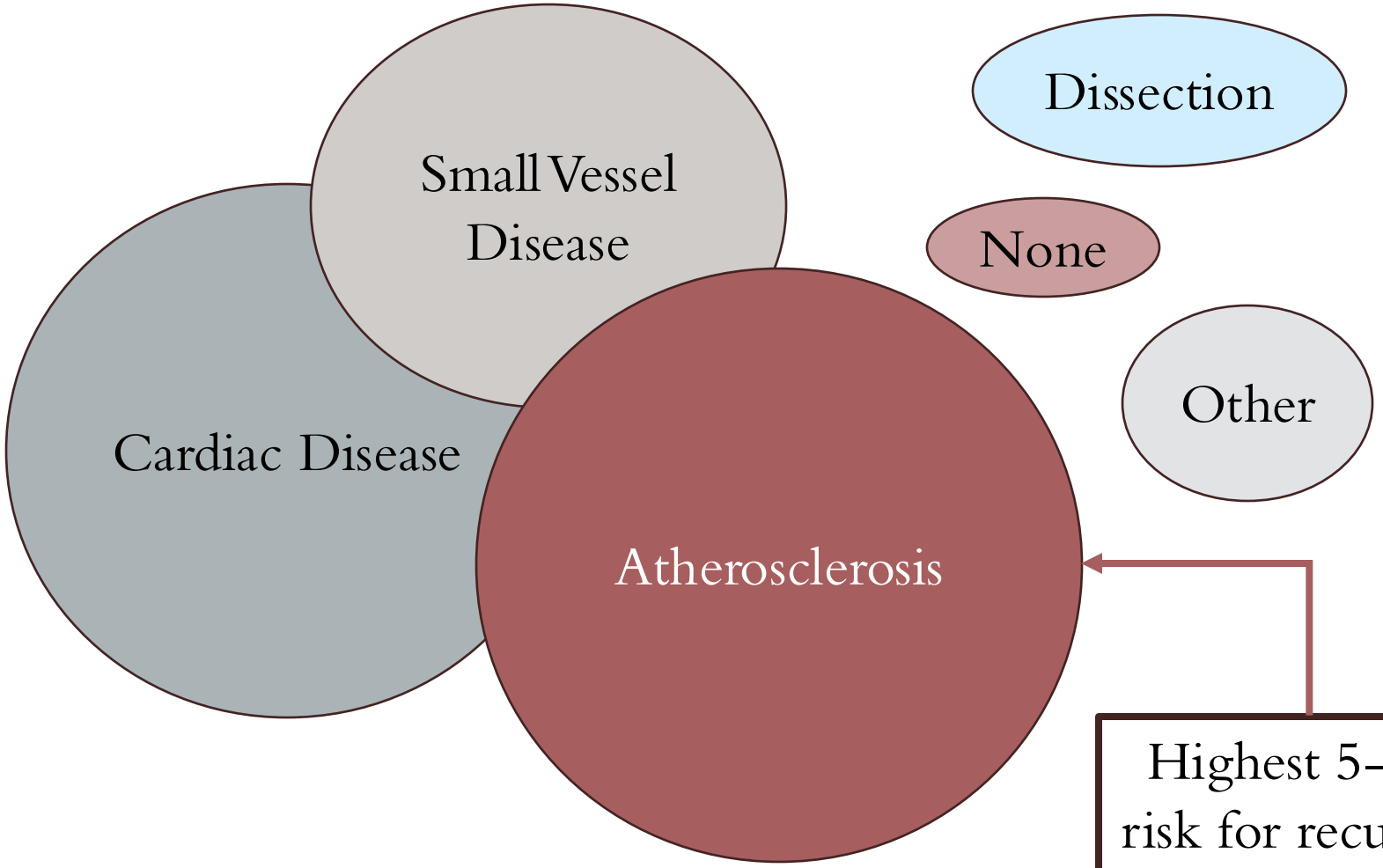
A second indicates vulnerable health care.

RISK OF RECURRENCE AFTER TIA OR MINOR ISCHEMIC STROKE



N Skajaa Neurology 2021; G. Hobeaunu Lancet Neurol 2022;21:889. PERSIST Collaboratiors JAMA 2025; Del Bene JAMA Neuro 2025. RA Joundi Neurology 2024;104:e210131.

PRESUMED CAUSE (ASCOD) DETERMINES 2° PREVENTION



PC Lavallee JAMA Neuro 2023;80:1199

THREE BUCKETS FOR SECONDARY PREVENTION

Therapies for Unusual Causes

- Dissection
- Vasculitis
- FMD
- LVAD
- Melas
- Endocarditis
- More

Therapies for Specific Causes

- Carotid Stenosis
- Atrial Fibrillation
- PFO

Therapies for Risk Factors

- Hypertension
- Diabetes
- Hyperlipidemia
- Obesity
- Smoking
- Nutrition
- Physical Activity


SEALED FOR YOUR PROTECTION
PEEL HERE FOR DRUG FACTS
* Compare to the Active Ingredient in Bayer ®
ASPIRIN
3236 5-10
• Pain Reliever
• Fever Reducer
• Caffeine Free
For the temporary relief from the pain of:
• headache • muscle pain • toothache
• menstrual pain • pain and fever of colds
• minor pain of arthritis
100 TABLETS
325 mg each

DAPT AFTER TIA OR ISCHEMIC STROKE

Inspires Trial 2023

Candidates

- Within 12-72 hours of
- Minor ischemic stroke/high risk TIA
- No indication for anticoagulation
- No plans for revascularization

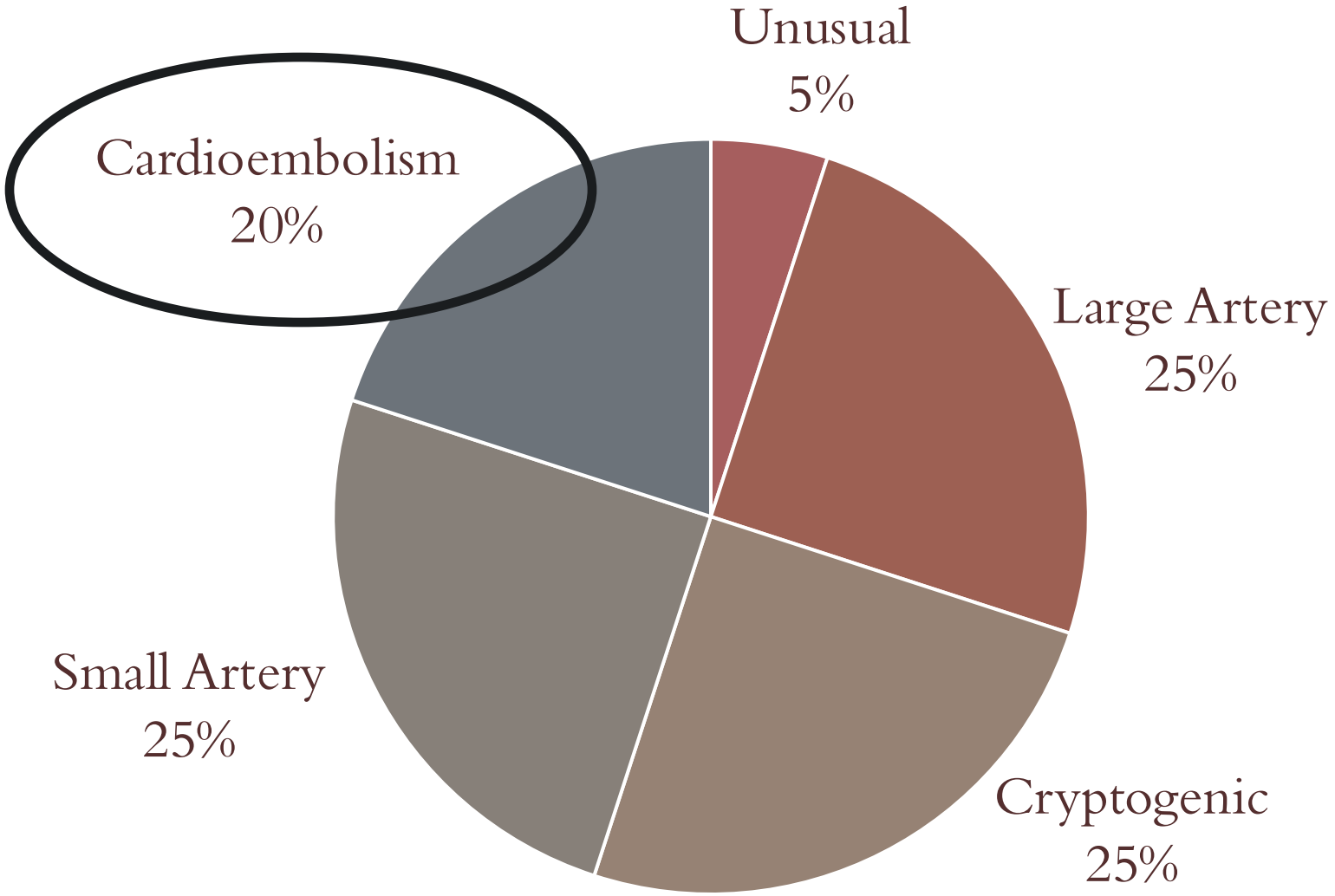
Stop at 21 days

- Then continue single agent
- Exception continue DAPT for 90 days if IC

Consider ticagrelor over clopidogrel, especially if CYP2C19 loss-of-function carrier

Y Wang NEJM 2013;369:11;Y Wang NEJM 2021;385:2520; SC Johnston NEJM 2020;383:207. DO Kleindorfer Stroke 2021;52:e364.Y Gao NEJM 2023;389:2413

ISCHEMIC STROKE ETIOLOGY



RG Hart Lancet Neurology 2014;13:429

AHA GUIDELINE ON AFIB/A FLUTTER IN PATIENTS WITH ISCHEMIC STROKE/TIA

Oral anticoagulation is recommended

Use a factor Xa inhibitor over warfarin

- Exceptions:
  - Severe mitral stenosis
  - Mechanical heart valve
  - Advanced renal disease (apixaban OK)

Start therapy:

Immediately after TIA

Within 2-14 days after minor event

After 14 days if high risk hemorrhagic conversion

LAA closure an option for selection patients

DO Kleindorfer Stroke 2021;52:e364. JA Goglar Circ 2024;149:e1

WHAT IS NEW SINCE 2021?

Earlier initiation of OAC may be considered.

- ELAN Trial: starting OAC within 48 hours of minor/mod stroke and on day 6 or 7 after major stroke "can be supported."★

2023 AHA/ACC atrial fibrillation guideline:

- Extended monitoring after stroke of uncertain cause
- OAC regardless of pattern: paroxysmal, persistent, long-standing, permanent.
- LAAO reasonable for selected persons
- More support for rhythm control & Lifestyle

★Risk recurrent stroke, systemic embolism, major hemorrhage, vascular death w/in 30 d: 2.9% early group, 4.1% later group.

U Fischer NEJM 2023; 388:2411. JA Joglar Circ 2024;149:e1

Should patients with atherosclerosis & stroke related to atrial fibrillation take an antiplatelet agent in addition to oral anticoagulation?*

*Answer: Generally, no except after PCI

S Yasuda NEJM 2019;381:1103; ML Hansen Ann Intern Med 2010;170:1433; JA Joglar circ 2024;149:e1. SS Virani Circ 2023;148:e9. D Ko JAMA 2025;333:329.

~6% of patients on OAC for ischemic stroke related to AF have recurrence by 1 year.

~10% of patients discontinue OAC each year.

Discontinuation increases risk for recurrent stroke (aOR=2.13)

MF Hindsholm JAMA Neurology 2024;81:805. AP Benz EHJ 2023;44:1807

GOALS BP RX AFTER STROKE

AHA/ACC 2018
<130/<80

AHA/ASA 2021
<130/<80

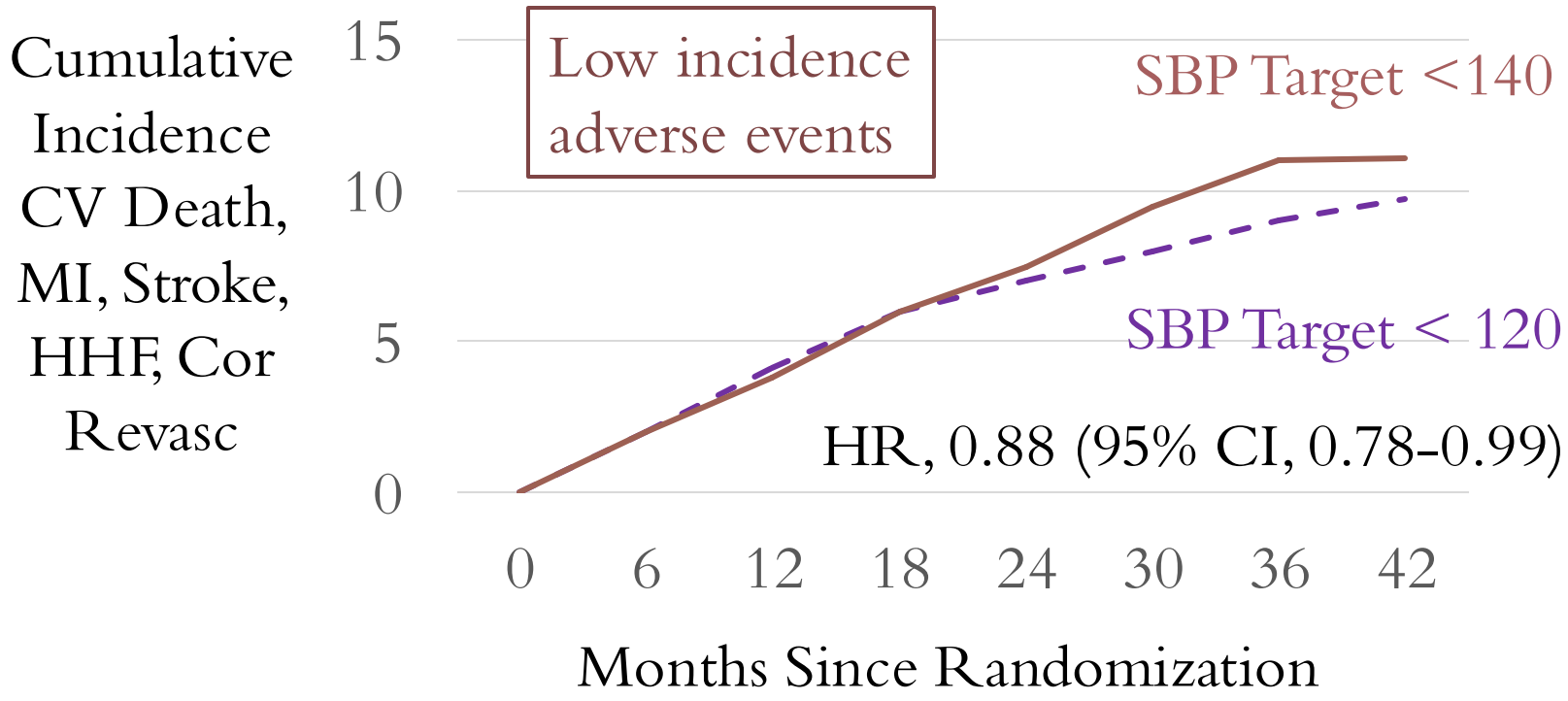
ESC 2024
120-129/70-79

ADA 2025
<130/<80

PK Whelton Hypertension 2018;71:e13. ADA Diab Care 2025;48 (suppl 1):S210. RM Carey Ann Intern Med 2018; 168:351; DO Kleindorfer Stroke 2021;52:e364-467. ESC EJC 2024;45:3912-4018

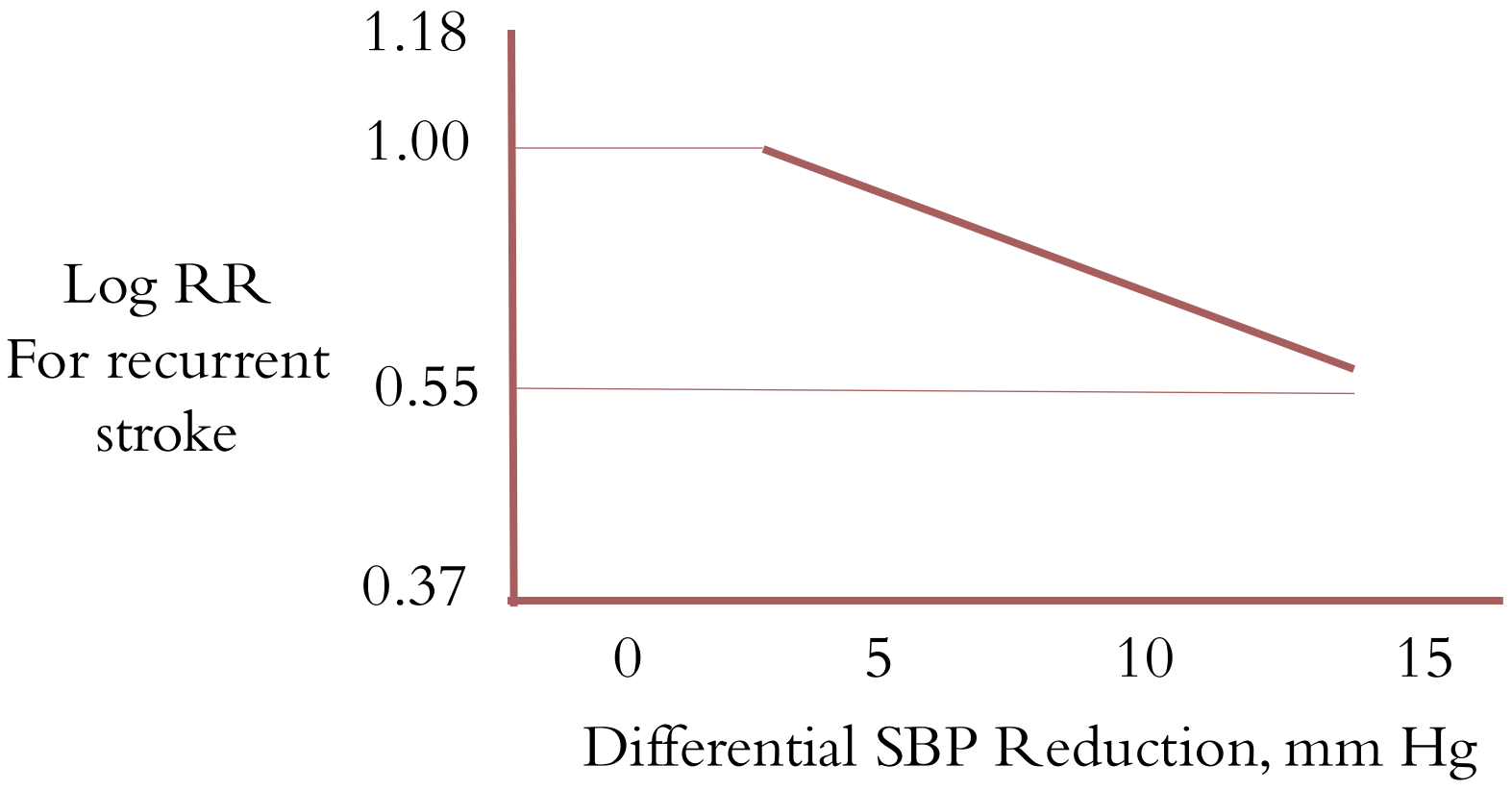
ESPRIT: AN OPEN LABEL TRIAL (N=11255)

Eligibility: ≥ 50 years of age
Average SBP 130-180 mm Hg
Established CVD or ≥2 risk factors
EF ≥35% and eGFR ≥45



J. Liu Lancet 2024. R Kazem Lancet 2024

A META-REGRESSION OF SBP AND RECURRENT STROKE



C-Y Hsu JAMA Neurology 2023;80:506

<40% of patients with stroke have BP <130/80
6 months after hospitalization

R Forman J Hypertension 2025;43:715

WHY ATTEND TO DIABETES IN PATIENTS WITH STROKE?

It affects 30% of patients

It is associated with increased risk for recurrent stroke

Management is highly effective for prevention of vascular events

META-ANALYSIS
GLP1 RA THERAPY TO REDUCE RISK FOR MACE* OR STROKE
(N=8 RCTS)

Outcome	HR	95% CI	P	NNT
MACE*	0.86	0.80-0.93	<0.0001	65
CV Death	0.87	0.80-0.94	0.0010	163
F & NF MI	0.90	0.83-0.98	0.020	175
F & NF Stroke	0.83	0.76-0.92	0.0002	198

*MACE=myocardial infarction, stroke, cardiovascular death

N Sattar Lancet Diab Endo 2021;9:653

BOTTOM LINE: T2D & STROKE

Most patients, especially after ischemic stroke, should be on an SGLTi, a GLP1-RA, or both.

All patients should receive support for guideline-directed risk reduction including:

- Physical activity
- Diet
- Lipids
- Blood pressure
- Smoking
- Sleep

LIPID MANAGEMENT - WHAT'S OLD?

1.
Rx success is LDL <70mg/dL rather than "intensive Rx."

2.
Statins cause muscle symptoms less often than we thought. <u>But</u> Discontinuation remains common (25% in first year)

3.
We have options to get to goal of <70mg/dL

- Moderate dose statin combined with ezetimibe.
- PCSK9 inhibitors (e.g., evolocumab)
- Bempedoeic acid may be an option for patients who do not tolerate statin therapy.

P Amarenco NEJM 2020;382:9. B-K Kim Lancet 2022;400:380. SE Nissan NEJM 2023;388:1353. CTTC Lancet 2022;400:832. S-J Hong JAMA 2023;329:1078. SJ Nicholls JAMA 2024; B Mugawar QJM 2025;118:143. Y Vinagradova BMJ 2016;353:i3305

LIPID MANAGEMENT
WHAT ELSE IS OLD?

3.

A lower LDL target (< 55 mg/dL) may be appropriate for some patients after TIA or ischemic stroke with:

- Recent acute coronary syndrome
- History of MI, PVAD, especially if also:
  - Diabetes mellitus
  - Polyvascular disease (more than one vascular bed)
  - Previous CABG

CP Cannon NEJM 372:2387-97. MS Sabatine NEJM 2017;376:1713-22. RS Rosenson, J Lopez-Sendon. Management of LDL-C in secondary prevention of cardiovascular disease. UpToDate (accessed 5/6/25).

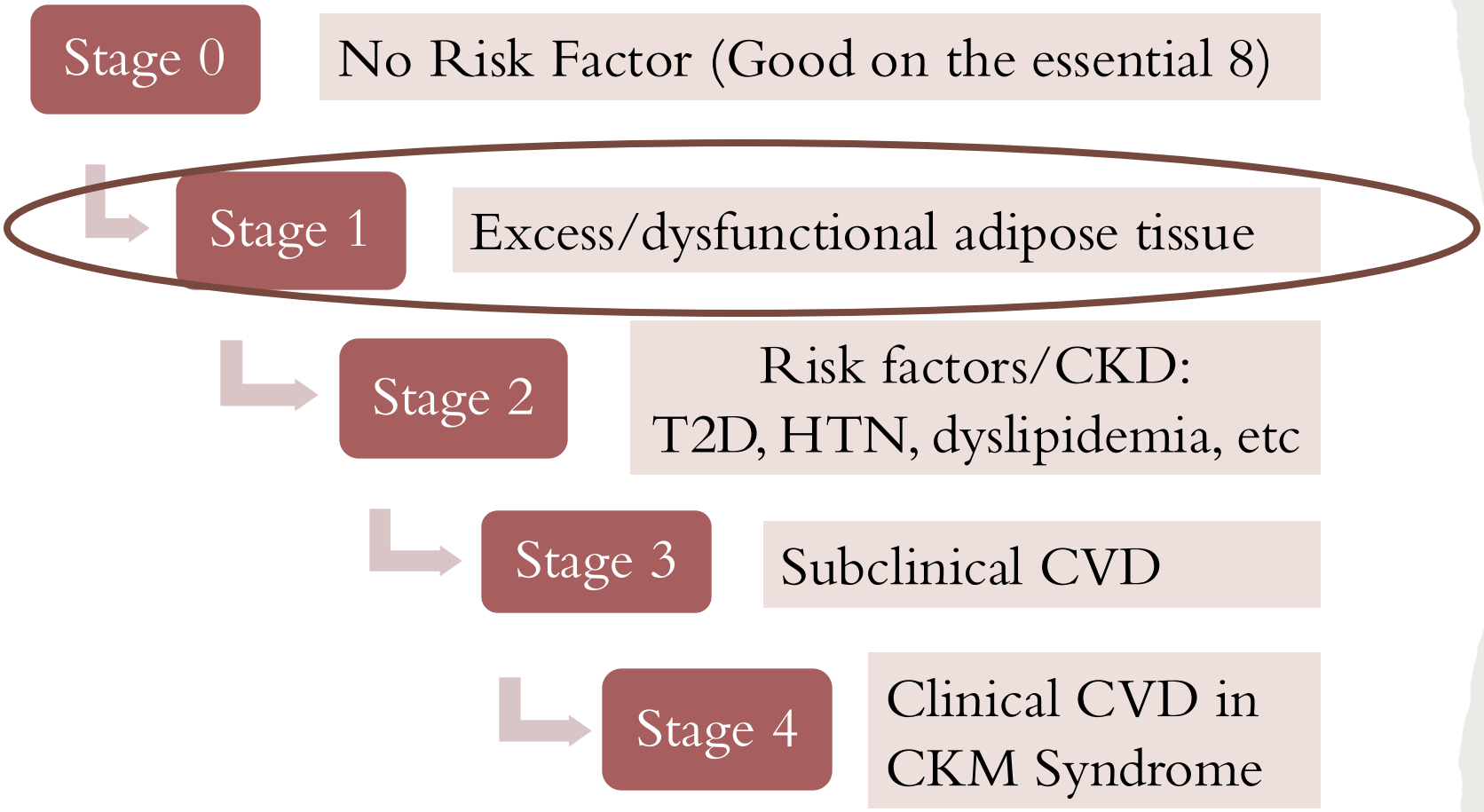
LIPID MANAGEMENT - WHAT'S NEW

1.
Inclisiran (Leqvio): a siRNA molecule directed to PCSK9
FDA approved as adjunct to diet and statin for lowering LDLc (no CVOT published).
Injected every 6 months

2.
Lepodisiran: a siRNA targets hepatic lipoprotein(a) synthesis.
Not FDA approved.
Injected every 6 months
Phase III trial (ACCLAIM-Lp(a) is underway

KK Ray NEJM 2020;382:1507. SE Nissen NEJM 2025;392:1671

CARDIOVASCULAR-KIDNEY-METABOLIC SYNDROME



NC Ndumele Circ 2023;148:1606-1635

OBESITY AFTER STROKE

Question	Answer
Is obesity* in stroke a chronic disease?	Controversial
Should we advise patients with stroke and obesity of the health benefits from achieving a healthy weight?	Yes
Should we assist patients with stroke and obesity to achieve a healthy weight?	Yes
*BMI $\geq$ 30 kg/m^2	

ADA Diabetes Care 2024;47:S145. WT Garvey Endocrine Practice 2016;22 (suppl 3). SZ Yanovski JAMA Int Med 2024; F. Rubino Lancet diabetes endocrinol 2025.

NOT ALL OBESITY IS CAUSING HARM

"Clinical Obesity" present if:

- Evidence of excess adiposity (e.g., BMI ≥30) and
- There is obesity-related organ dysfunction* or
- Limitations of daily activities

*Selected criteria for obesity-related tissue/ organ dysfunction	
Sleep apnea	Cluster of ↑glucose, ↑TG, ↓HDL
HFrEF or HFpEF	MASLD with fibrosis
Atrial fibrillation	Microalbuminuria with ↓eGFR
Pulmonary HTN	Chronic severe hip or knee pain
Hypertension	↓mobility or ADL

F. Rubino Lancet Diab Endocrinol 2025

BENEFICIAL EFFECTS OF WEIGHT LOSS

↓ Blood Pressure	↑ Insulin sensitivity
↓ CRP	↓ Triglyceride
↓ Glucose	↑ HDL

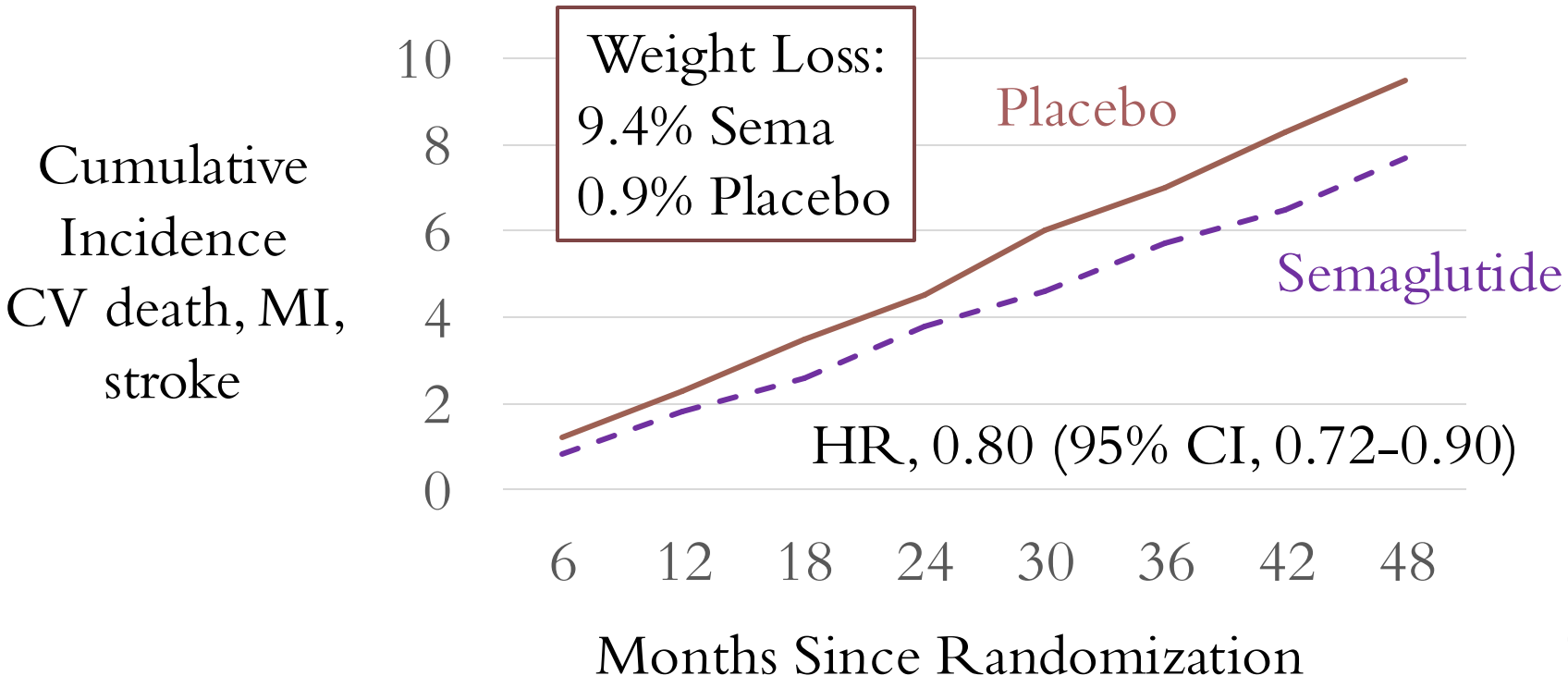
- Effects are proportional to weight loss
- Minimal beneficial loss ≈ 5%

JB Dixon JAMA 2008;299:316-323; ME Lean Lancet 2018;391:403; K KF Petersen Diabetes;54:603; DPP Research Gp Lancet 2009;374::1677-86; JPH Wilding NEJM 2021;

SELECT TRIAL

18% of participants

Eligibility: ≥ 45 years of age
BMI ≥ 27 kg/m^2
Established CVD (MI, stroke, PAD)
No diabetes, ESKD, or CHF



AM Lincoff NEJM 2023;389:2221

PROPORTION OF PATIENTS AT GOAL FOR 2°PREVENTION A FEW YEARS AFTER STROKE*

On antiplatelet
98%

Not Smoking
84%

On Statin Therapy
≤70%

On OAC
80%

BP < 140/90
≤75%

On GLP1 or SGL2i
30%

BMI <30 kg/m^2

*if eligible for the therapy

AC Stuart SVN 2016; 1:108. J Aivo Stroke 2023;54:781. DM Bravata 2018;75:419. RD Lopes Stroke 2011;42:3477. C-E Lim EJPC 2023. J Aivo Stroke;2023:781.

WHAT WE HAVE COVERED

- Dual antiplatelet therapy
- OAC for atrial fibrillation
- Hypertension
- Diabetes
- Lipids
- Obesity

See ‘em soon

See ‘em often

Get ‘em to goal
(guideline directed therapy)

WN Kernan Stroke 2021;52:e558

END

Thank You

Walter Kernan
Yale School of Medicine
Walter.kernan@yale.edu