Corewell Health™

Comorbid Conditions in Stroke: Impact and Management

Presented by Macy Shupp and Brent Zahn

Topics Covered

- Hyperlipidemia
- Hypertension
- Heart Failure
- Anemia
- Depression
- Dementia

For each topic we will cover:

- Prevalence
- Screening
- Impact
- Management

Corewell Health™

Hyperlipidemia

Hyperlipidemia: Prevalence

-Approximately 55% of acute ischemic stroke (AIS) patients present with dyslipidemia defined by elevated LDL, triglycerides, or low HDL based on a 2020 cross-sectional study of 200 ischemic stroke patients

-Epidemiological data consistently show a direct association between higher total and LDL cholesterol levels and increased ischemic stroke risk, particularly for large artery atherosclerotic strokes.

-From 1999 to 2023, age-adjusted stroke mortality among U.S. adults with hyperlipidemia rose sharply from 1.38 to 7.46 per 100,000 reflecting the growing impact of dyslipidemia as a driver of ischemic stroke.

-A 2025 topical review in *Stroke* emphasizes that elevated LDL and total cholesterol are strong, modifiable risk factors for ischemic stroke, reinforcing the need for aggressive lipid management in AIS prevention.

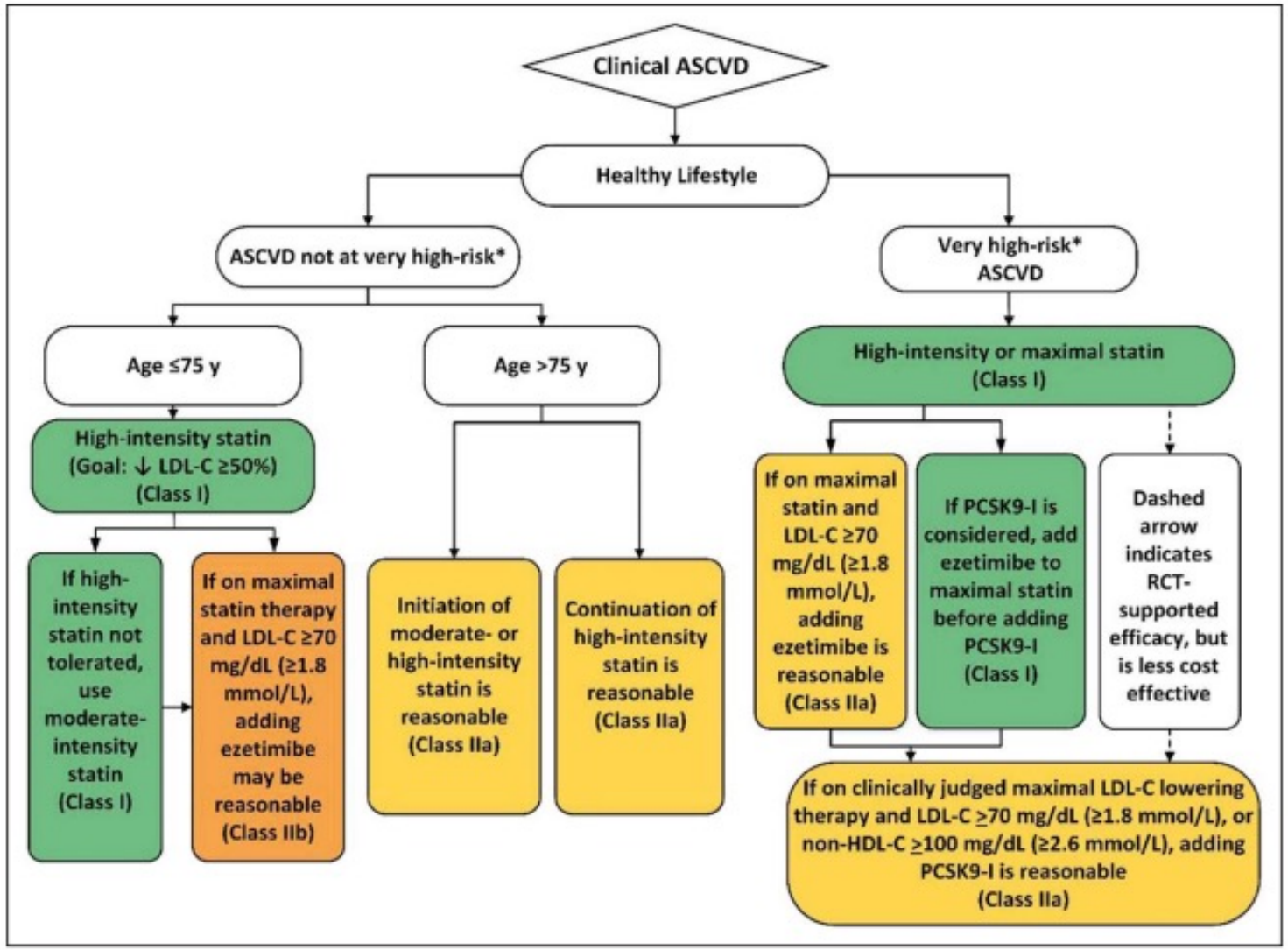
Hyperlipidemia: Risk

- Elevated LDL-C is a major risk factor for ischemic stroke: Higher LDL cholesterol levels significantly increase the risk of atherosclerotic cardiovascular disease (ASCVD), including ischemic stroke, due to plaque formation and arterial narrowing.
- Hyperlipidemia contributes to recurrent stroke risk: Patients with prior ischemic stroke or TIA are considered very high-risk ASCVD; aggressive LDL-C lowering (<70 mg/dL) is recommended to reduce recurrence and overall vascular events.

Table 4. Very High-Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation[54.1-40])
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)[54.1-15,54.1-17]
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

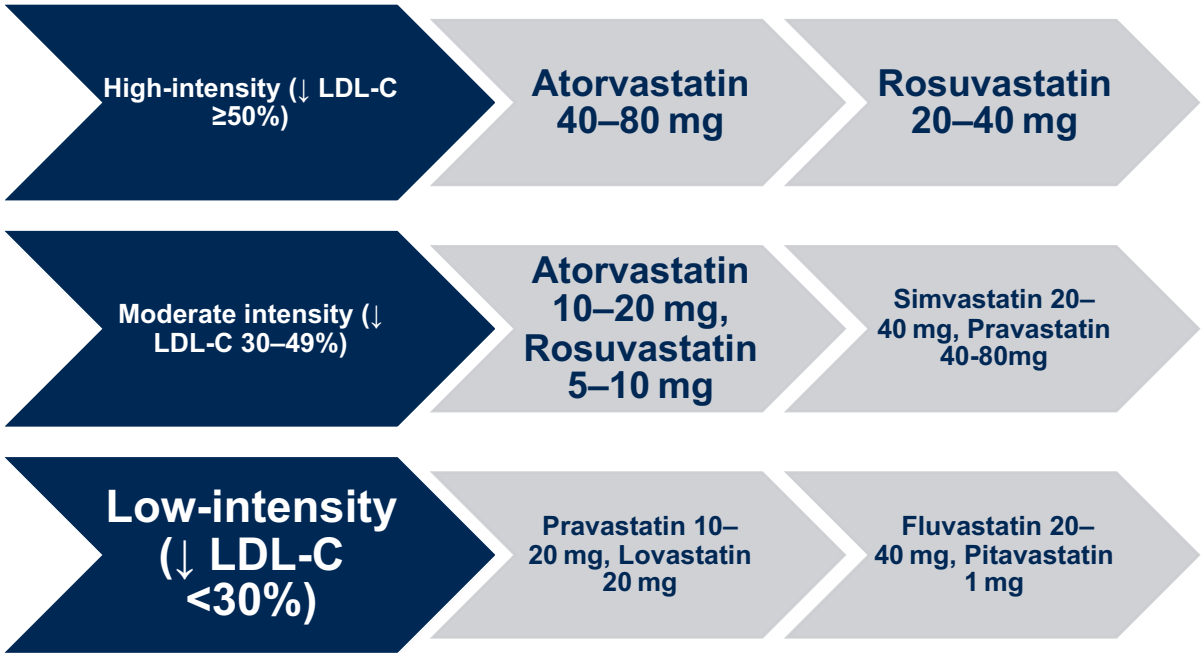
Hyperlipidemia



Hyperlipidemia: Lifestyle Modifications

Adopt	Engage in	Weight	Avoid
Heart-healthy diet: Adopt a diet rich in vegetables, fruits, whole grains, legumes, nuts, and fish while limiting saturated fats, trans fats, sodium, and added sugars.	Regular physical activity: Engage in at least 150 minutes per week of moderate-intensity aerobic exercise or 75 minutes of vigorous activity, plus muscle-strengthening activities.	Weight management: Achieve and maintain a healthy body weight to improve lipid profile and reduce cardiovascular risk.	Avoid tobacco and limit alcohol: Complete smoking cessation and moderation of alcohol intake are strongly advised.

Hyperlipidemia: Oral Medications



Non-Statin Oral Therapies

Ezetimibe

- Recommended as first add-on if LDL-C remains ≥70 mg/dL on maximally toleratedstatin, especially post-acute ischemic stroke or clinical ASCVD
- Bile Acid Sequestrants
  - May be considered (e.g., cholestyramine, colesevelam) when LDL-C targets not metwith statin + ezetimibe – though less commonly used
- Fibrates & Niacin
  - Not routinely recommended as LDL-C lowering agents; may be used in select patientswith severe hypertriglyceridemia, but no significant stroke prevention benefit per guidelines

Stroke-Specific Context (Primary & Secondary Prevention)

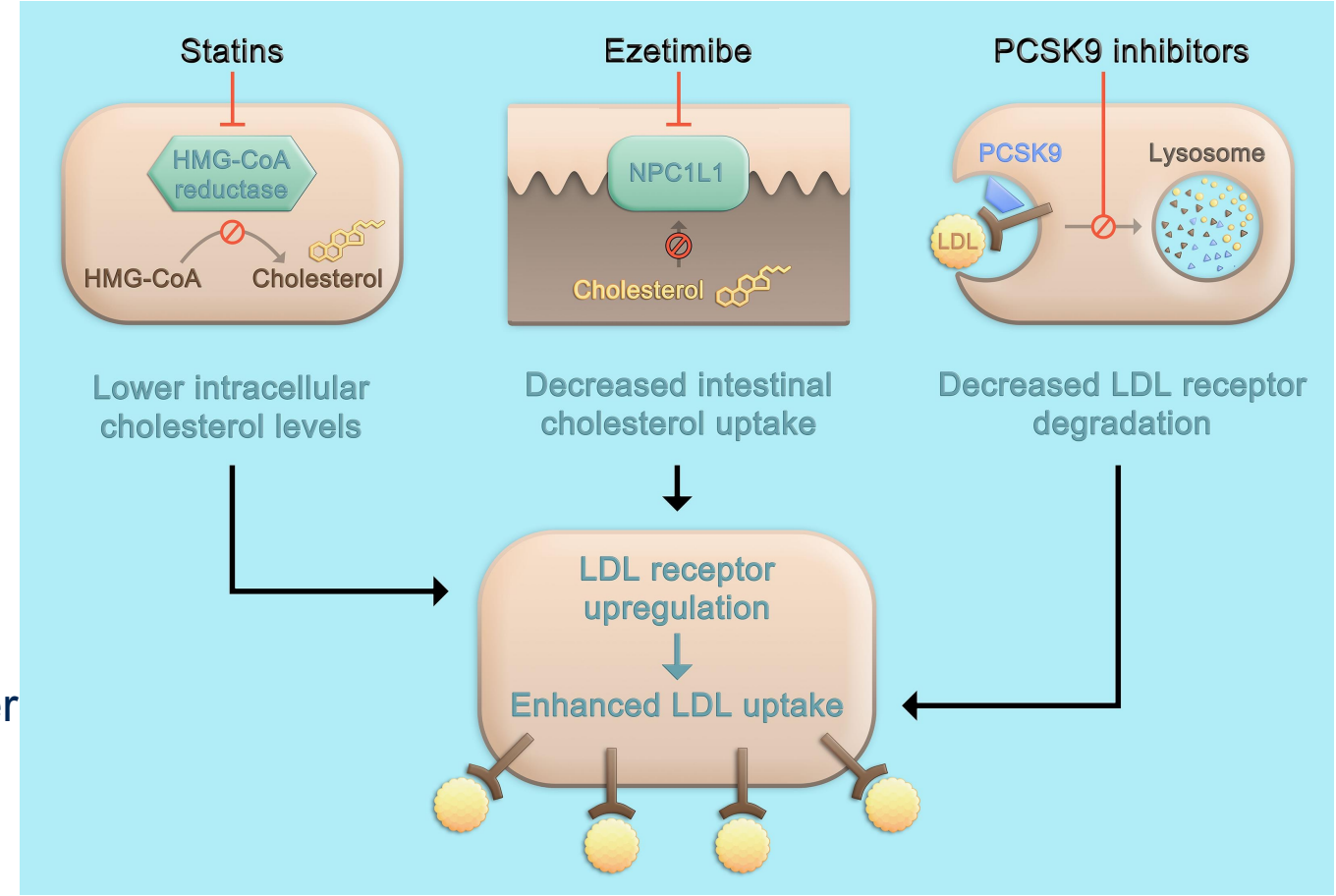
- From the 2021 AHA/ASA Stroke Prevention Guideline:
- Atorvastatin 80 mg daily is the preferred high-intensity statin for AIS patients to achieve LDL-C <70 mg/dLIf LDL-C remains >70 mg/dL on maximally tolerated statin,
- Add ezetimibe, and if still uncontrolled, consider a PCSK9 inhibitor

Statins

- Inhibit HMG-CoA reductase
  - Decreased cholesterol synthesis
  - Increased LDL receptor expression
  - Increased LDL clearance

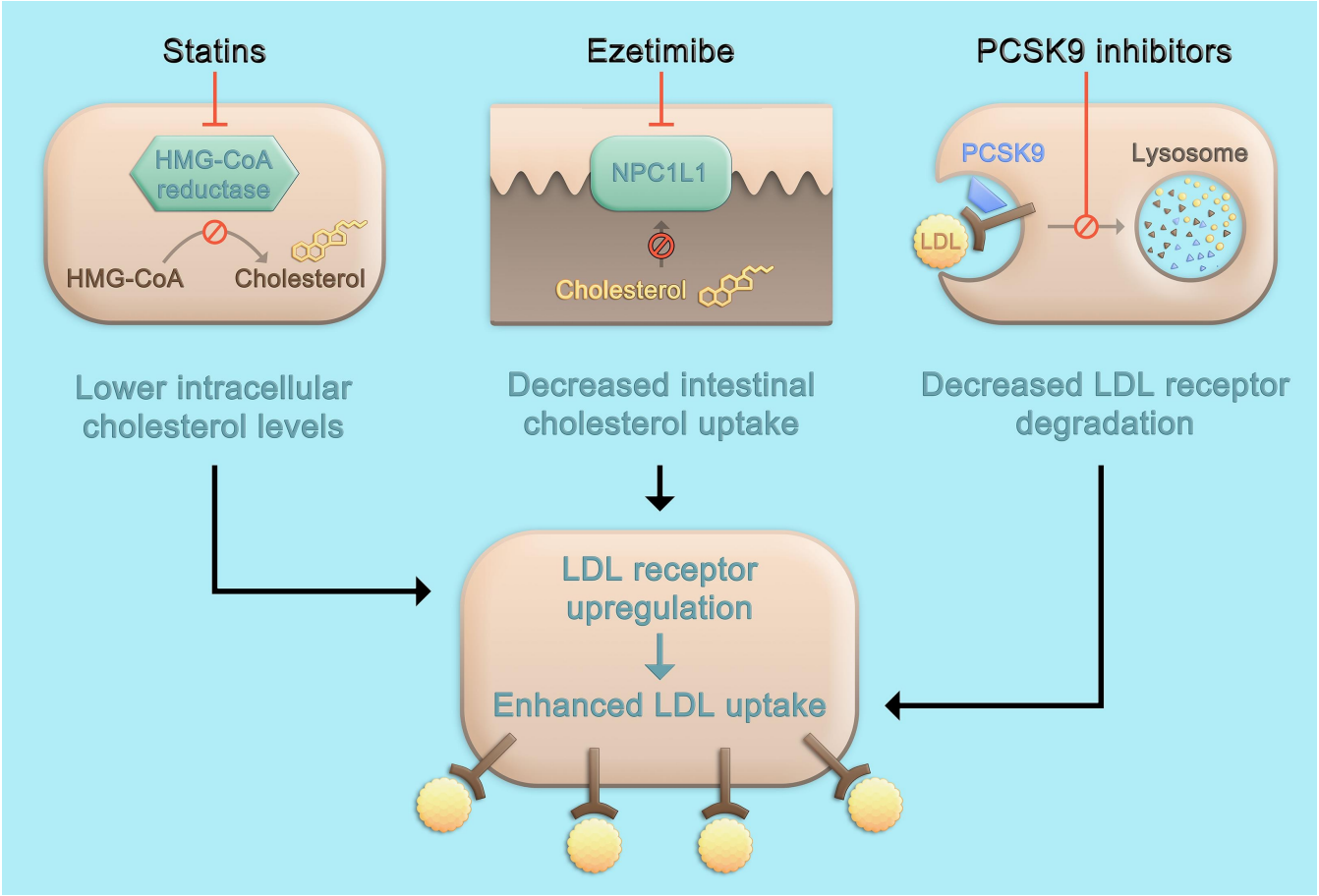
Post ischemic stroke

- High intensity statin recommended to reduce recurrence risk
  - ≥ 75 moderate/high intensity
- Pearls
  - Statins contraindicated with significant liver disease
  - Can cause rhabdomyolysis
  - Decreases LDL ~50%



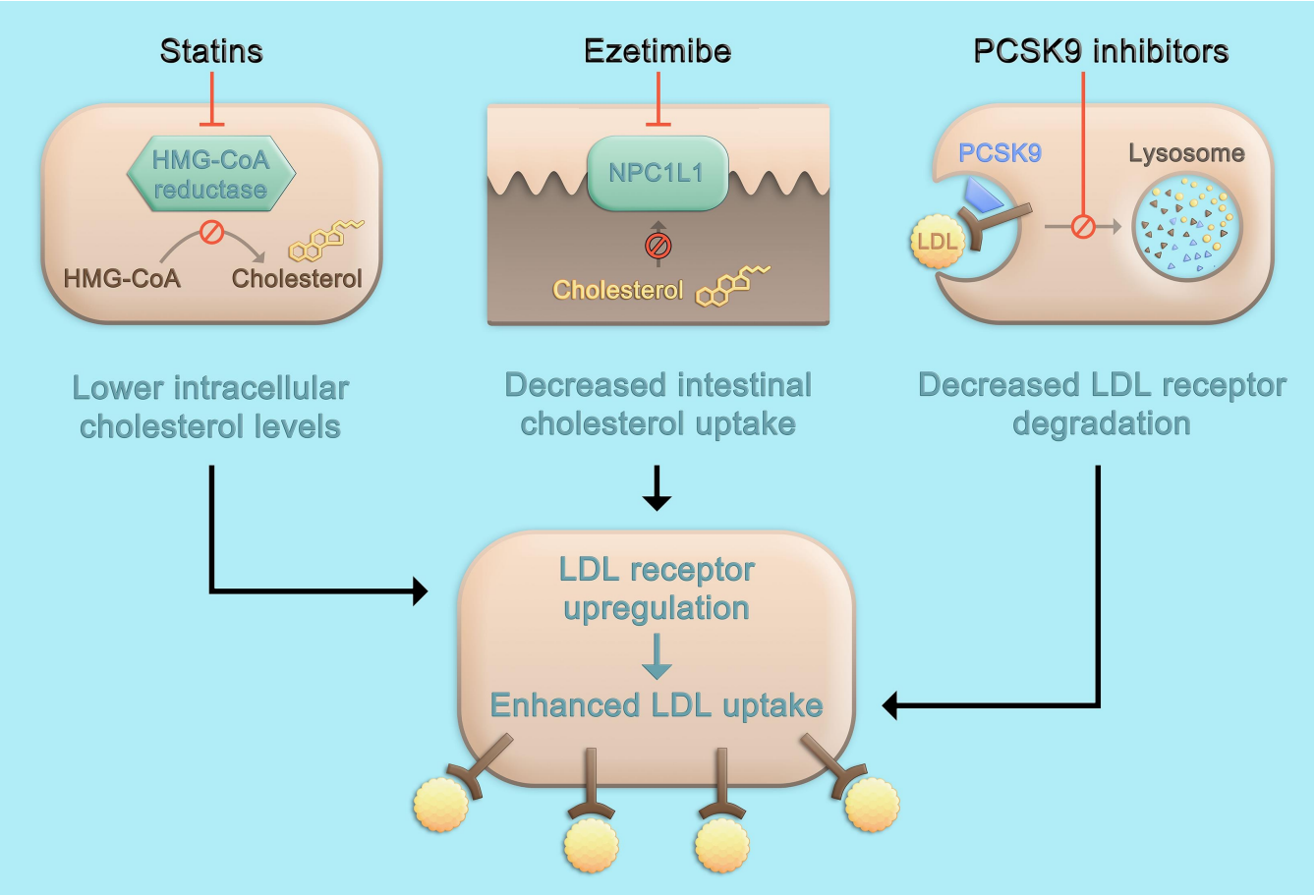
Ezetimibe

- Inhibits NPC1L1 transporter in small intestine
  - Decreases intestinal absorption of cholesterol
  - Decreased hepatic cholesterol stores
  - Increases LDL receptor expression
- When to add:
  - LDL goal not achieved with statin alone
- Pearls
  - Decreases LDL ~18-25%
  - Minimal side effects
  - Reduced CV events when in combination with a statin



PCSK9 Inhibitors

- Block PCSK9 preventing degradation of LDL receptors
  - Increased receptors on hepatocytes > increased LDL clearance
- When to add to therapy:
  - On maximally tolerated statin ± ezetimibe
  - Persistently elevated LDL despite adequate therapy
- Pearls:
  - Alirocumab and evolocumab- every 2-4 weeks
  - Inclisarin- every 6 months
  - ~15% relative risk reduction in major cardiovascular events
  - Decreases LDL ~50-65%



Corewell Health™

Hypertension

Corewell Health™

Hypertension: Prevalence

-Nearly 47.7% of U.S. adults have hypertension (BP ≥130/80 mm Hg or taking antihypertensive medication) based on data from August 2021–August 2023, making it one of the most prevalent risk factors for stroke and cardiovascular disease.

-Hypertension is the most potent modifiable risk factor for stroke, contributing to approximately 14% of cardiovascular deaths in the U.S. second only to coronary heart disease and significantly raising the risk of both ischemic and hemorrhagic stroke.

-For every 10 mm Hg reduction in systolic blood pressure, risk of stroke decreases by about 27%, underscoring the critical importance of BP control for stroke prevention as emphasized in the 2025 ACC/AHA hypertension guideline.

-Among adults with hypertension, more than one-third are unaware of their condition, and only about 20.7% have their BP controlled to <130/80 mm Hg, highlighting a significant gap in hypertension management and stroke prevention.

Hypertension

- **Hypertension is the strongest modifiable risk factor for stroke**: Both ischemic and hemorrhagic stroke risk rises steeply with elevated blood pressure, as emphasized in AHA/ASA stroke prevention guidelines.
- **Risk increases progressively with higher systolic and diastolic BP**: Even prehypertension (≥120/80 mm Hg) is associated with increased stroke risk compared to normotension.
- **Effective BP control significantly reduces stroke incidence**: Lowering systolic BP by 10 mm Hg can reduce stroke risk by about 27%, according to ACC/AHA hypertension management recommendations.
- **Target BP <130/80 mm Hg** for most patients with prior ischemic stroke or TIA, provided therapy is well tolerated.
- Initiate or resume **antihypertensive treatment within days after an acute ischemic stroke** (once neurologically stable) to reduce risk of recurrent stroke and other vascular events.

Hypertension: Lifestyle Modifications

- **Healthy Diet**:
  - Adopt a diet rich in fruits, vegetables, whole grains, legumes, nuts, and fish.
  - Limit saturated fats, trans fats, sodium, and added sugars.
  - Dietary patterns such as DASH or Mediterranean diet are strongly recommended.
- **Regular Physical Activity**:
  - At least 150 minutes/week of moderate-intensity aerobic activity or 75 minutes/week of vigorous activity, plus muscle-strengthening exercises.
- **Weight Management**:
  - Achieve and maintain a healthy BMI to reduce blood pressure, improve lipid profile, and lower stroke risk.
- **Smoking Cessation & Alcohol Moderation**:
  - Complete avoidance of tobacco products.
  - Limit alcohol intake (≤2 drinks/day for men, ≤1 drink/day for women).
- **Stress Management & Adequate Sleep**:
  - Behavioral interventions and good sleep hygiene are encouraged for overall cardiovascular health.

Hypertension: Oral Medications

Blood Pressure Goal for Secondary Stroke Prevention

- Target: <130/80 mm Hg (AHA/ASA 2021 guideline)
- Initiate or resume therapy within days after acute ischemic stroke once neurologically stable.

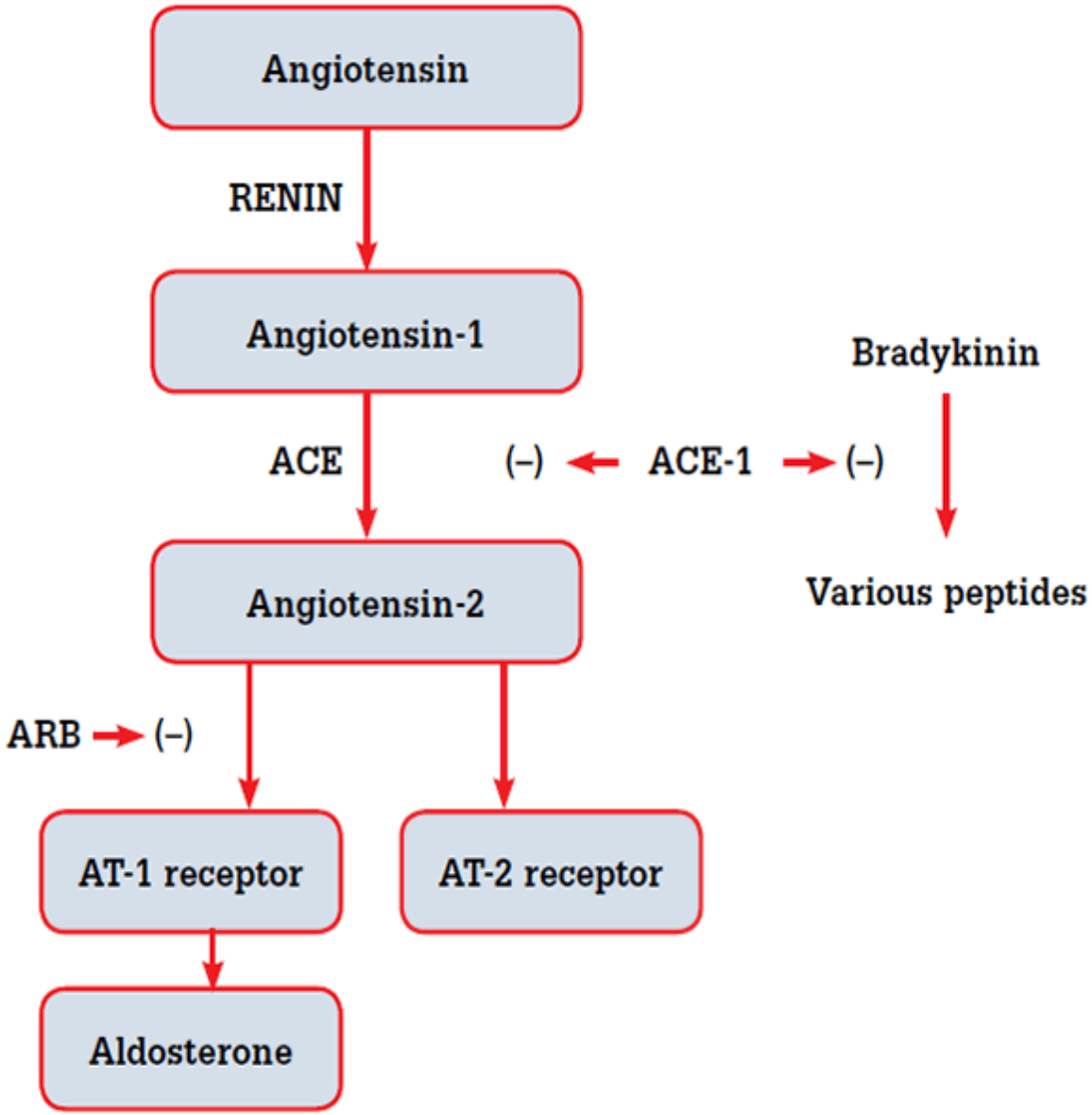
Preferred Antihypertensive Classes in Stroke

Class	Examples	Stroke-Specific Notes
Thiazide Diuretics	Chlorthalidone 12.5–25 mg daily, Hydrochlorothiazide 12.5–25 mg daily	Strong evidence for reducing recurrent stroke risk; often part of combination therapy
ACE Inhibitors	Lisinopril 10–40 mg daily, Enalapril 5–20 mg daily	Preferred in combination with thiazide for secondary prevention
ARBs	Losartan 50–100 mg daily, Valsartan 80–320 mg daily	Alternative if ACE inhibitor not tolerated
Calcium Channel Blockers (DHP)	Amlodipine 5–10 mg daily, Felodipine 5–10 mg daily	Useful as add-on therapy for BP control

- Combination therapy (e.g., ACE inhibitor + thiazide) is often required to achieve BP <130/80 mm Hg.
- Beta-blockers are not first-line for stroke prevention unless another indication exists (e.g., heart failure, post-MI).
- Lifestyle modification remains essential alongside pharmacologic therapy.

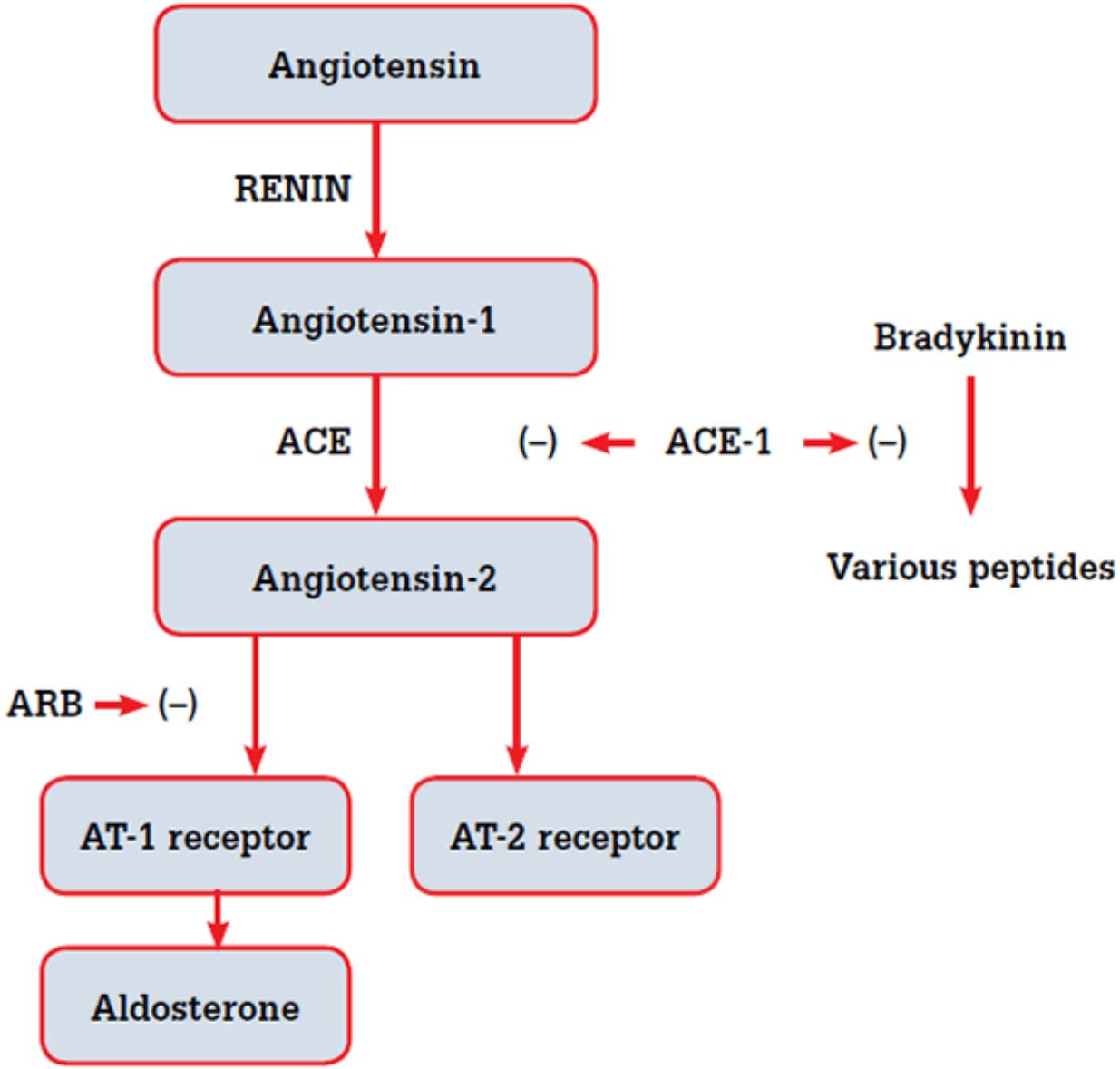
ACE Inhibitors

- Common medications: lisinopril, enalapril
- Inhibits conversion of angiotensin-1 to angiotensin-2
    - Increased blood vessel dilation
    - Lower blood pressure
    - Decreased fluid volume
- When to add
    - First line for patients with comorbidities of:
        - Diabetes
        - Chronic kidney disease
        - High ASCVD risk
    - Previous stroke
        - Improves blood pressure control and vascular risk reduction
- Pearls:
    - Common adverse events
        - Cough
        - Hyperkalemia
        - Angioedema (rare)
    - Can be used in combination with other agents (thiazide or CCB)



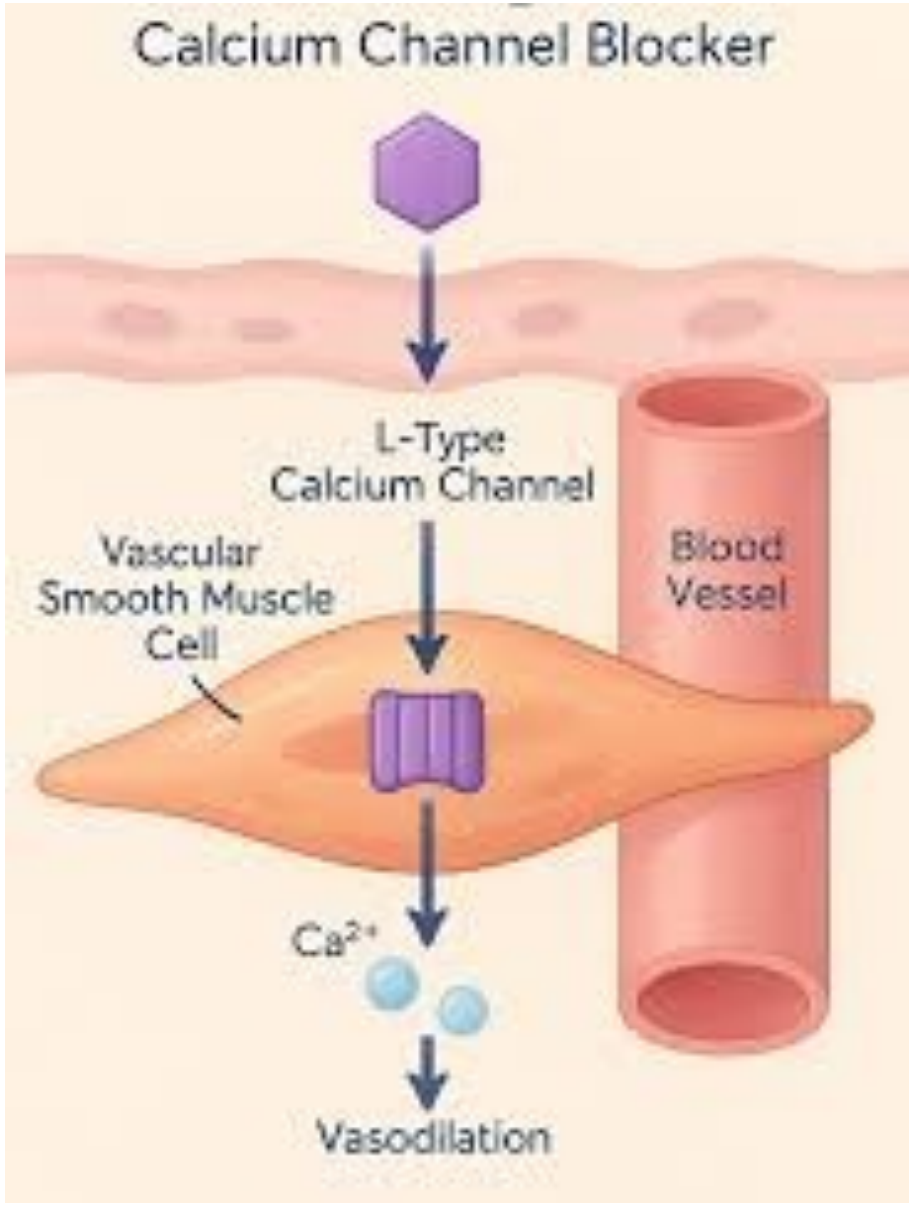
ARBs

- Common medications: losartan, valsartan
    - Previous stroke
        - Improves blood pressure control and vascular risk reduction
- Blocks angiotensin-2 from binding to AT-1 receptor
    - Prevents vasoconstriction= relaxed blood vessels
- When to add:
    - Previous stroke
        - Improves blood pressure control and vascular risk reduction
        - Patients allergic or intolerant to ACE inhibitors
- Pearls:
    - Avoid in pregnancy and bilateral renal stenosis
    - Adverse effects: hyperkalemia, hypotension (less cough than ACE inhibitors)
    - Can be used in combination with other agents (thiazide or CCB)



Calcium Channel Blockers

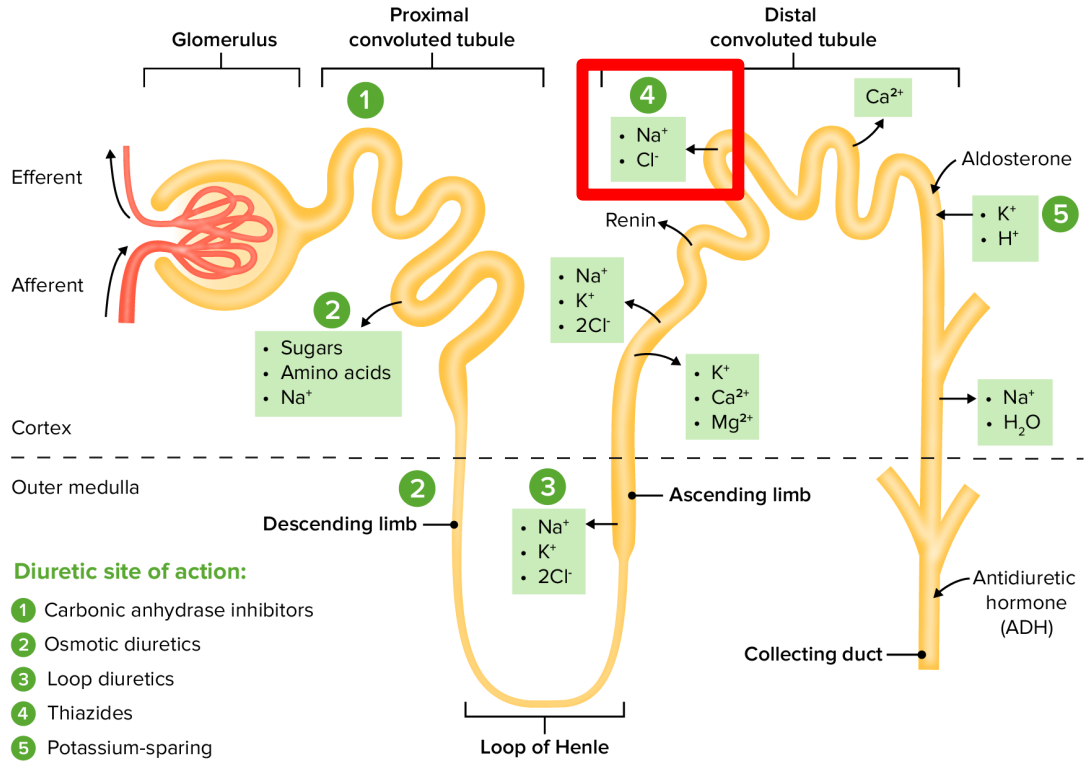
- Common medications: amlodipine, nifedipine
- Blocks L-type calcium channels
  - Decreases calcium influx into vascular smooth muscle and myocardium
  - Increases vasodilation decreasing blood pressure
- When to add:
  - Blood pressure control when ACE/ARB is not tolerated
- Pearls:
  - Can cause side effects of edema(swelling), flushing, or headache
  - Can be combined with ACE/ARB and thiazide for control



Thiazide Diuretics

- Common medications: Hydrochlorothiazide (HCTZ), chlorthalidone
- Inhibit Na/Cl symporter in distal convoluted tubule of kidney
- Increases sodium and water excretion > decreased plasma volume> decreased blood pressure
- When to add:
- BP control as part of a multi-drug regimen

- Pearls:
- Adverse effects: hypokalemia, hyponatremia
- Monitor electrolytes
- Often used in combination with ACE/ARB and CCB



Corewell Health™

Heart Failure

Heart Failure: Prevalence

-Heart failure affects about 6.7 million U.S. adults and is projected to rise to over 8 million by 2030, according to AHA Heart Disease and Stroke Statistics .

-HF significantly increases ischemic stroke risk, particularly in patients with reduced ejection fraction and concurrent atrial fibrillation, as noted in AHA/ASA stroke prevention guidelines .

-Annual stroke incidence in HF patients without AF is ~1–2%, but rises to 4–5% with AF, highlighting the additive risk of arrhythmia .

-Guidelines recommend aggressive management of vascular risk factors (BP <130/80 mm Hg, statin therapy for ASCVD, anticoagulation if AF present) to reduce stroke risk in HF patients .

Heart Failure: Lifestyle Modifications

- **Sodium Restriction**
  - Limit sodium intake to <2–3 grams/day to reduce fluid retention and congestion.
- **Fluid Management**
  - For patients with advanced HF or hyponatremia, consider fluid restriction to ~1.5–2 liters/day.
- **Weight Monitoring**
  - Daily weight checks to detect early fluid accumulation; report weight gain of ≥2–3 lbs in 24 hrs or ≥5 lbs in a week.
- **Physical Activity**
  - Regular aerobic exercise (walking, cycling) is recommended for stable HF patients to improve functional capacity.
  - Avoid strenuous activity during decompensation.
- **Alcohol & Tobacco**
  - Avoid alcohol (especially in alcoholic cardiomyopathy) and complete smoking cessation.
- **Diet Quality**
  - Emphasize heart-healthy diet (DASH or Mediterranean): fruits, vegetables, whole grains, lean proteins, low saturated fat.
- **Weight Control**
  - Maintain healthy BMI; obesity and cachexia both worsen HF outcomes.
- **Vaccinations**
  - Annual influenza and pneumococcal vaccines recommended.

Heart Failure: Oral Medications

Key medications in Heart Failure		
ACE/ARB/ARNI	Lisinopril, losartan Entresto (sacubitril/valsartan)	ACEi (e.g., lisinopril) or ARB if ACE not tolerated ARNi (sacubitril/valsartan) preferred for HFrEF
Beta-Blockers	Metoprolol, bisoprolol, carvedilol	Improve survival & reduce hospitalizations in HFrEF
Mineralocorticoid Receptor Antagonists (MRA)	Spironolactone or eplerenone	Recommended in symptomatic HFrEF to reduce mortality
SGLT2 inhibitor	Dapagliflozin, empagliflozin	Reduce HF hospitalizations, CV death, and aid in post-stroke cardiovascular risk reduction
Diuretics	furosemide	volume overload symptom control

Post-Stroke Diabetic & HF Patients

- SGLT2 inhibitors beneficial across HF spectrum and linked to reduced recurrent stroke/CV events

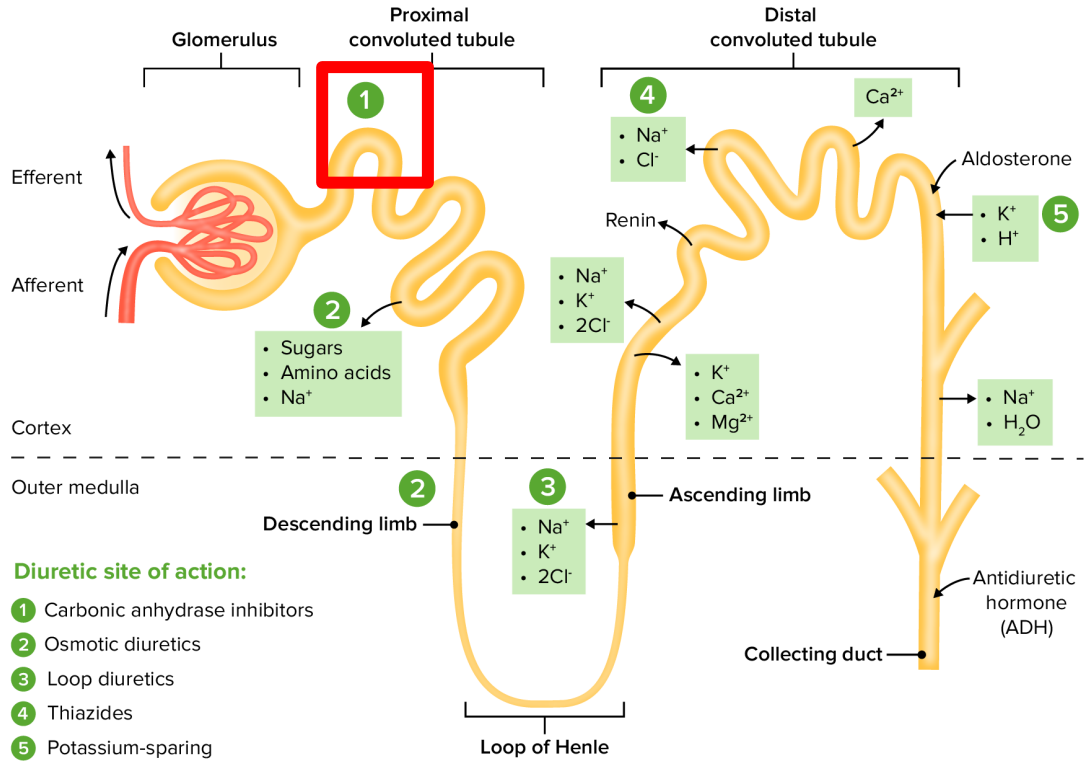
Hypertensive Stroke Patients

- RAS blockade (ACEi/ARB) favored for BP control and secondary stroke prevention

SGLT2 Inhibitors

- Common medications: Farxiga, Jardiance
- Inhibit renal SGLT2 in proximal tubules → promote glucosuria & natriuresis.
- When to add:
    - Recommended for HFrEF (EF ≤40%) and HFpEF (EF >40%), whether diabetic or not

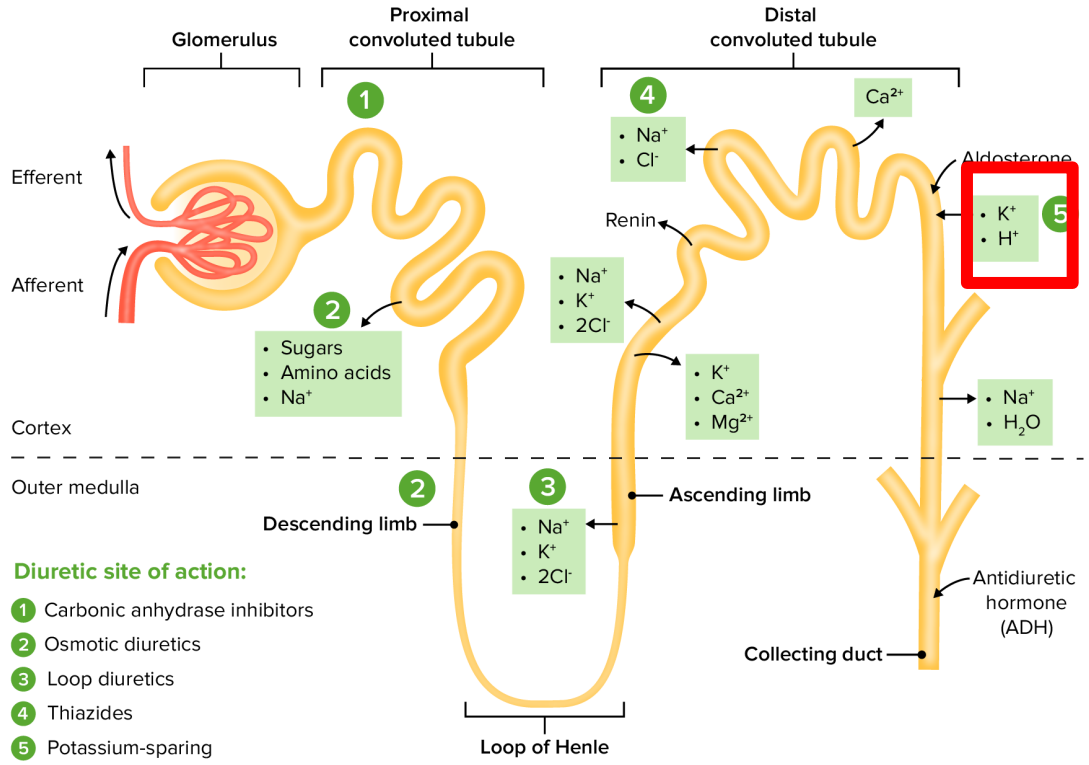
- Pearls:
- Adverse effects: Euglycemic DKA, UTI
    - ↓ hospitalizations, ↓ CV mortality, renal benefits across all HF stages
    - Genital infections (candidiasis) are common; rare risk of euglycemic DKA



Mineralocorticoid Receptor Antagonist

- Common medications: Spironolactone, Eplerenone
- Competitively blocks aldosterone receptors in the distal nephron, reducing expression of aldosterone-induced proteins (e.g., ENaC and Na^+/K^+-ATPase)
- Leads to natriuresis, water excretion, potassium retention, and attenuation of aldosterone-mediated fibrosis and inflammation in the heart and vessels

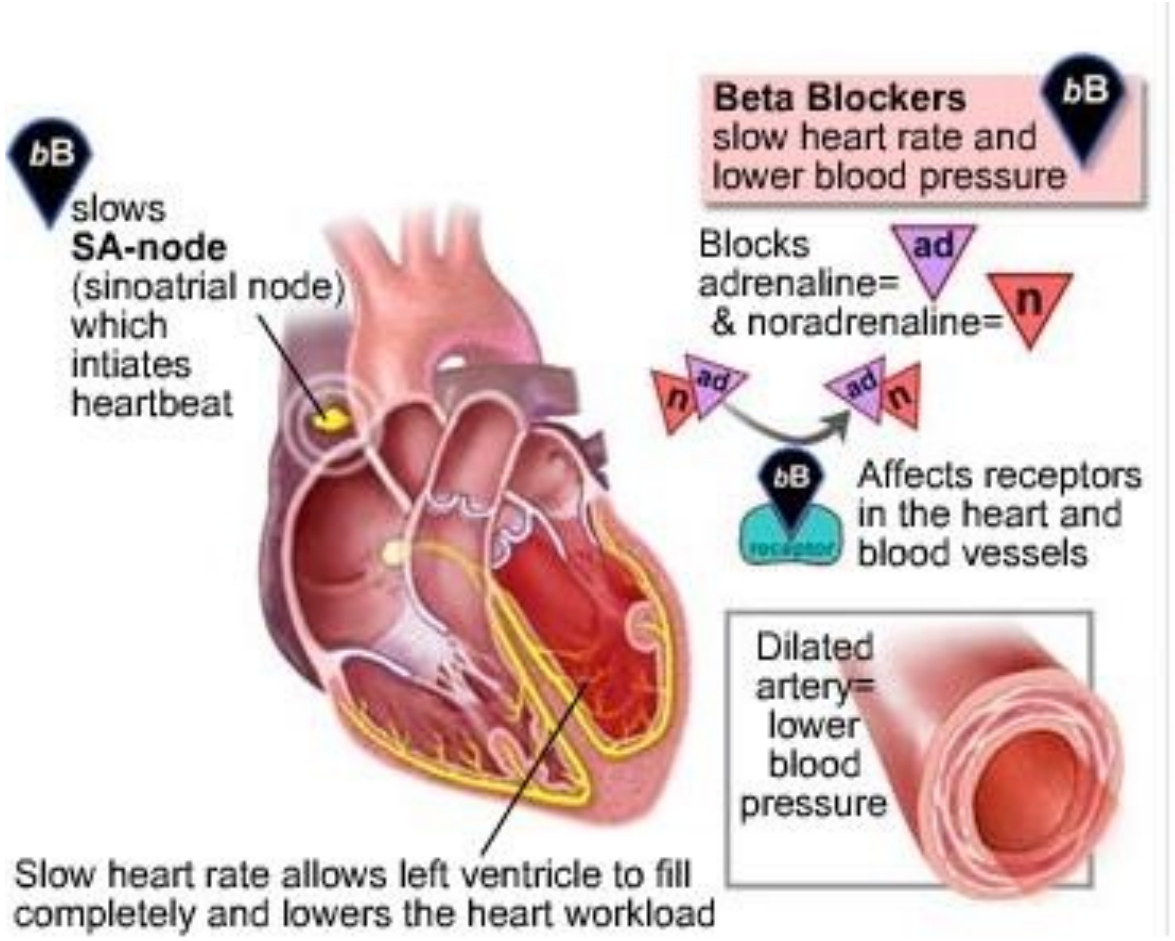
- When to add:
  - Recommended for HFrEF (EF ≤40%) and HFpEF (EF >40%), whether diabetic or not
- Pearls:
  - Adverse effects: hyperkalemia, fatigue, dizziness, hypotension, elevated creatinine
  - As an add-on for resistant hypertension, spironolactone lowers BP and reduces cardiovascular events including stroke.
  - Check K^+ and renal function at baseline, at 1 and 4 weeks, then periodically every 3–6 months.



Beta-Blockers

- Common medications: Metoprolol, Carvedilol
- Block β-adrenergic receptors → ↓ sympathetic stimulation.
- Leads to ↓ HR and myocardial oxygen demand, ↑ diastolic filling time.

- When to add:
  - Recommended for HFrEF (EF ≤40%)
- Pearls:
- Adverse effects: fatigue, bradycardia, hypotension
- Avoid in severe bradycardia, acute decompensated HF, asthma (non-selective agents)



Brent Zahn
PGY1 Pharmacy Resident
Corewell Health Beaumont Troy Hospital
1/13/26

Corewell Health™

Anemia

Anemia: Prevalence

Anemia affects 15-40% of acute stroke patients and is associated with worse outcomes including increased mortality, longer hospital stays, and poorer functional recovery

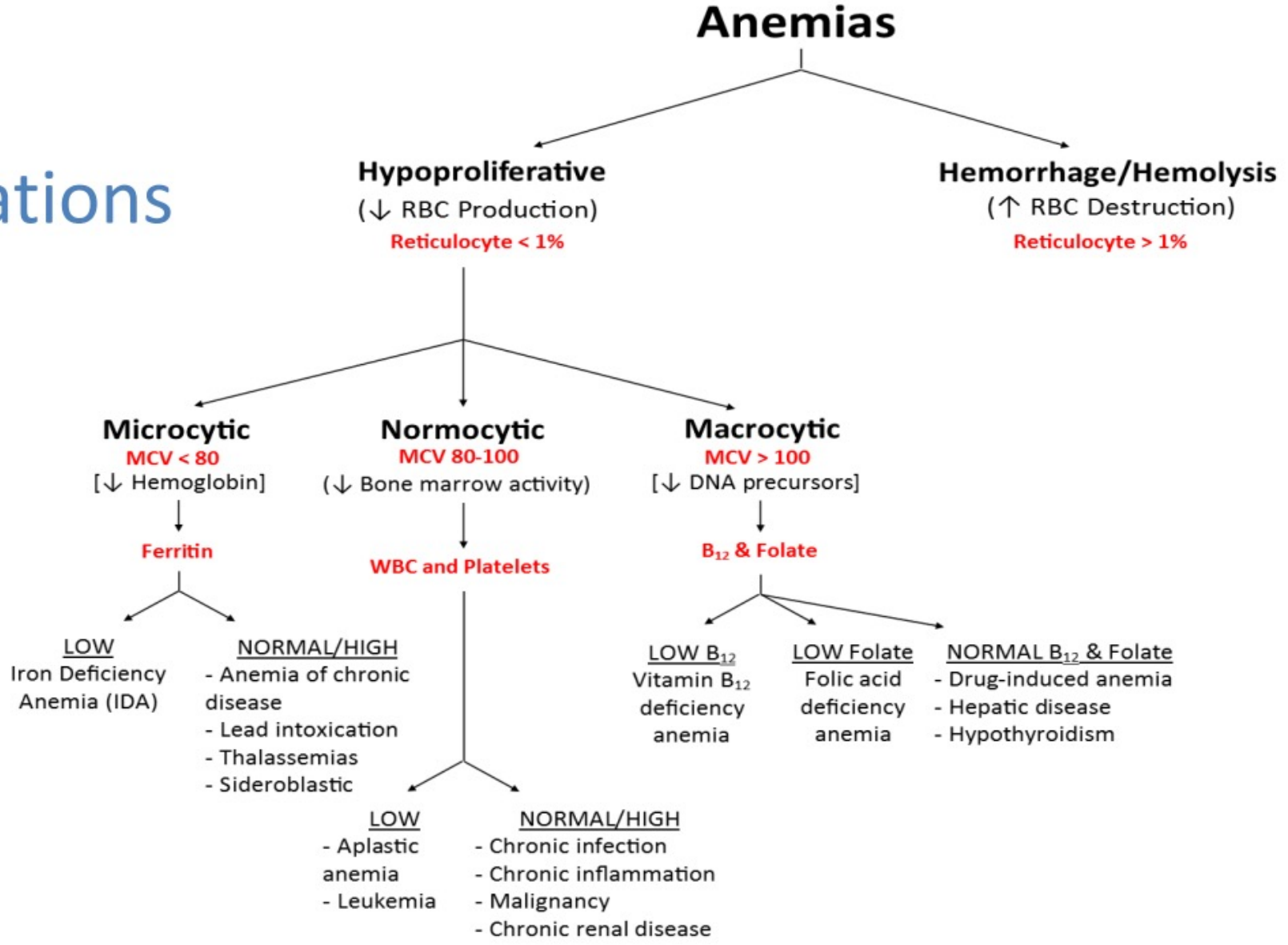
Anemia has been termed "the fifth cardiovascular risk factor" due to its impact on cerebrovascular events

Both hypoproliferative (iron deficiency, thalassemia) and hyperproliferative (sickle cell disease) anemias increase stroke risk

Bidirectional causality demonstrated: stroke increases anemia risk, and anemia (particularly IDA and aplastic anemia) increases stroke risk

Anemia

Anemia Classifications



Anemia: Risks

Anemia at admission is associated with 15.2% higher one-year mortality on average

Consider screening for iron deficiency in stroke survivors, as iron deficiency increases 5-year all-cause mortality risk

Patients with cerebrovascular disease lack normal cerebrovascular reserve and may develop brain hypoxia at hemoglobin levels >6 g/dL, unlike healthy individuals

Anemia increases length of stay by 1.7 days on average

Hemoglobin improvement during hospitalization positively correlates with functional recovery and shorter hospital stays

Anemia

	Normal Adult Male	Normal Adult Female	Range
1. Hemoglobin FIRST STEP	≥13.0 g/dL	≥12.0 g/dL	12.0 – 18.0 g/dL
2. Hematocrit	~45%	~40%	35.0 – 50.0 %
3. Red Blood Cell Count (RBC)	--	--	3.90 – 5.00 M/uL
4. Mean Corpuscular Volume (MCV)	--	--	80 – 100 fl
5. Mean Corpuscular Hemoglobin (MCH)	--	--	27.0 – 32.0 pg
6. Mean Corpuscular Hemoglobin Concentration (MCHC)	--	--	32.0 – 35.0 g/dL
7. Reticulocyte	--	--	~1% of circulating RBCs
8. Red Blood Cell Distribution Width (RDW)-If high can indicate MIXED anemia	--	--	11.5 – 15.0%
9. Serum Iron	65 – 177 ug/dL	50 – 170 ug/dL	50 – 177 ug/dL
10. Total Iron-Binding Capacity (TIBC)	--	--	250 – 370 ug/dL
11. Transferrin Saturation (TSAT) (%): Serum iron/TIBC x 100=Available Fe	--	--	20 – 50%
12. Serum Ferritin: =Storage Fe	18 – 270 ng/mL	18 – 160 ng/mL	18 – 270 ng/mL
13. Vitamin B_{12}			>200 pg/mL
14. Serum Folate			2-20 ng/mL

Anemia: Lifestyle Modifications

Address underlying causes: nutritional deficiencies (iron, vitamin B12, folate), chronic disease, blood loss

Dietary iron intake alone shows limited association with iron deficiency correction in stroke patients

- For both heme and non-heme iron

Monitor for modifiable risk factors including chronic inflammation and occult bleeding

Anemia: Oral Medication

Oral iron supplementation with ferrous salts, ferrous sulfate 325 mg daily, is the first-line therapy for iron deficiency

- No oral formulation has demonstrated clear superiority over others in efficacy or tolerability

Alternate-day dosing may optimize absorption and reduce side effects

How to take:

- Iron should ideally be taken in the morning on an empty stomach with vitamin C or citrus juice
- Vitamin C co-administration on an empty stomach enhances absorption by forming iron chelates and reducing ferric to ferrous iron, though supporting evidence is mixed
- Tea and coffee are potent inhibitors (tea reduces absorption by 90%) and should be avoided within one hour of dosing
- Calcium supplements, antacids, H2 inhibitors, and proton pump inhibitors also impair absorption

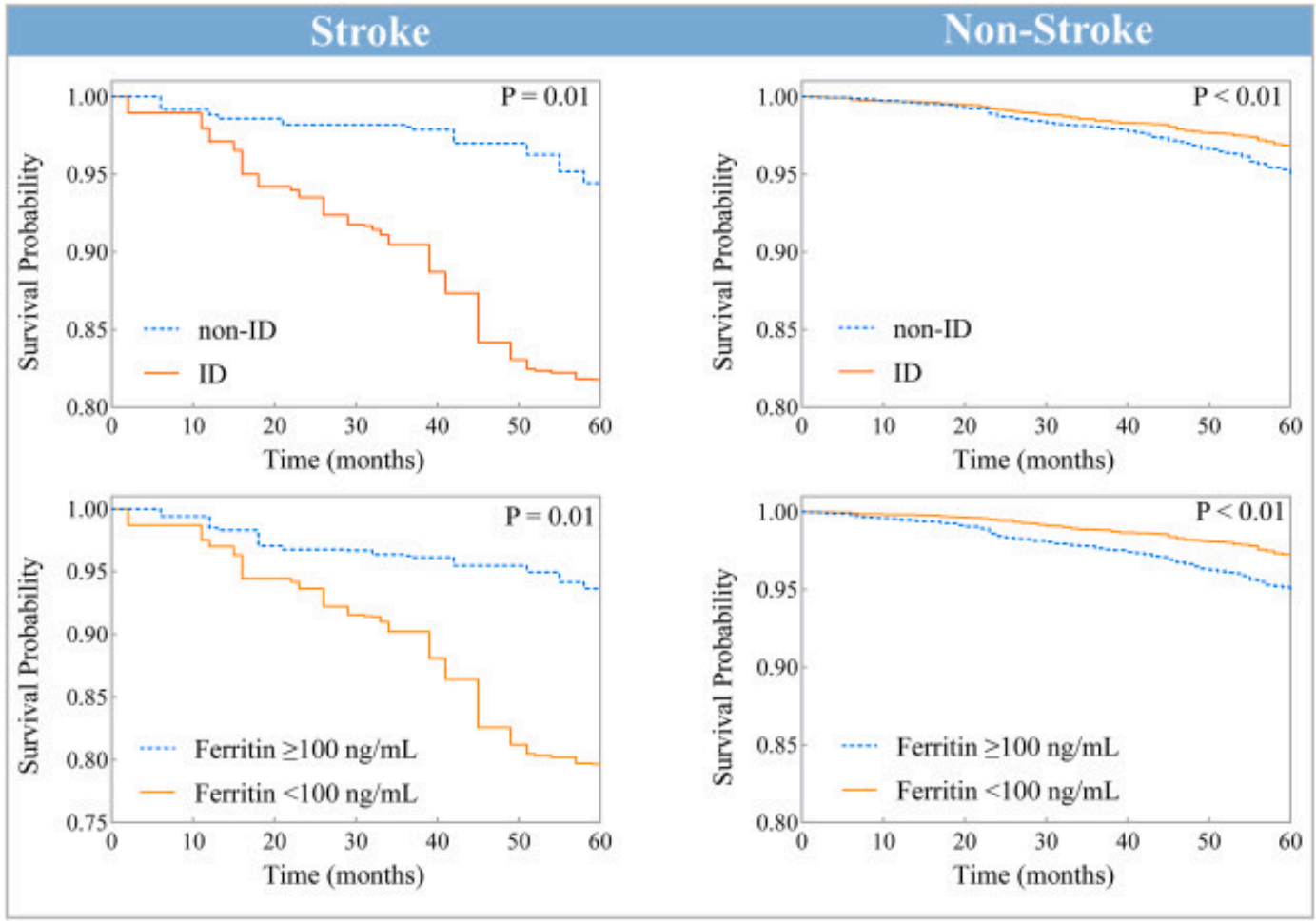
Anemia: IV Medication

Intravenous iron (ferric carboxymaltose, ferric derisomaltose) is indicated for patients with oral intolerance, malabsorption, or need for rapid repletion

- Take whatever your insurance covers
- Some agents require multiple infusions

These formulations allow high-dose administration with excellent safety profiles, though phosphate monitoring is recommended due to hypophosphatemia risk

In anemia of inflammation, intravenous iron is more reliable than oral therapy



Anemia: A Note on EPO

Erythropoietin (EPO)

An endogenous hormone that serves as the primary regular of red blood cell production

EPO possesses both neuroprotective and hematopoietic properties

Lack of robust studies in anemic stroke patients limits current recommendations

Potential future therapeutic avenue combining anemia correction with neuroprotection

Corewell Health™

Depression

Depression: Prevalence

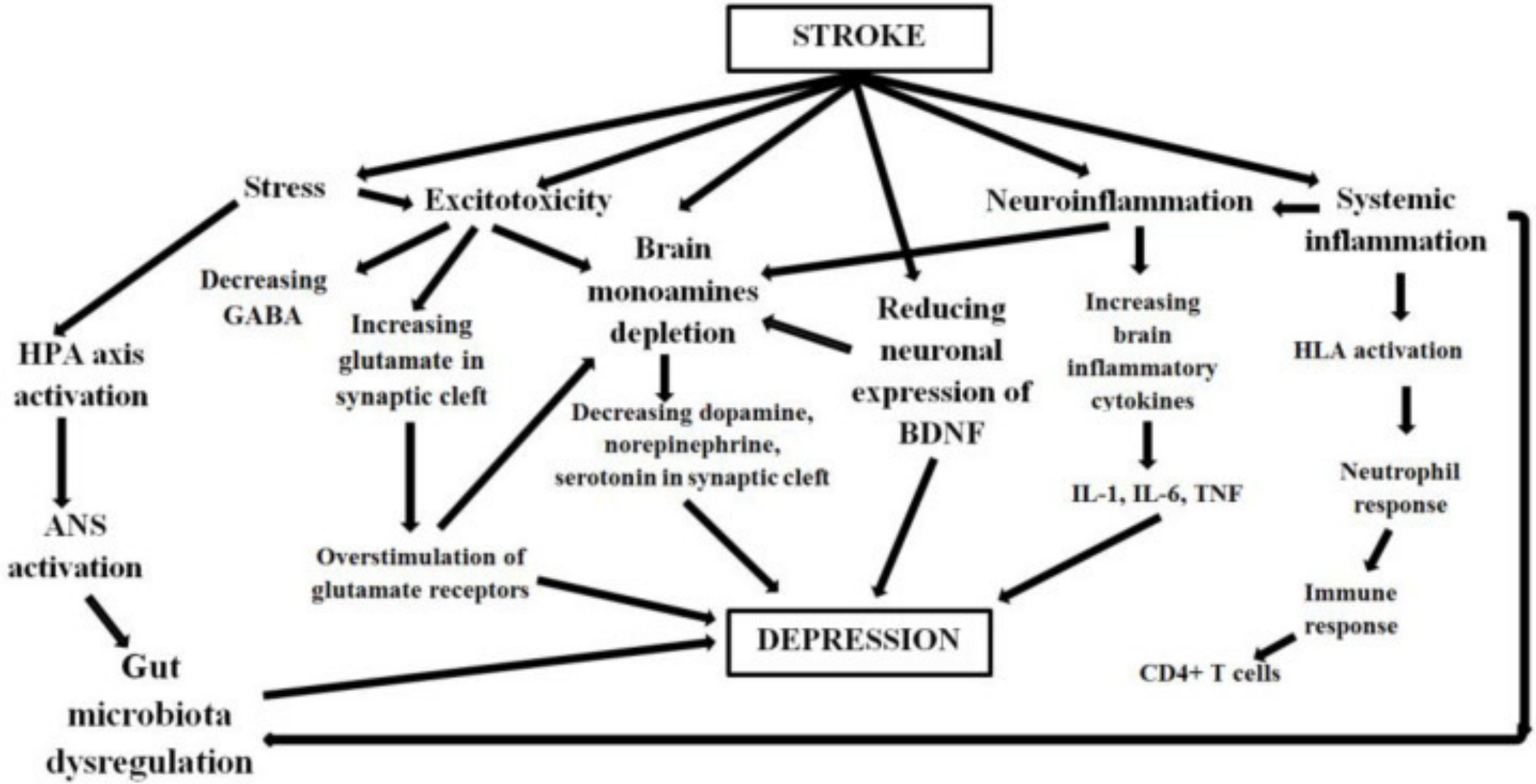
Depression affects up to one-third of stroke survivors at any time

Post-stroke depression is common, treatable, and early treatment leads to better outcomes

When it happens: Most commonly develops in the first year after stroke

Why it matters: Depression can affect recovery, daily functioning, and quality of life

Risk factors: Physical disability, stroke severity, prior depression, cognitive changes


STROKE
Stress
Excitotoxicity
Neuroinflammation
Systemic inflammation
Decreasing GABA
Increasing glutamate in synaptic cleft
Brain monoamines depletion
Reducing neuronal expression of BDNF
Increasing brain inflammatory cytokines
HLA activation
HPA axis activation
Decreasing dopamine, norepinephrine, serotonin in synaptic cleft
IL-1, IL-6, TNF
Neutrophil response
ANS activation
Overstimulation of glutamate receptors
Immune response
DEPRESSION
CD4+ T cells
Gut microbiota dysregulation

Depression: Lifestyle Modifications

Exercise and physical activity: Both aerobic exercise and aquatic therapy help reduce depression symptoms

Mind-body practices: Mindfulness meditation and acceptance therapy show promising results

Social connection: Social support programs providing emotional support and rehabilitation information are beneficial when continued for at least 8 weeks

Structured activities: Behavioral activation therapy shows positive outcomes

- Doing happy things makes you happy

Music therapy: Exercise combined with music may enhance benefits

Personal preference: Many activities are highly personal, so find what works best for you, some enjoy being in nature, reading, activities, etc

Depression: Medications

First-line medications: SSRIs,such as citalopram, escitalopram, fluoxetine, paroxetine, effectively reduce depression symptoms

How they work: Help restore brain chemical balance

Important considerations:

- Side effects may include gastrointestinal symptoms or central nervous system effects
- Discuss any concerns with healthcare provider
- Regular monitoring is important
- Lots of trial to find the best fit, it is difficult and arduous

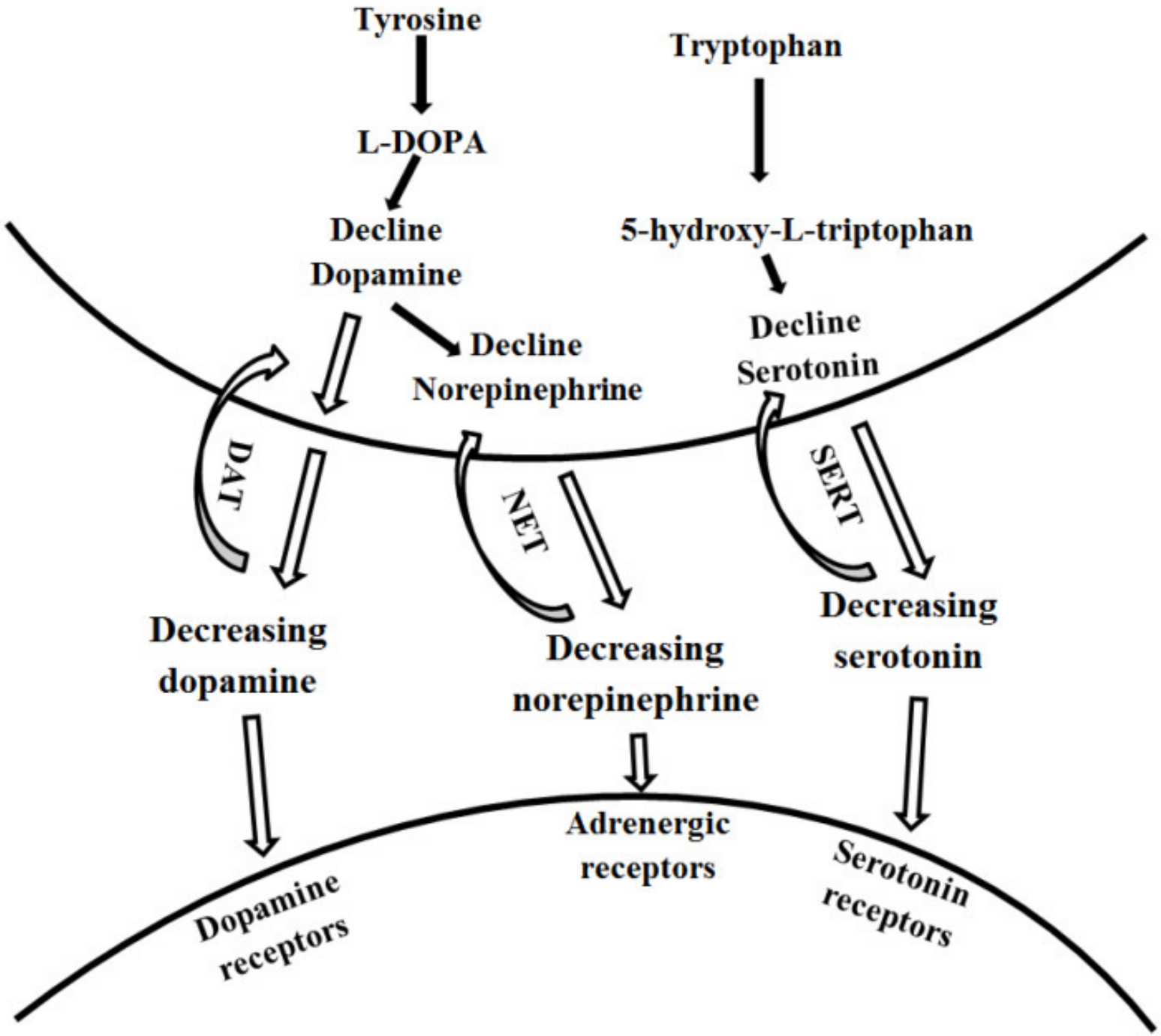

Tyrosine
L-DOPA
Decline
Dopamine
Tryptophan
5-hydroxy-L-triptophan
Decline
Norepinephrine
Decline
Serotonin
DAT
NET
SERT
Decreasing
dopamine
Decreasing
norepinephrine
Decreasing
serotonin
Dopamine
receptors
Adrenergic
receptors
Serotonin
receptors

Table 3
Pharmacological parameters of six SSRIs.

Pharmacological parameters	Fluoxetine	Citalopram	Escitalopram[a]	Fluvoxamine	Paroxetine	Sertraline
Oral bioavailability %	> 80	80 ± 13	80 ± 13	53	Dose-dependent	> 44
$t_{1/2}$ in hours	53 ± 41	33 ± 4	27–32	18	17 ± 3	23
Protein binding %	94	80	55	77	95	98
Cytochrome P-450 Isoenzymes, CYP	2D6, 2C9	3A4, 2C19	3A4, 2C19	1A2, 2D6, 3A4, 2C9	2D6	2D6
Active metabolites	Yes	Yes	No	No	No	No
Concentrations in CSF in nM	26	110	31	–	7	–
K_i in nM[b]						
5HTT	0.81	9.6	2.5	2.22	0.125	0.29
NAT	244	5029	6514	1300	40	417
DAT	3600	> 100,000	> 100,000	9100	500	25
5-HT/NE	301	523	2605	586	320	1423

References: Goodman & Gilman's, The pharmacological basis of therapeutics (In Brunton LL, Lazo JS, Parker KL, Eds). 11th Edition.
Lenox RH and Alan Frazer. Mechanism of action of antidepressants and mood stabilizers. In Davis KL, Charney D, Coyle JT, Nemeroff C (Eds) Neuropsychopharmacology — The fifth generation of progress. Lippincott Williams and Wilkins, Philadelphia, 2002, pp. 1139–1163. McGraw Hill, New York 2006; Mandrioli et al. (2012); Nikisch et al. (2004); Owens, Knight, and Nemeroff (2001); Pastoor and Gobburu (2014); Paulzen et al. (2016).

[a] S-(+) enantiomer of citalopram.

[b] Ki = potency at human transporters for serotonin (5-HT), norepinephrine (NE), dopamine (DA).

Depression: Medication Benefits

Many studies have shown that SSRIs help with stroke recovery

- A recent meta-analysis of 52 trials examined the efficacy of SSRIs to reduce disability among 4,060 participants with a recent stroke. The authors concluded that SSRIs may improve recovery after stroke.
- In the FOCUS trial, 1,564 patients with a recent stroke and focal neurological deficits were allocated to the fluoxetine (20 mg/day) group, and 1,563 patients were allocated to a matching placebo group (59). The primary outcome was functional status, measured with the mRS, at 6 months. Fluoxetine was not better than placebo in reducing disability following stroke, although it effectively prevented depressive disorders
- When compared with patients who received placebo or underwent problem-solving therapy, stroke patients who received escitalopram improved in global cognitive functioning, immediate memory, and delayed memory

Depression: Medication Benifits

In humans, antidepressants have been reported to improve motor, cognitive, and functional outcomes

- In this double-blind, placebo-controlled trial, 118 stroke patients undergoing physical rehabilitation were randomly assigned to receive fluoxetine, 20 mg/day, or placebo for 3 months starting 5–10 days after the onset of stroke. The primary outcome measure was the change in Fugl-Meyer Motor Scale scores (FMMS; lower scores indicate more severe impairment) following the intervention. The improvement in FMMS score at day 90 was significantly greater in the fluoxetine group than in the placebo group. Furthermore, the number of patients that achieved independence was higher in the fluoxetine group

Depression: Therapy

Cognitive-behavioral therapy (CBT): Short-term, structured therapy focusing on current problems and developing coping skills

- Can be used alone or combined with medication
- Shows significant benefits for depression symptoms

Brain stimulation therapies: Repetitive transcranial magnetic stimulation (rTMS) of the brain's left frontal area shows efficacy

- Non-invasive and well-tolerated
- Often combined with medication for enhanced effect

Combination approaches: Acupuncture combined with medication or rTMS combined with medication may provide additional benefits

Corewell Health™

Dementia

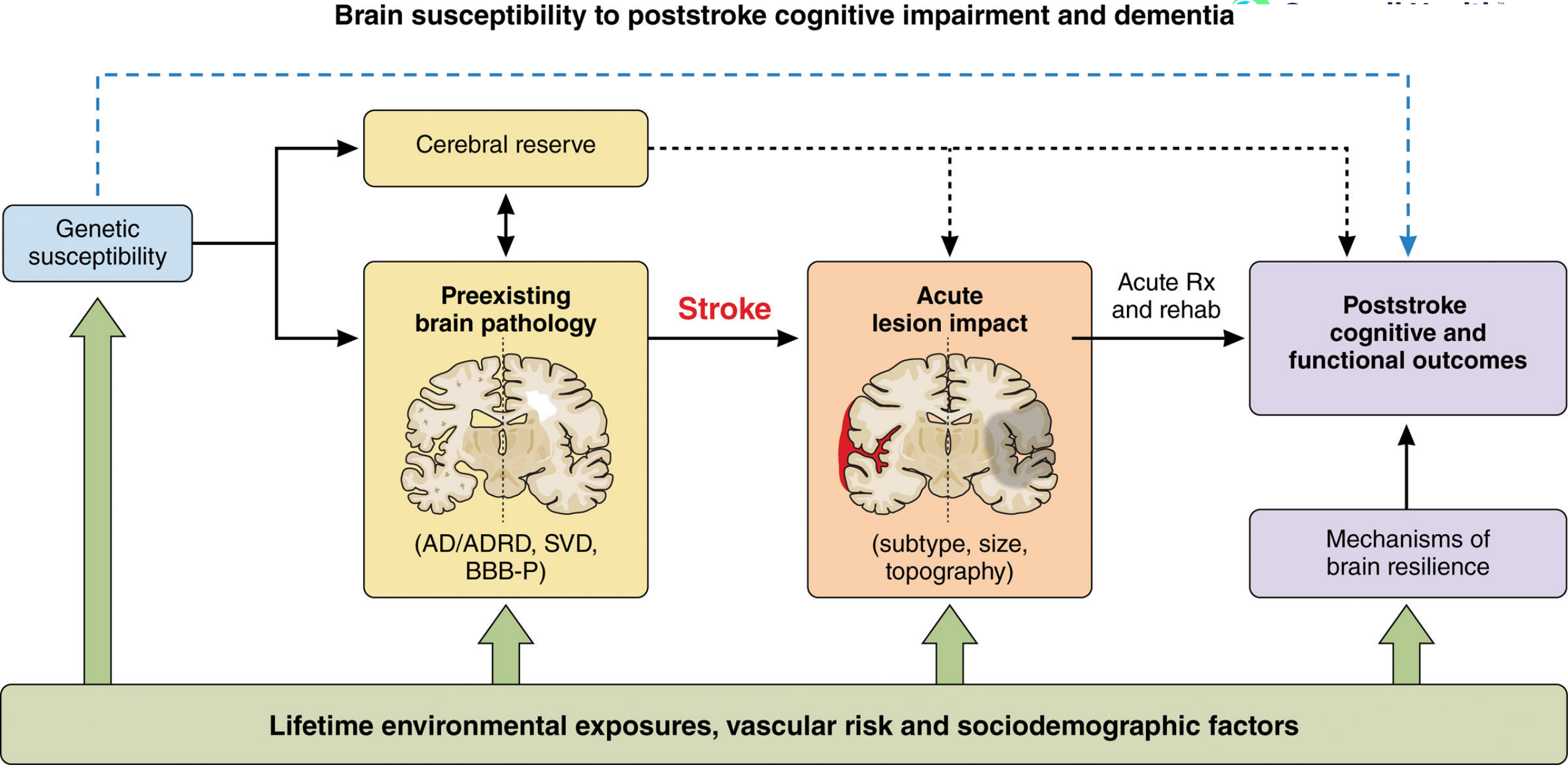
Dementia: Prevalence

Post-stroke dementia affects up to one-third of stroke survivors

Dementia is commonly associated with mixed neuropathology, typically Alzheimer disease with cerebrovascular pathology

Worldwide dementia burden: 47 million currently, projected to reach 131 million by 2050

Post-stroke cognitive impairment (PSCI) increases risk of death, disability, and institutionalization


Brain susceptibility to poststroke cognitive impairment and dementia
Cerebral reserve
Genetic susceptibility
Preexisting brain pathology
(AD/ADRD, SVD, BBB-P)
Stroke
Acute lesion impact
(subtype, size, topography)
Acute Rx and rehab
Poststroke cognitive and functional outcomes
Mechanisms of brain resilience
Lifetime environmental exposures, vascular risk and sociodemographic factors

Dementia: Screening

Screen when cognitive complaints arise or clinician concern exists about cognitive-related activities of daily living

Early detection in acute stroke units is essential; assess for cognitive changes over time

Recommended screening: before hospital discharge, during first year, and possibly later

We do not have anything, yet, that can reverse dementia, but we have ways to slow the progression. Ergo, early detection is essential

Montreal Cognitive Assessment (MoCA) or Mini-Mental State Examination

- MoCA is preferred due to less ceiling effect and greater sensitivity to mild cognitive impairment, particularly in subacute phases

Consider comprehensive neuropsychological evaluation when standard screening is inconclusive or when stroke-related impairments (aphasia, motor weakness, neglect) complicate assessment

Assess pre-stroke cognition using Informant Questionnaire for Cognitive Decline in the Elderly

Dementia: Lifestyle Modifications

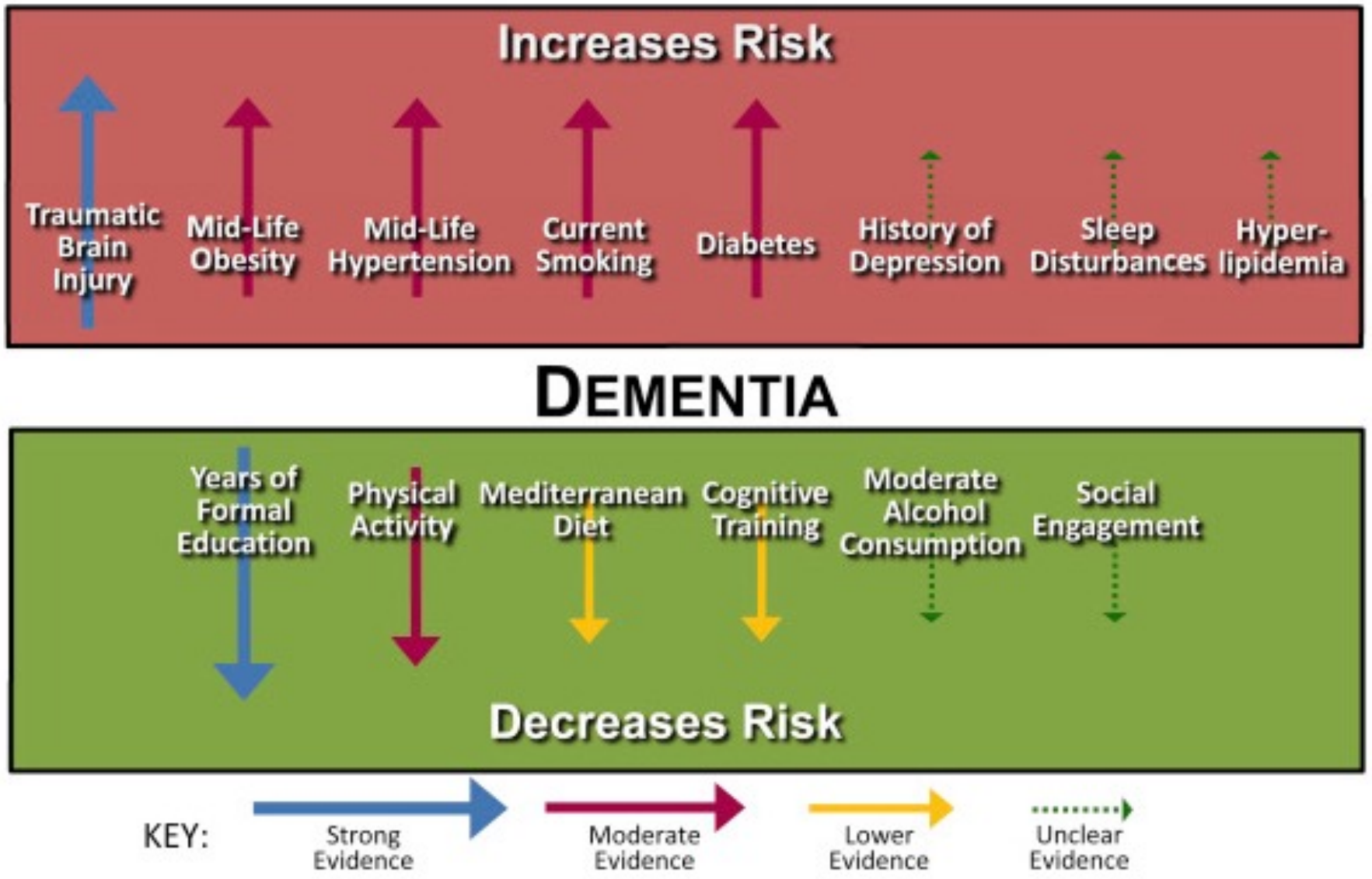
Evidence-Based Interventions

- Cognitively engaging activities (reading, puzzles), physical exercise (walking, aerobic activity), and socialization (family gatherings) provide benefit
- Aerobic exercise improves functional ability, walking endurance, balance, cardiovascular health, and secondary stroke prevention
- Multidomain lifestyle interventions show promise: FINGER trial demonstrated decreased cognitive decline risk with combined nutritional counseling, social stimulation, physical/cognitive training, and vascular risk factor management

Practical Recommendations

- Lifestyle modifications may help patients live independently at home longer
- Address modifiable cardiovascular risk factors, estimated to account for one-third of AD cases

Dementia


Increases Risk
Traumatic Brain Injury
Mid-Life Obesity
Mid-Life Hypertension
Current Smoking
Diabetes
History of Depression
Sleep Disturbances
Hyper-lipidemia
DEMENTIA
Years of Formal Education
Physical Activity
Mediterranean Diet
Cognitive Training
Moderate Alcohol Consumption
Social Engagement
Decreases Risk
KEY:
Strong Evidence
Moderate Evidence
Lower Evidence
Unclear Evidence

Dementia: Classic Medications

Acetylcholinesterase inhibitors (e.g., donepezil) for mild to severe Alzheimer disease dementia

Memantine (alone or as add-on therapy) for moderate to severe dementia

- The standard symptomatic treatments (donepezil, rivastigmine, galantamine, and memantine) show variable responses based on APOE4 status. In mild cognitive impairment, donepezil showed more profound effects in APOE4-positive individuals, though this may reflect easier detection of conversion to dementia rather than true differential efficacy

Rivastigmine for symptomatic Parkinson disease dementia

Dementia: New Medications

New drug treatments targeting amyloid-beta and tau may slow disease progression when implemented early by impacting AD-related brain changes

- The newly approved anti-amyloid therapies, lecanemab (Leqembi) and donanemab (Kisunla), are FDA-approved for mild cognitive impairment or mild dementia stage of Alzheimer's disease

APOE4 carriers demonstrate enhanced treatment response to these agents, particularly lecanemab, but also face increased risk of amyloid-related imaging abnormalities (ARIA)

Gene therapy and immunotherapy under investigation

Anti-inflammatory agents studied without convincing efficacy evidence to date

Dementia: Genetic Marker APOE4

Apolipoprotein E4 (apoE4) is one of three common isoforms of apolipoprotein E, a lipid transport protein that differs from the other isoforms (apoE2 and apoE3) by a single amino acid substitution at positions 112 and 158

- ApoE4 is the strongest genetic risk factor for late-onset Alzheimer's disease
- This genetic variant is carried by one-fifth of the world's population

Despite higher ARIA frequency in homozygotes, no evidence indicates greater clinical seriousness compared to heterozygotes, and slower titration with donanemab can reduce ARIA by three-fold in homozygotes

APOE4 homozygosity significantly increases both pre-stroke and post-stroke dementia risk, with homozygous carriers showing a 3-4-fold increased risk of post-stroke dementia independent of cerebrovascular burden

- However, heterozygous APOE4 carriers (ε4/ε3) show no consistent association with post-stroke cognitive impairment at 3 or 12 months