Chronic Disease Clinical Conundrums in Geriatric Patients

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DISCLOSURE

- The speakers do not have any actual or potential conflicts of interest to report in relation to this presentation

LEARNING OBJECTIVES

- Describe rationale for weaker levels of evidence and the exclusion of geriatric patients from either clinical practice guidelines or in the development of research trials
- Compare and contrast treatment guidelines and primary literature sources for the management of diabetes, hypertension and hyperlipidemia in geriatric patients
- Utilizing a patient case, apply primary literature and/or clinical practice guidelines to make a recommendation regarding appropriateness of therapy for diabetes, hypertension and hyperlipidemia management in an elderly patient

LEGEND

- AACE = American Association of Clinical Endocrinologists
- AAFP = American Academy of Family Physicians
- ACC = American College of Cardiology
- ACP = American College of Physicians
- ADA = American Diabetes Association
- ADE = Adverse drug event
- ADL = Activities of daily living
- AGS = American Geriatrics Society
- AHA = American Heart Association
- AKI = Acute kidney injury
- ASCVD = Atherosclerotic cardiovascular disease
- BMJ = British Medical Journal
- BP = Blood pressure
- CAC = Coronary artery calcium
- CPG = Clinical practice guideline
- CV = Cardiovascular
- CVD = Cardiovascular disease
- DBP = Diastolic blood pressure

LEGEND

- DM = Diabetes mellitus
- DPP4i = Dipeptidyl peptidase 4 DPP-4 inhibitors
- ESC = European Society of Cardiology
- ESH = European Society of Hypertension
- FDA = Food and Drug Administration
- GLP-1RA = Glucagon-like peptide-1 receptor agonist
- HFrEF = Heart failure with reduced ejection fraction
- HLD = Hyperlipidemia
- HR = Hazard Ratio
- HTN = Hypertension
- IADL = Instrumental activities of daily living
- JAMA = Journal of the American Medical Association
- LDL = Low density lipoprotein
- MACE = Major adverse CV events
- MCC = Multiple chronic conditions
- MI = Myocardial infarction

LEGEND

- NEJM = New England Journal of Medicine
- NKDA = No known drug allergies
- NNH = Number needed to harm
- NNT = Number needed to treat
- PP = Pulse pressure
- RCT = Randomized controlled trial
- SBP = Systolic blood pressure
- SGLT2i = Sodium-glucose co-transporter 2 inhibitor
- TZD = Thiazolidinedione
- US = United States

Case Presentation: SB

SB is a 76 y/o woman with PMH HTN, HFrEF with ejection fraction 38%, HLD, and type 2 DM. She has NKDA. She has no cognitive dysfunction, but requires assistance with laundry and finances.

Current medications:

Current medications
Carvedilol 3.125 mg BID
Glipizide 5 mg daily
Lisinopril 5 mg daily
Metformin 500 mg BID
Spironolactone 12.5 mg daily

Current labs and vitals:

Lab/vital	Value
Blood pressure	148/76 mmHg
Heart rate	70 bpm
BMI	21.6 kg/m^2
SCr;eGFR	1.2 mg/dL;50 mL/min
K	4.1 mEq/L
HgA1C	8.2%
LDL	110 mg/dL

PHARMACY VISION 2020

TEST QUESTION 1

SB is a 76 y/o woman with PMH HTN, HFrEF with ejection fraction 38%, HLD, and type 2 DM. She has NKDA. Which of the following is true regarding SB's A1C goal?

a. She is classified as very complex and is at her goal of <8.5% per ADA
b. She is classified as healthy and her A1C is not at goal of <7-7.5% per AGS
c. She is classified as very complex and it is reasonable to individualize her A1C goal per AACE
d. She is classified as complex/intermediate and is at her goal of 8-9% per ESC

TEST QUESTION 2

SB is a 76 y/o woman with PMH HTN, HFrEF with ejection fraction 38%, HLD, and type 2 DM. She has NKDA. Which of the following precludes applying the results of SPRINT and HYVET to her blood pressure goal?

a. She has diabetes, and those with DM were excluded from SPRINT
b. She has heart failure, and those with heart failure were excluded from both trials
c. She does not meet the age criteria for SPRINT of over 80 years
d. A and B are correct
e. A, B, and C are correct

TEST QUESTION 3

SB is a 76 y/o woman with PMH HTN, HFrEF with ejection fraction 38%, HLD, and type 2 DM. She has NKDA. Which of the following is appropriate to consider prior to initiating statin therapy in SB?

a. Calculate her risk using the SCORE tool and consider measuring CAC
b. Consider lowering her LDL by 20-30% because she has type 2 DM
c. Calculate her risk using the PCE and consider her life-expectancy
d. Counsel her on BP lowering prior to considering a statin

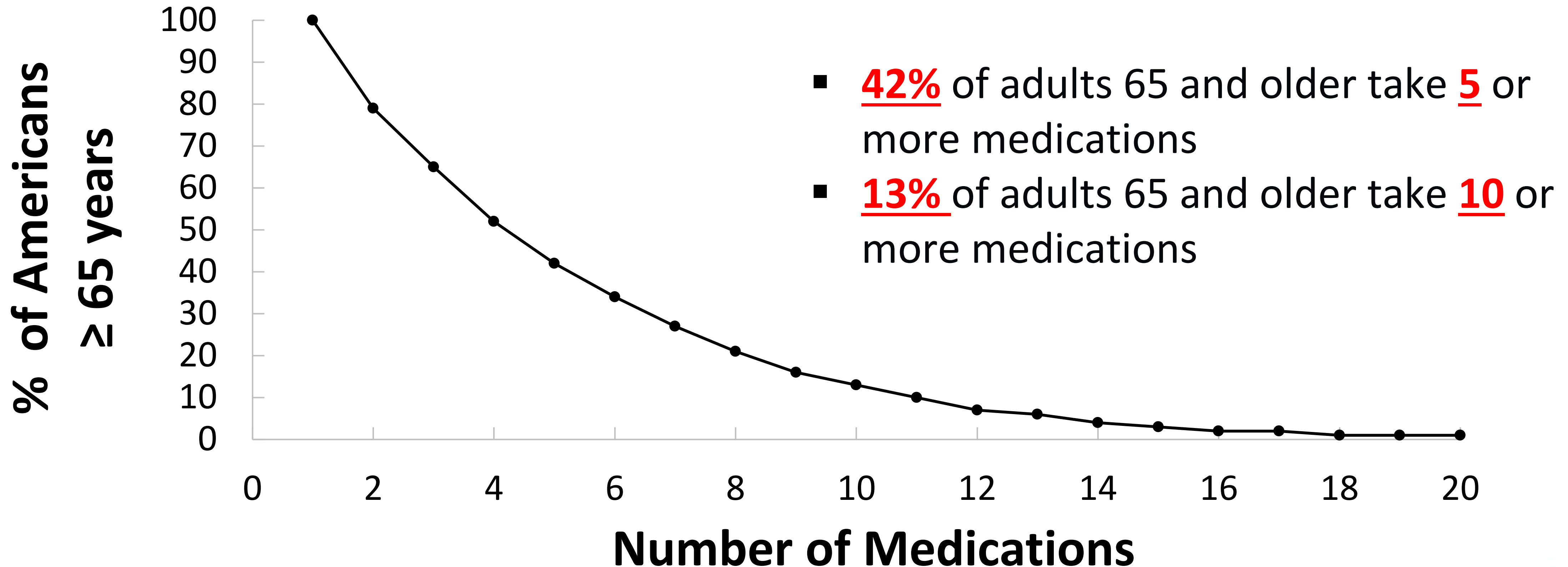
An Aging Population

- US undergoing drastic shift in population demographics
  - From 2010 to 2020, population 65 and older grew 34.2%
    - "Baby Boomers" aging (persons born 1946-1964)
  - By 2030, 20% of the population will be 65 and older

- 3 out of every 4 persons 65 and older are diagnosed with at least *one* chronic medical condition
  - Providing care for elderly patients with MCC accounts for more than two-thirds of US health care expenditures

1. 65 and Older Population Grows Rapidly as Baby Boomers Age [news release]. United States Census Bureau; June 25, 2020.
2. *Clin Geriatr Med*. 2019;35(1):1-12.

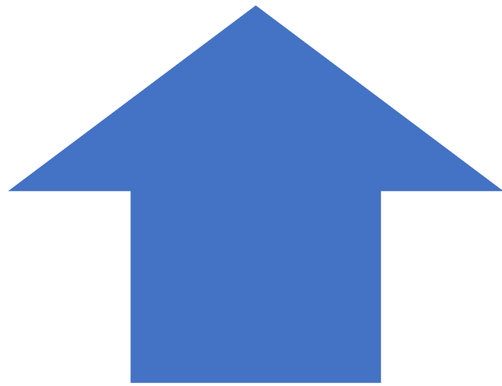
AGE AND MEDICATION USE



- **42%** of adults 65 and older take **5** or more medications
- **13%** of adults 65 and older take **10** or more medications

3. IMS Institute for Healthcare Informatics. Avoidable Costs in U.S. Healthcare. June 2013.

AGE AND MEDICATION USE



Costs

ADEs

Falls

Adherence

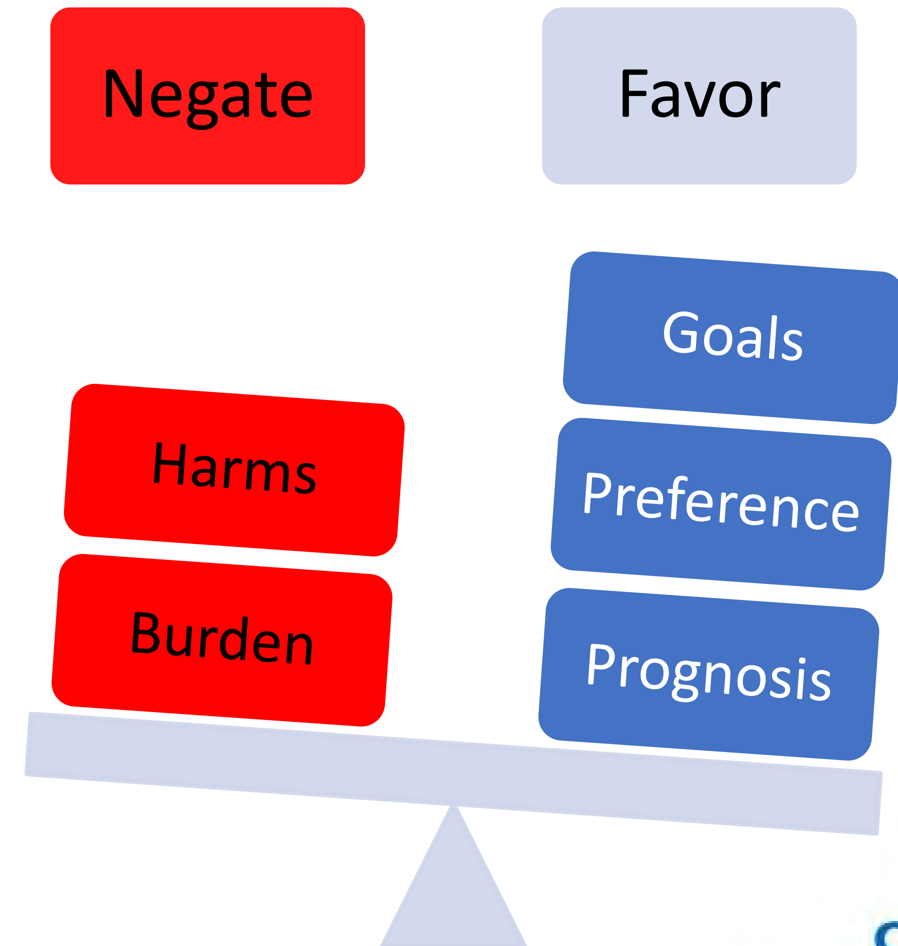
Functional status

Quality of life

4. *Expert Opin Drug Saf*. 2014;13(1):57-65.

FINDING BALANCE

- Utilize shared decision making
  - Include relevant caregivers
- Health outcome goals: activities most important to individual
- Care burden: workload imposed by healthcare on patients, effect on quality of life
- Healthcare preference: workload patients are willing or not willing to do or receive



5. *J Am Geriatr Soc*. 2019;67(4):665-673.

Five Principles of Geriatric Management

1. Elicit patient preferences
2. Recognize limitations of evidence
3. Weigh harms, burdens, benefits, prognosis
4. Balance complexity with feasibility
5. Choose therapies to enhance quality of life

5. *J Am Geriatr Soc*. 2019;67(4):665-673.

Geriatric 5Ms Framework

Mind

Mobility

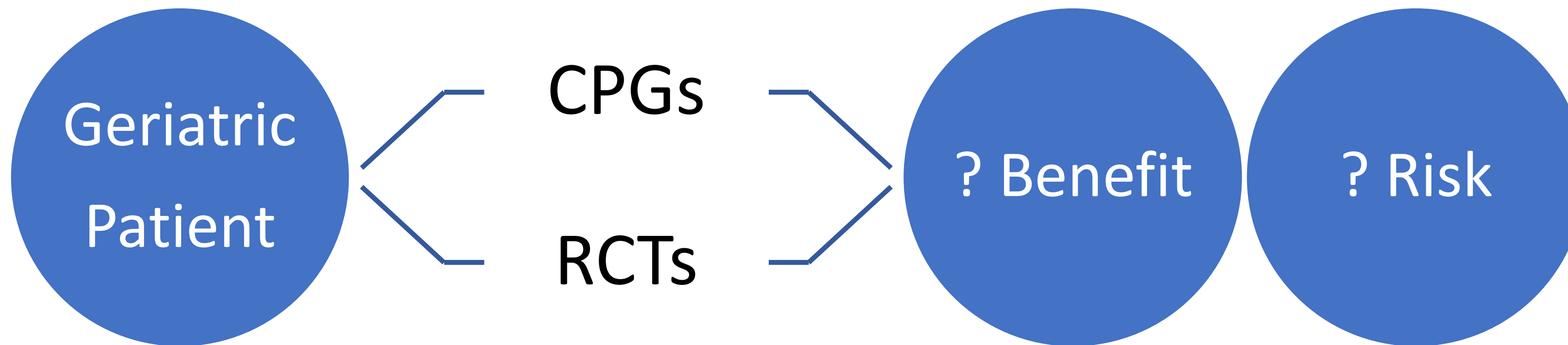
Medications

Multi-complexity

Matters Most

6. *J Am Geriatr Soc*. 2017;65:2115.

CLINICAL CONUNDRUM



5. *J Am Geriatr Soc*. 2019;67(4):665-673.

UNCERTAINTY OF RESEARCH

CLINICAL TRIAL DESIGN:

- Exclusion criteria disproportionately affects older adults
- Unexplained age cutoffs/limits
- Trial endpoints may not align with treatment goals
  - Symptomatic, quality of life outcomes more pertinent

CLINICAL PRACTICE GUIDELINES:

- Often focused on single disease state
  - Limited applicability to older adults with MCC
- Assimilated from an evidence base with varying study populations
  - Risk assessment, management complexity

5. *J Am Geriatr Soc*. 2019;67(4):665-673.
7. *J Gen Intern Med*. 2011;26(7):783-790.

Uncertainty of Research

- Common exclusion criteria in the literature:

  - Physical disability
  - Functional limitations
  - Decreased life expectancy
  - Cognitive impairment
  - Residence in a care facility

5. *J Am Geriatr Soc*. 2019;67(4):665-673.
7. *J Gen Intern Med*. 2011;26(7):783-790.

UNCERTAINTY OF RESEARCH

- FDA has provided guidance to industry for drug development, trial research
  - E7 Studies in Support of Special Populations: Geriatrics
    - "To assess the benefit/risk balance of a drug that will be used in the geriatric population, these patients should be appropriately represented in clinical trials"
    - Promote participation of older patients with comorbidities
    - Study designs should seek comparisons between older and younger participants

8. *Fed Regist.* 2012;77:9948-9949.
9. *Arch Gerontol Geriatr*. 2017;72:99-102.

Review of trends in the selective exclusion of older participants from randomised clinical trials

Purpose	• To assess trends in published RCTs with unexplained upper age limits
Methods	• All RCTs from BMJ, JAMA, Lancet, and NEJM were reviewed (1998-2015) for unexplained, specified upper age cutoffs
Results	• **71% (n=3083)** of RCTs had no explicit upper age limit • **26.9% (n=1168)** of RCTs had an upper age limit that was unexplained

9. *Arch Gerontol Geriatr.* 2017;72:99-102.

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REVIEW OF TRENDS IN THE SELECTIVE EXCLUSION OF OLDER PARTICIPANTS FROM RANDOMISED CLINICAL TRIALS

	BMJ	JAMA	Lancet	NEJM	Total
Total RCTs	618	925	1213	1585	4341
RCTs for >65 years old	57 (9.2%)	23 (2.5%)	38 (3.1%)	43 (2.7%)	**161 (3.7%)**

- A statistically significant decrease in the proportion of RCTs with unjustified age limits (r -0.609, p = 0.007) occurred from 1998-2015

9. *Arch Gerontol Geriatr.* 2017;72:99-102.

SYSTEMATIC REVIEW OF CPG'S RECOMMENDATIONS ABOUT PRIMARY CARDIOVASCULAR DISEASE PREVENTION FOR OLDER ADULTS

Purpose	• To examine the extent to which international CPGs for primary prevention of CVD address older adults
Methods	• Systematic review of CPGs on the assessment and/or management of CVD risk (or HTN and high cholesterol)
Outcomes	• To identify if CPGs provided mention of evidence, barriers to implementation and tailoring of treatment to older people

10. *BMC Fam Pract*. 2015;16:104.

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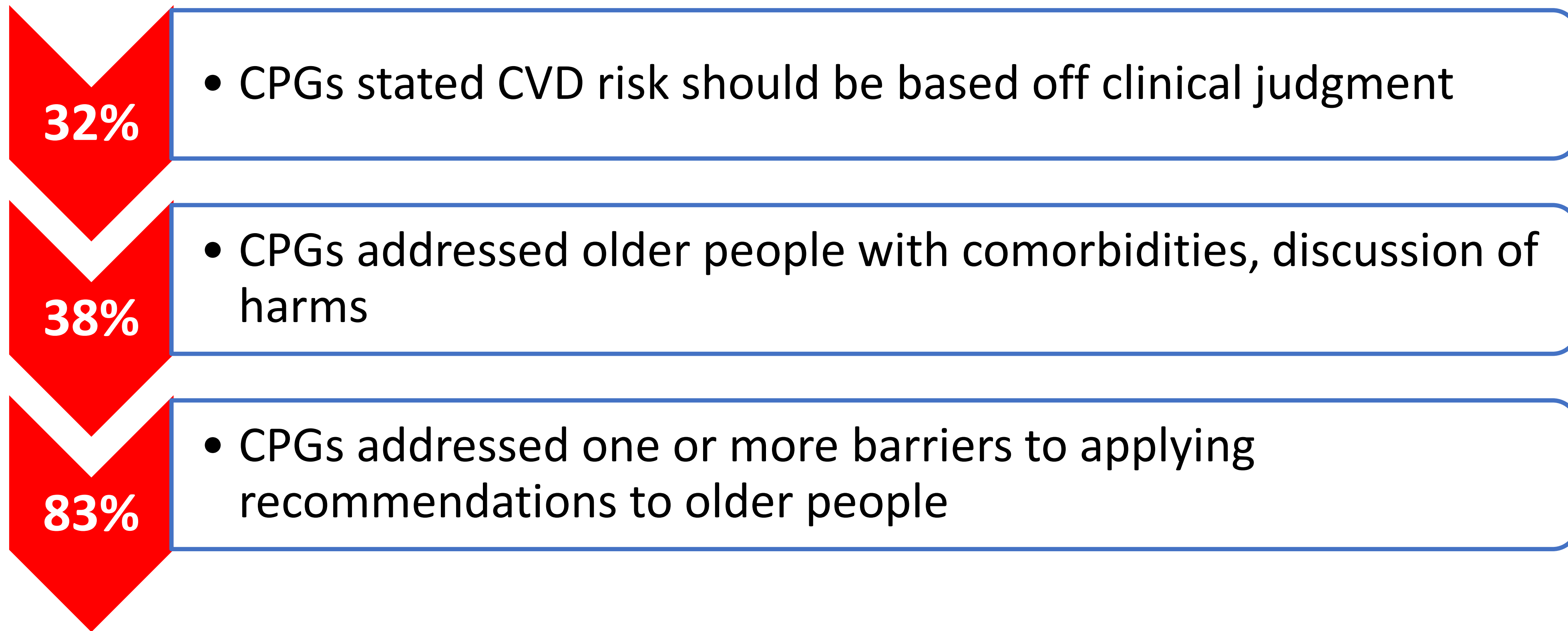
SYSTEMATIC REVIEW OF CPG'S RECOMMENDATIONS ABOUT PRIMARY CARDIOVASCULAR DISEASE PREVENTION FOR OLDER ADULTS

- Overview of CPG criteria for inclusion (n=47):
  - Available evidence for older people
    - Potential harms/benefits, knowledge gaps
  - Barriers to implementation for older people
    - Complexity of risk assessment/management
    - Time needed to treat to benefit
    - Social support/caregiver burden
  - Tailoring treatment to older people's preferences
    - Quality of life, comorbid burdens, harms/benefits of treatment

10. *BMC Fam Pract*. 2015;16:104.

SYSTEMATIC REVIEW OF CPG'S RECOMMENDATIONS ABOUT PRIMARY CARDIOVASCULAR DISEASE PREVENTION FOR OLDER ADULTS



10. *BMC Fam Pract*. 2015;16:104.

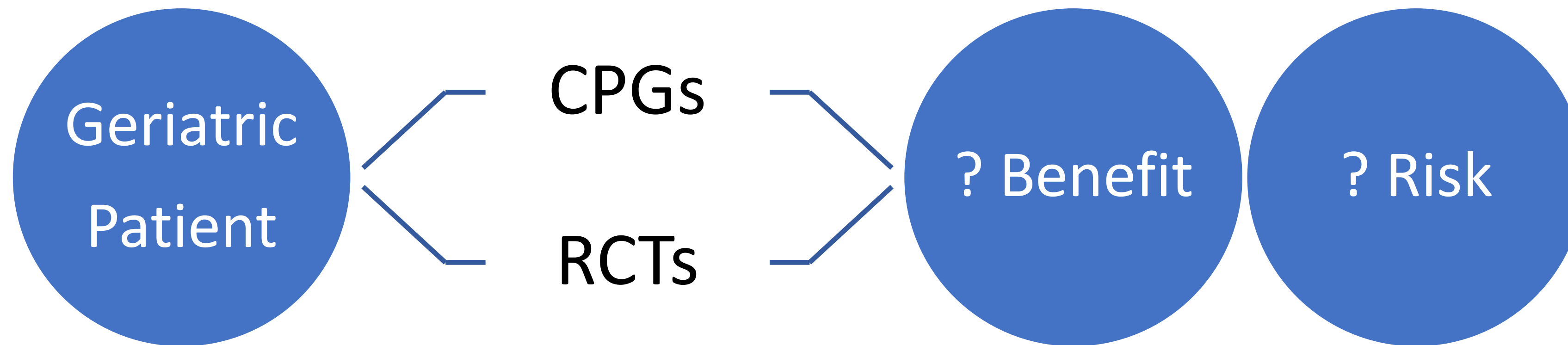
UNCERTAINTY OF RESEARCH: SUMMARY

- Are disease-specific, evidence-based guidelines and research applicable?

Yes	Uncertain	No
• Patient: functional, >10 year life expectancy, limited comorbidity • Proceed with care as usual	• Patient: presence of MCC, 2-10 year life expectancy • Care follows Five Principles of Geriatric Management	• Patient: limited life expectancy, advanced disease • De-escalate treatment, symptomatic management

5. *J Am Geriatr Soc*. 2019;67(4):665-673.

Clinical Conundrum – DM



5. *J Am Geriatr Soc*. 2019;67(4):665-673.

OLDER ADULTS AND DM

- 1 out of every 5 people with DM are ≥ 65 years old
  - Equivalent to 136 million worldwide
    - 19.3% of total population 65 to 99 years old
- Persons with DM are at higher risk for CVD

11. *IDF Diabetes Atlas*. 9th Edn (2019).
12. *Lancet*. 2010; 375: 2215-2222.

Principles of DM Treatment in Older Adults

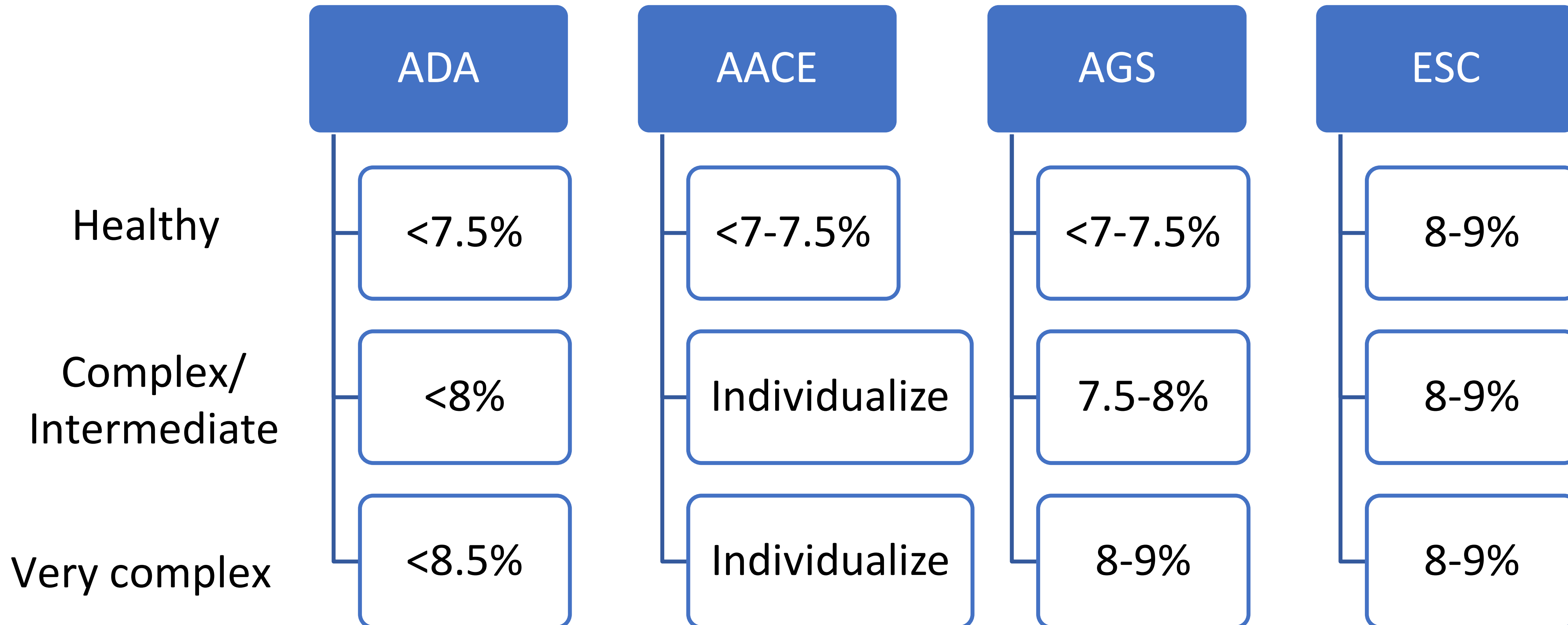
- Avoid hypoglycemia
- Avoid symptoms of hyperglycemia
- Prevent macrovascular complications

Health Status Classifications

Healthy	Complex/ Intermediate	Very complex
Few coexisting conditions	MCC	End stage illnesses
No ADL/IADL impairment	2+ IADL impairments	Mod-severe cognitive decline
No cognitive decline	Mild-mod cognitive impairment	Limited life expectancy

13. *Diabetes Care*. 2020;43(Suppl 1):S152-S162.
14. *Endocr Pract*. 2020;26(1):107-139.
15. *J Am Geriatr Soc*. 2013; 61(11): 2020–2026.

DM Goals of Therapy



13. *Diabetes Care*. 2020;43(Suppl 1):S152-S162.
14. *Endocr Pract*. 2020;26(1):107-139.
15. *J Am Geriatr Soc*. 2013; 61(11): 2020–2026.
16. *Eur Heart J*. 2020;41(2):255-323.

Intensive vs. Standard Glucose Control

Trial	Duration (years, median)	Age (average)	A1c (intensive arm)	A1c (standard arm)	Outcome
ADVANCE	5	66.6	6.5%	7.3%	**No Δ in MACE**
ACCORD	3.7	62.2	6.4%	7.5%	**No Δ in MACE**
VADT	5.6	60.4	6.9%	8.4%	**No Δ in MACE**

17. *N Engl J Med*. 2008;358(24):2560-72.
18. *N Engl J Med*. 2008;358(24):2545-59.
19. *N Engl J Med*. 2009;360(2):129-39.

ACCORD – Subgroup Analysis

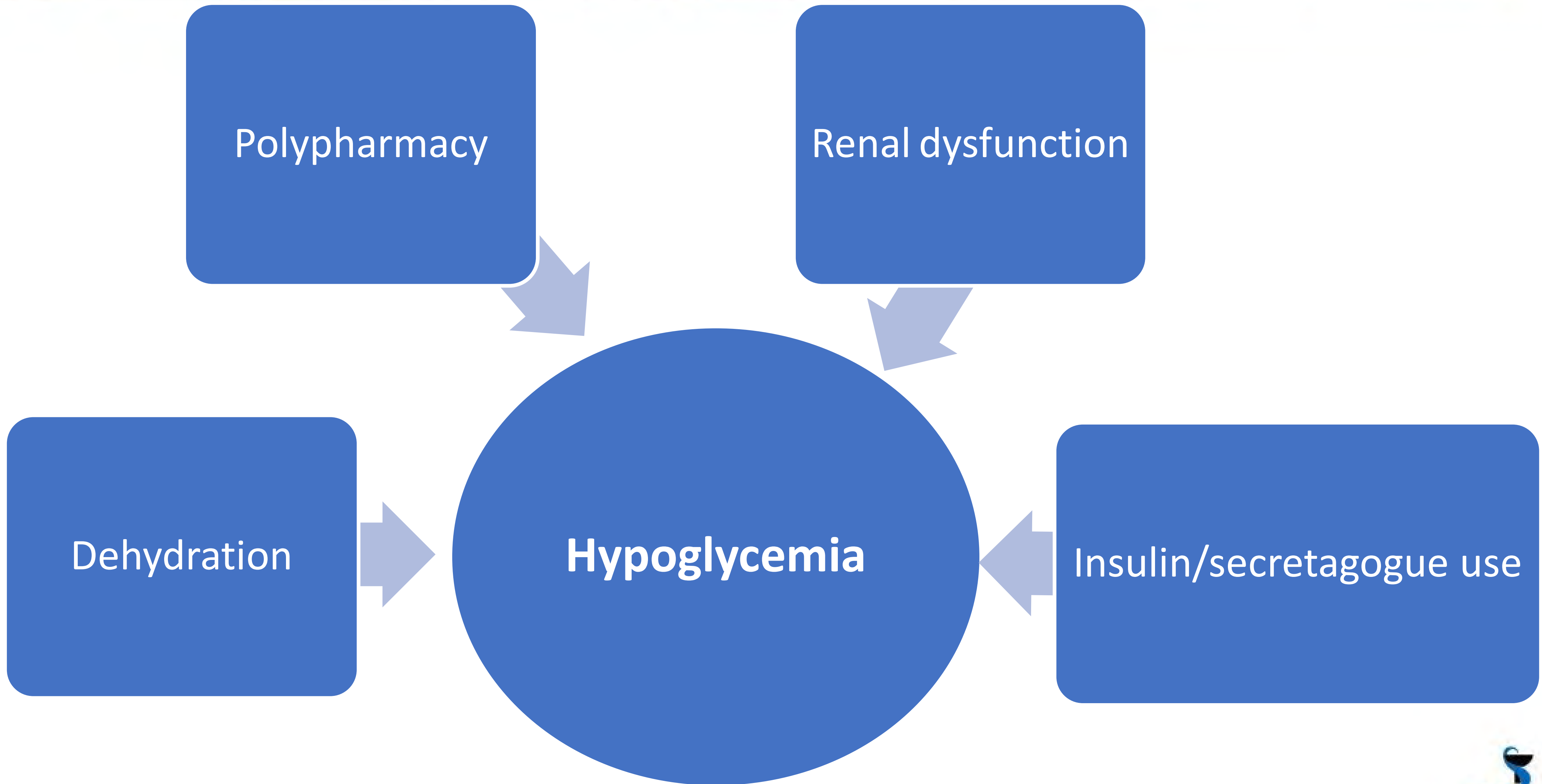
- Patients ≥65 years old in the intensive arm (n=1,732) vs. standard arm (n=1,743)
  - No MACE benefit
- Hypoglycemia requiring medical assistance
  - Annual incidence: **4.45%** vs. **1.36%**
    - HR 2.93; 95% CI 2.31-3.73
  - NNH: **32**
    - ✓ NNH for <65 years old: 61

20. *Diabetes Care*. 2014;37(3):634-43.

ACCORD, ADVANCE, VADT Takeaways

- For all patients, a more stringent A1C goal does not reduce major adverse cardiovascular events
- In those ≥ 65 years of age
  - No MACE benefit from intense A1C reduction
  - ***Significant increase*** in hypoglycemia when this is attempted

17. *N Engl J Med*. 2008;358(24):2560-72.
18. *N Engl J Med*. 2008;358(24):2545-59.
19. *N Engl J Med*. 2009;360(2):129-39.
20. *Diabetes Care*. 2014;37(3):634-43.


Polypharmacy
Renal dysfunction
Dehydration
Hypoglycemia
Insulin/secretagogue use

Examining Benefit – Reduction in MACE*

Trial	NNT	Duration (yr, median)	Elderly subgroup analysis
LEADER (liraglutide)	53	3.8	≥60 yrs favored liraglutide vs placebo (NOT statistically significant)
SUSTAIN-6 (semaglutide)	43	2.1	≥65 yrs favored semaglutide vs placebo (NOT statistically significant)

*Cardiovascular death, MI, stroke

21. *N Engl J Med*. 2016;375(4):311-22.
22. *N Engl J Med*. 2016;375(19):1834-1844.

Examining Benefit – Reduction in MACE

Trial	Outcome	NNT	Duration (yr, median)	Elderly
EMPA-REG OUTCOME (empagliflozin)	CV death, MI, stroke	63	3.1	≥65 yrs old significantly favored empagliflozin for both outcomes
	CV death	45		
DECLARE-TIMI 58 (dapagliflozin)	CV death, hospitalization for heart failure	111	4.2	Age subgroup analysis showed similar outcomes

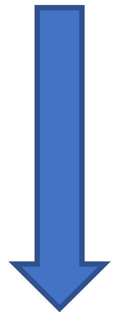
23. *N Engl J Med*. 2015;373(22):2117-28.
24. *N Engl J Med*. 2019;380(4):347-357.

DECLARE-TIMI 58: ELDERLY SUBGROUP ANALYSIS

- Number of participants
  - ≥65 – 75 years: 6,811
  - ≥75: 1,096
- Primary composite outcome - similar to overall results
  - Difference in CV death + hospitalization for heart failure
    - *Significant in those aged 65-75* (vs <65 or ≥75)

25. *Diabetes Care*. 2020;43:468-475.

DECLARE-TIMI 58: Elderly Subgroup Analysis



Age Group (years)	Serious adverse events*	Major hypo-glycemia*◊	Fractures*	AKI*
<65	107.3	1.7	11.2	4.2
65-75	131.2	2.6	15.8	5.4
≥75	191.1	6.5	17.4	9.3

*Reported per 1,000 person-years; $p < 0.0001$ for all interactions

◊Less frequent with dapagliflozin vs placebo

25. *Diabetes Care*. 2020;43:468-475.

CARDIOVASCULAR OUTCOME TRIALS TAKEAWAYS

- Elderly patients may not significantly benefit from addition of GLP-1RA with regards to MACE
- Elderly patients may benefit from SGLT2i
  - Concomitant heart failure (dapagliflozin)
  - MACE (empagliflozin)
  - Caution with ADE

21. *N Engl J Med*. 2016;375(4):311-22.
22. *N Engl J Med*. 2016;375(19):1834-1844.
23. *N Engl J Med*. 2015;373(22):2117-28.
24. *N Engl J Med*. 2019;380(4):347-357.
25. *Diabetes Care*. 2020;43:468-475.

APPLYING GERIATRIC 5M TO DIABETES

Mobility
- Hypoglycemia
- Drugs with fracture risk

Mind
- Hypoglycemia

Medications
- Hypoglycemia
- Other ADE
- Polypharmacy

Multi-complexity
- Drug – disease interaction

Matters most

6. *J Am Geriatr Soc*. 2017;65:2115.

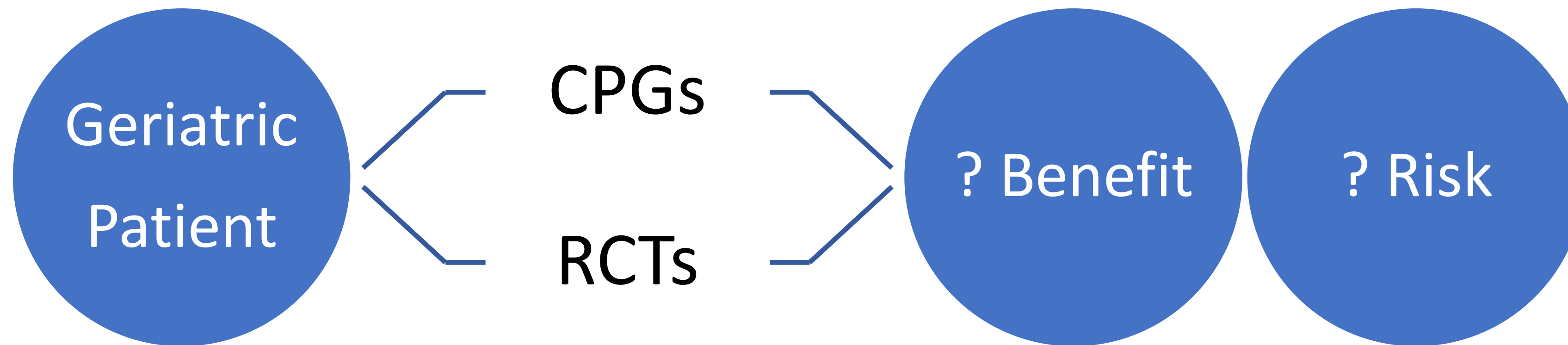
TREATMENT OF DM IN THE ELDERLY

Safer	Use with caution	Avoid if possible
• Metformin • TZD • DPP4i • GLP-1RA	• Insulin • SGLT2i • Meglitinide	• Sulfonylurea

OLDER ADULTS AND DM: SUMMARY

- Guidelines are changing to incorporate less stringent A1C goals
  - Risk of hypoglycemia
  - Avoidance of hyperglycemia
  - Prevention of macrovascular complications
- Incorporate Geriatric 5M model into treatment regimen selection

CLINICAL CONUNDRUM – HTN



5. *J Am Geriatr Soc*. 2019;67(4):665-673.

OLDER ADULTS AND HTN

- 70% of older adults (≥65 years) have HTN
  - Major risk factor for CV morbidity and mortality
  - Lower DBP is associated with increased PP and CVD risk
  - Reverse causality:
    - Low SBP readings may be related to increased morbidity and mortality
    - Exacerbate already low DBP leading to poorer coronary perfusion
      - ✓ "J-shaped" curve

26. *Circulation*. 2015;131(4):e29-e322.
27. *Circ Res*. 2019;124(7):1045-1060.

Evaluation of Older Adults and HTN

1. Confirm presence of permanent HTN
2. Exclude secondary causes
3. Evaluate CVD risk
4. Assess functional status of patient

27. *Circ Res*. 2019;124(7):1045-1060.

HTN Goals of Therapy

	ACC/AHA (2017)	ACP/AAFP (2017)	ESC/ESH (2018)
Definition of Older Patients	≥65 years	≥60 years	Elderly: 65-79 years Very old: ≥80 years
Threshold for Initiating Pharmacotherapy	≥130/80 mmHg	SBP ≥150 mmHg	Elderly: ≥140/90 mmHg Very old: ≥160/90 mmHg
HTN Goal of Therapy	<130/80 mmHg	SBP <150 mmHg	SBP 130-139 mmHg DBP 70-79 mmHg

26. *Circulation*. 2015;131(4):e29-e322.
27. *Circ Res*. 2019;124(7):1045-1060.

Major RCTs for HTN of Older Adults

HYVET Trial:

- Treatment of HTN in Patients 80 Years of Age or Older
- Aimed to resolve clinical uncertainty about risks and benefits of HTN in patients ≥80 years old
  - Target BP <150/80 mmHg

SPRINT Trial:

- A Randomized Trial of Intensive versus Standard Blood-Pressure Control
- Aimed to confirm the hypothesis that a lower SBP goal of <120 mmHg would reduce clinical events more than an SBP goal <140 mmHg

28. *N Engl J Med*. 2008;358(18):1887-1898.
29. *N Engl J Med*. 2015;373(22):2103-2116.

HYVET and SPRINT Trials: Methods

Trial	Methods
HYVET	• Design: Double-blind, randomized, placebo controlled • Setting: 195 centers in 13 countries (not the US) • Analysis: Intention to treat
SPRINT	• Design: Open-label, randomized • Setting: 102 sites in the US and Puerto Rico • Analysis: Intention to treat

28. *N Engl J Med*. 2008;358(18):1887-1898.
29. *N Engl J Med*. 2015;373(22):2103-2116.

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HYVET AND SPRINT TRIALS: POPULATIONS

Trial	Key Inclusion and Exclusion Criteria
HYVET	• Age ≥80 (no upper age limit) years with persistent HTN (sustained SBP ≥160 mmHg) • Excluded patients with secondary HTN
SPRINT	• Age ≥50 years with SBP of 130-180 mmHg • On ≤4 medications for HTN • At increased "risk" for CV events • Excluded patients with stroke, DM

28. *N Engl J Med*. 2008;358(18):1887-1898.
29. *N Engl J Med*. 2015;373(22):2103-2116.

Closer Look at SPRINT Trial Inclusion

- Definition of "risk":
  - Presence of clinical or subclinical CVD (other than stroke)
  - Chronic Kidney Disease (eGFR 20-59 ml/min/1.73 m^2 within past 6 months)
  - Framingham Risk Score ≥15%
  - **Age ≥75 years old**
- Clinical CVD:
  - Previous myocardial infarction, coronary artery bypass grafting/stenting, peripheral artery disease with revascularization, etc.
- Subclinical CVD:
  - Left ventricular hypertrophy, ankle brachial index ≤0.90, Coronary artery calcium ≥400 Agatston units

28. *N Engl J Med*. 2008;358(18):1887-1898.
29. *N Engl J Med*. 2015;373(22):2103-2116.

Shared Exclusion Criteria: HYVET and SPRINT

Congestive Heart Failure

Nursing home resident

Dementia

Condition expected to limit survival

Renal failure

28. *N Engl J Med*. 2008;358(18):1887-1898.
29. *N Engl J Med*. 2015;373(22):2103-2116.

HYVET AND SPRINT TRIALS: INTERVENTION

Trial	Interventions
HYVET	• Patients received 1.25 mg indapamide ± 2-4 mg perindopril • Patients followed every 3 months for first year, then every 6 months thereafter
SPRINT	• Patients randomized to intensive (goal SBP <120 mmHg) and standard (goal SBP <140 mmHg) treatment arms • Medications adjusted per practice standard • Patients followed monthly for first 3 months, then every 3 months thereafter

28. *N Engl J Med*. 2008;358(18):1887-1898.
29. *N Engl J Med*. 2015;373(22):2103-2116.

HYVET and SPRINT Trials: Outcomes

Trial	Primary and Secondary Outcomes
HYVET	• Primary: fatal or nonfatal stroke • Secondary: death (any cause, CV cause, cardiac cause, stroke)
SPRINT	• Primary: composite outcome of the first occurrence of myocardial infarction (MI), non-MI acute coronary syndrome (ACS), stroke, heart failure or death attributable to CVD • Secondary: individual components as above

28. *N Engl J Med*. 2008;358(18):1887-1898.
29. *N Engl J Med*. 2015;373(22):2103-2116.

HYVET AND SPRINT TRIALS: BASELINE CHARACTERISTICS

Characteristic	HYVET Intervention (n=1933)	SPRINT Intensive (n=4678)
Age Age ≥75 years – n (%)	83.6±3.2 years ---	67.9±9.4 years 1317 (28.2%)
CVD – n (%) Age ≥75 years – n (%)	223 (11.5%) ---	940 (20.1%) 338 (25.7%)
Baseline SBP mmHg Age ≥75 years	173.0±8.4 ---	139.7±15.8 141.6±15.7

28. *N Engl J Med*. 2008;358(18):1887-1898.
29. *N Engl J Med*. 2015;373(22):2103-2116.
30. *JAMA*. 2016;315(24):2673-2682.

HYVET AND SPRINT TRIALS: BASELINE CHARACTERISTICS

Characteristic	HYVET Intervention (n=1933)	SPRINT Intensive (n=4678)
Baseline DBP mmHg Age ≥75 years	90.8±8.5 ---	78.2±11.9 71.5±11
Statin use – n (%) Age ≥75 years	---	1978 (42.6%) 682 (51.8%)
Aspirin use – n (%) Age ≥75 years	---	2406 (51.6%) 820 (62.3%)

28. *N Engl J Med*. 2008;358(18):1887-1898.
29. *N Engl J Med*. 2015;373(22):2103-2116.
30. *JAMA.* 2016;315(24):2673-2682.

HYVET Trial Results

1.8 Year Median Follow Up	Primary Outcome (Rate per 1000 Patient-Years)		
	Intervention	Placebo	Unadjusted Hazard Ratio (95% CI)
Stroke			
Fatal or nonfatal – n (%)	12.4 (51)	17.7 (69)	0.70 (0.49-1.01), p=0.06
Death from stroke – n (%)	6.5 (27)	10.7 (42)	**0.61 (0.38-0.99), p=0.046**
Death (any cause) – n (%)	47.2 (196)	59.6 (235)	**0.79 (0.65-0.95), p=0.02**

28. *N Engl J Med*. 2008;358(18):1887-1898.

HYVET TRIAL RESULTS

- Target blood pressure was reached in 19.9% of placebo group patients and 48% of intervention group patients ($p<0.001$)

2 Year Follow Up	Blood Pressure Reduction (± Standard Deviation)	
	Intervention	Placebo
SBP mmHg	29.5±15.4	14.5±18.5
DBP mmHg	12.9±9.5	6.8±10.5

28. *N Engl J Med*. 2008;358(18):1887-1898.

SPRINT Trial Results ≥75 Years Old

3.14 Year Median Follow Up	Primary Outcome (% with Outcome Events per Year)		
	Intensive	Standard	Hazard Ratio (95% CI)
Primary composite outcome – n (%)	102 (2.59%)	148 (3.85)	**0.66 (0.51-0.85), p=0.001**
Secondary outcomes			
Heart Failure – n (%)	35 (0.86%)	56 (1.41%)	**0.62 (0.4-0.95), p=0.03**
All cause mortality – n (%)	144 (3.64%)	205 (5.31%)	**0.68 (0.54-0.84), p<0.001**

29. *N Engl J Med*. 2015;373(22):2103-2116.
30. *JAMA*. 2016;315(24):2673-2682.

SPRINT Trial Results ≥75 Years Old

3.14 Year Median Follow Up	Blood Pressure Reduction (Least-Square Means)	
	Intensive	Standard
SBP mmHg	123.4 (123-123.9)	134.8 (134.3-135.2)
DBP mmHg	62 (61.7-62.3)	67.2 (66.8-67.5)

29. *N Engl J Med*. 2015;373(22):2103-2116.
30. *JAMA*. 2016;315(24):2673-2682.

HYVET AND SPRINT TRIALS SAFETY

- HYVET Safety:
  - Serious Adverse Events
    - 358 in intervention group and 448 in placebo group ($p=0.001$)
    - Five deemed due to medication
- SPRINT Safety ≥75 years old:
  - Serious Adverse Events
    - 637 in both intervention and standard group

28. *N Engl J Med*. 2008;358(18):1887-1898.
29. *N Engl J Med*. 2015;373(22):2103-2116.
30. *JAMA*. 2016;315(24):2673-2682.

HYVET AND SPRINT TAKEAWAYS

- Treatment of HTN in older adults can still be beneficial
  - Further research needed to evaluate patients with MCC, those who reside in residential care facilities and more frail patients
- Goals of therapy still controversial
  - Varying literature has used different SBP and DBP treatment targets
  - Serious adverse events may not differ between intensive and standard treatments
    - Hypotension, electrolyte imbalances and kidney injury more commonly occur

28. *N Engl J Med*. 2008;358(18):1887-1898.
29. *N Engl J Med*. 2015;373(22):2103-2116.
30. *JAMA.* 2016;315(24):2673-2682.

Older Adults and HTN Summary

Preserved	Loss of Function/Preserved	Loss of Function
• Patient: functional, independent, no MCC • Goal SBP 120-140 mmHg • Titrate medication cautiously	• Patient: presence of MCC, moderate cognitive, functional decline, some loss of ADL • Detailed frailty assessment	• Patient: limited life expectancy, advanced disease • Goal SBP 150 mmHg • Reduce medication burden, if able

- ADL = Activities of Daily Living

27. *Circ Res*. 2019;124(7):1045-1060.

APPLYING GERIATRIC 5M TO HTN

Mobility
- Hypotension

Mind

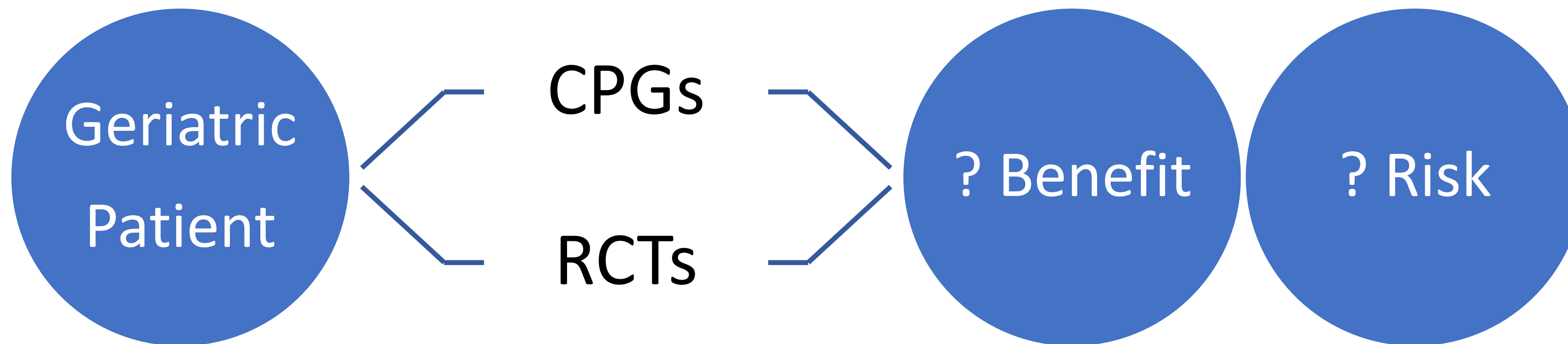
Medications
- ADE
- Polypharmacy

Multi-complexity
- Lack of evidence

Matters most

6. *J Am Geriatr Soc*. 2017;65:2115.

Clinical Conundrum – Primary prevention of ASCVD



5. *J Am Geriatr Soc*. 2019;67(4):665-673.

ASCVD IN THE ELDERLY

- 60% of death in those over 85 is due to ASCVD
- Decrease in total cholesterol by 10%
  - ↓ CV death by 20% in persons > 70 years of age
  - ↓ CV death by 18% in persons > 80 years of age
- Age alone places elderly patients over threshold for statin use based on commonly used ASCVD calculators

31. *J Am Geriatr Soc*. 2018;66(11):2188-96.
32. *Arch Gerontol Geriatr.* 2010;50(1):114-8.

PRINCIPLES OF PRIMARY PREVENTION IN THE ELDERLY

1. Assess ASCVD risk score

2. Consider risk enhancing factors

3. Address modifiable factors

Other patient specific factors

Preferences
Goals
Life-expectancy

PRIMARY REVENTION: TIME TO BENEFIT

MI prevention — **2 years**

Stroke prevention — **5 years**

33. *J Am Geriatr Soc.* 2018;66(2):229-34.

ASCVD Risk Calculators

PCE

- ACC/AHA
- Valid until 79 years

FRE

- VA/DoD
- Not well validated beyond 75 years

QRISK2

- NICE-UK
- Only calculator valid until age 80, through 84
- Age >70 → moderate risk

SCORE

- ESC/EAS
- **Not valid for >65 years**

PCE = Pooled Cohort Equation FRE = Framingham Risk Estimator SCORE = Systemic Coronary Risk Estimation

34. *Drugs & Aging*. 2019;36:687-699.
35. *BMJ*. 2008;336(7659):1475-82.

CONSIDER RISK ENHANCING FACTORS

- *Coronary artery calcium**
- FH of premature ASCVD
- 1° hypercholesterolemia
- CKD
- Metabolic syndrome
- Inflammatory conditions
- Premature menopause
- High-risk race/ethnicity
- Lipids/biomarkers
  - Apolipoprotein B, lipoprotein A, triglycerides
- Ankle brachial index <0.9

36. AHA/ACC Guideline on the Management of Blood Cholesterol. *J Am Coll Cardiol*. 2018
37. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. *Circulation*. 2019.

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TREATMENT GUIDANCE

Guideline	65 years old	>75 years old
ESC/EAS	SCORE n/a beyond age 65 Consider with HTN, smoking, DM, and dyslipidemia	
AHA/ACC 2018	≥7.5% 10-yr risk per PCE with LDL 70-189	Risk discussion, consider CAC Reasonable to consider moderate intensity statin for LDL 70-189
ACC/AHA 2019	≥7.5% 10-yr risk per PCE with LDL 70-189	No recommendation
VA/DoD	Consider moderate intensity statin for 6-12% 10-yr risk per FRE or PCE Indicated for ≥ 12% 10-yr risk per FRE or PCE	

36. AHA/ACC Guideline on the Management of Blood Cholesterol. *J Am Coll Cardiol*. 2018
37. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. *Circulation*. 2019.
38. *G Ital Cardiol (Rome)*. 2017; 18(7)5477-612.
39. VA/DoD clinical practice guideline for the management of dyslipidemia for cardiovascular risk reduction. Guidelines. 2014

Primary prevention: JUPITER and HOPE-3

	JUPITER	HOPE-3
N	17,802	12,705
Population	LDL <130 mg/dL and elevated C-reactive protein	Intermediate risk for first event
Intervention	Rosuvastatin 20 mg vs placebo	Rosuvastatin 10 mg vs placebo
Outcome	3-point MACE	3-point MACE
Follow-up	2.2 years	5.0 years
Result	47% Risk reduction (HR, 0.53; 95% CI, 0.40-0.69; **P<0.0001**)	24% Risk reduction (HR, 0.76; 95% CI, 0.64-0.91; **P=0.002**)

40. *Circulation*. 2017;135(20):1979-81.

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PRIMARY PREVENTION: JUPITER AND HOPE-3 ≥70 YEARS OF AGE SUBANALYSIS

	JUPITER	HOPE-3
N	5696 (32% of participants)	3,086 (24% of participants)
Population	LDL <130 mg/dL and elevated C-reactive protein	Intermediate risk for first event
Intervention	Rosuvastatin 20 mg vs placebo	Rosuvastatin 10 mg vs placebo
Outcome	3-point MACE	3-point MACE
Follow-up	2.2 years	5.0 years
Result	39% Risk reduction (HR, 0.61; 95% CI, 0.43-0.86; **P=0.004**)	17% Risk reduction (HR, 0.83; 95% CI, 0.64-1.07; **P=0.16**)

40. *Circulation*. 2017;135(20):1979-81.

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PRIMARY PREVENTION: JUPITER AND HOPE-3 ELDERLY SUBANALYSIS

Limitations

- Rates of drug withdrawal increased as age increased
  - JUPITER: 21.6% in those ≥ 70 years of age
  - HOPE-3: 29.1% in those ≥ 70 year of age
- Not many participants ≥ 80 years of age

40. *Circulation*. 2017;135(20):1979-81.

ASSOCIATION OF STATIN USE WITH ALL-CAUSE AND CARDIOVASCULAR MORTALITY IN US VETERANS 75 YEARS AND OLDER

Study	Restrospective cohort	
Population	Veterans >75 with no hx ASCVD and no prior statin use	
Intervention/ Comparator	New statin use	No statin use
Outcome	All-cause mortality, All CV death	

41. *JAMA*. 2020;324(1):68-78.

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ASSOCIATION OF STATIN USE WITH ALL-CAUSE AND CARDIOVASCULAR MORTALITY IN US VETERANS 75 YEARS AND OLDER

Follow-up *(mean, years)*	6.8	
Group	**Statin**	**No statin**
n	57,178	326,981
All-cause mortality* *(1000 person-yrs)*	78.7	98.2
All CV death* *(1000 person-yrs)*	22.6	25.7

***P<0.001**

41. *JAMA*. 2020;324(1):68-78.

Association of Statin Use With All-Cause and Cardiovascular Mortality in US Veterans 75 Years and Older

Strengths	Limitations
• Average age 81 years of age • Inclusion of participants >90 years of age • Large sample size • Longer duration of follow-up vs JUPITER or HOPE-3	• White men • Simvastatin most commonly used • Claims data • ADEs not assessed • LDL not measured

41. *JAMA*. 2020;324(1):68-78.

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APPLYING GERIATRIC 5M TO PRIMARY PREVENTION

Mobility
- Statin-associated muscle symptoms

Mind

Medications
- Drug interactions
- Polypharmacy

Multi-complexity

Matters most
- Life-expectancy
- Time to benefit

6. *J Am Geriatr Soc*. 2017;65:2115.

PRIMARY PREVENTION IN THE ELDERLY: SUMMARY

- Usually it is reasonable to continue the use or initiate statin therapy in those ≥ 65 years old
- Consider time to benefit
- Utilize Geriatric 5M principles when making treatment decisions

GERIATRIC MANAGEMENT PRINCIPLES

- Pharmacists' Role:
  - ✓ Incorporate patients' health outcome goals, healthcare preferences into pharmacotherapy treatment decisions
  - ✓ Minimize care burden by stopping inappropriate/unnecessary medications, judicious medication monitoring
  - ✓ Review and adjust self-management tasks to promote adherence
  - ✓ Prioritize pharmacotherapies with symptomatic and quality of life benefits

5. *J Am Geriatr Soc*. 2019;67(4):665-673.

Case Presentation: SB

SB is a 76 y/o woman with PMH HTN, HFrEF with ejection fraction 38%, HLD, and type 2 DM. She has NKDA. She has no cognitive dysfunction, but requires assistance with laundry and finances.

Current medications:

Current medications
Carvedilol 3.125 mg BID
Glipizide 5 mg daily
Lisinopril 5 mg daily
Metformin 500 mg BID
Spironolactone 12.5 mg daily

Current labs and vitals:

Parameter	Value
Blood pressure	148/76 mmHg
Heart rate	70 bpm
BMI	21.6 kg/m^2
SCr;eGFR	1.2 mg/dL;50 mL/min
K	4.1 mEq/L
HgA1C	8.2%
LDL	110 mg/dL

TEST QUESTION 1

SB is a 76 y/o woman with PMH HTN, HFrEF with ejection fraction 38%, HLD, and type 2 DM. She has NKDA. Which of the following is true regarding SB's A1C goal?

a. She is classified as very complex and is at her goal of <8.5% per ADA
b. She is classified as healthy and her A1C is not at goal of <7-7.5% per AGS
c. She is classified as very complex and it is reasonable to individualize her A1C goal per AACE
d. She is classified as complex/intermediate and is at her goal of 8-9% per ESC

TEST QUESTION 1

SB is a 76 y/o woman with PMH HTN, HFrEF with ejection fraction 38%, HLD, and type 2 DM. She has NKDA. Which of the following is true regarding SB's A1C goal?

a. She is classified as very complex and is at her goal of <8.5% per ADA
b. She is classified as healthy and her A1C is not at goal of <7-7.5% per AGS
c. She is classified as very complex and it is reasonable to individualize her A1C goal per AACE
d. **She is classified as complex/intermediate and is at her goal of 8-9% per ESC**

TEST QUESTION 2

SB is a 76 y/o woman with PMH HTN, HFrEF with ejection fraction 38%, HLD, and type 2 DM. She has NKDA. Which of the following precludes applying the results of SPRINT and HYVET to her blood pressure goal?

a. She has diabetes, and those with DM were excluded from SPRINT
b. She has heart failure, and those with heart failure were excluded from both trials
c. She does not meet the age criteria for SPRINT of over 80 years
d. A and B are correct
e. A, B, and C are correct

TEST QUESTION 2

SB is a 76 y/o woman with PMH HTN, HFrEF with ejection fraction 38%, HLD, and type 2 DM. She has NKDA. Which of the following precludes applying the results of SPRINT and HYVET to her blood pressure goal?

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c. She does not meet the age criteria for SPRINT of over 80 years
d. **A and B are correct**
e. A, B, and C are correct

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TEST QUESTION 3

SB is a 76 y/o woman with PMH HTN, HFrEF with ejection fraction 38%, HLD, and type 2 DM. She has NKDA. Which of the following is appropriate to consider prior to initiating statin therapy in SB?

a. Calculate her risk using the SCORE tool and consider measuring CAC
b. Consider lowering her LDL by 20-30% because she has type 2 DM
c. Consider her life expectancy and consider measuring CAC
d. Counsel her on BP lowering prior to considering a statin

TEST QUESTION 3

SB is a 76 y/o woman with PMH HTN, HFrEF with ejection fraction 38%, HLD, and type 2 DM. She has NKDA. Which of the following is appropriate to consider prior to initiating statin therapy in SB?

a. Calculate her risk using the SCORE tool and consider measuring CAC
b. Consider lowering her LDL by 20-30% because she has type 2 DM
c. **Consider her life expectancy and consider measuring CAC**
d. Counsel her on BP lowering prior to considering a statin

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6. Tinetti M, Huang A. The geriatrics 5M's: a new way of communicating what we do. *J Am Ger Soc*. 2017;65:2115.
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9. Thake M, Lowry A. A systematic review of trends in the selective exclusion of older participant from randomised clinical trials. *Arch Gerontol Geriatr*. 2017;72:99-102. doi:10.1016/j.archger.2017.05.017
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13. American Diabetes Association. 12. Older Adults: *Standards of Medical Care in Diabetes-2020*. *Diabetes Care*. 2020;43(Suppl 1):S152-S162. doi:10.2337/dc20-S012

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16. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41(2):255-323. doi:10.1093/eurheartj/ehz486
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20. Miller ME, Williamson JD, Gerstein HC, et al. Effects of randomization to intensive glucose control on adverse events, cardiovascular disease, and mortality in older versus younger adults in the ACCORD Trial. *Diabetes Care*. 2014;37(3):634-43.
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24. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019;380(4):347-357. doi:10.1056/NEJMoa1812389
25. Cahn A, Mosenzan O, Wiviott SD, et al. Efficacy and Safety of Dapagliflozin in the Elderly: Analysis from the DECLARE-TIMI 58 Study. *Diabetes Care*. 2020;43:468-475. doi:10.2337/dc19-1476
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