Clinical Pearls in Geriatric Pharmacy

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Disclaimer and Conflicts of Interest

- No financial disclosures or conflicts of interest
- The contents of this presentation do not represent the views of the U.S. Department of Veterans Affairs or the United States Government
- This presentation will include discussion of off label/experimental use of SGLTS inhibitors

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Objectives

- Analyze the role of statins for primary prevention in the older adult population
- Identify additional benefits for SGLT2 inhibitors beyond management of diabetes

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Older Adults and Statins for Primary Prevention

- Adults over the age of 75 are one of the fastest growing age groups in the US population
- Incidence of ASCVD increases with age and is a leading cause of death in the US
  - Elderly patients are underrepresented in statin trials
- Current guidelines have vague recommendations for patients 75 years and older

Ortman J, Velkoff V, Hoga H. An Aging Nation: The Older Population in the United States: Population Estimates and Projections. 2014.

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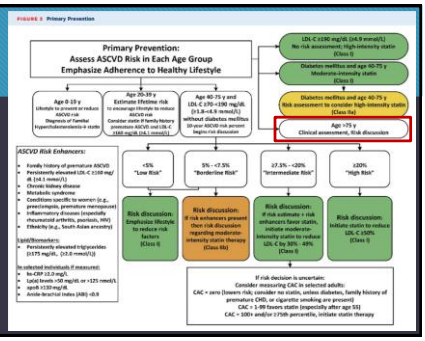
2019 ACC/AHA Guidelines



Arnett D, Blumenthal R, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. 2019; 74(10): e178-232.

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JAMA | Original Investigation

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

- Retrospective cohort study from 2002-2012 (n=326,981)
- Adults 75 years of age and older (avg 81 years)
  - Statin-naïve with no history of ASCVD
  - Included patients typically excluded from clinical trials
    - Cancer, dementia, CKD, liver disease, etc.
- Conducted across the VA health system
  - Utilized information in VA system and CMS claims data

Association of Statin Use With All-Cause and Cardiovascular Mortality in US Veterans 75 Years and Older. Orkaby, A, Driver, J, Ho, Y, et al. JAMA. 2020; 324(1): 68-74.

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Outcomes

- Primary outcomes
  - All-cause mortality
  - Cardiovascular mortality
- Secondary outcomes
  - Myocardial infarction
  - Ischemic stroke
  - Revascularization (CABG/PCI)
  - Composite ASCVD events

Association of Statin Use With All-Cause and Cardiovascular Mortality in US Veterans 75 Years and Older. Orkaby, A. Driver, J. Ho, Y. et al. JAMA. 2020; 324(1): 68-74.

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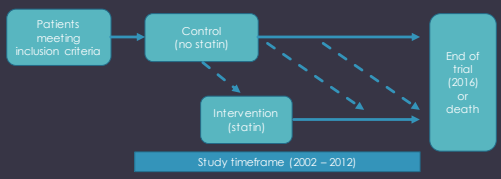
Study Design

- New-user study design



Association of Statin Use With All-Cause and Cardiovascular Mortality in US Veterans 75 Years and Older. Orkaby, A. Driver, J. Ho, Y. et al. JAMA. 2020; 324(1): 68-74.

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Results

- All-cause mortality (p-value < 0.001):
  - 78.7* in statin user group; 98.2 in non-statin user group
- Cardiovascular mortality (p-value < 0.001):
  - 22.6 in statin user group; 25.7 in non-statin user group

Statins Utilized:
Simvastatin (84.8%)
Lovastatin (11%)
Pravastatin (2.5%)
Fluvastatin (1.2%)
Atorvastatin & Rosuvastatin (0.5%)

- *incidence per 1000 patient-years

Secondary outcomes					
ASCVD composite (n = 123 379)*	66.3	70.4	−4.05 (−5.09 to −3.02)	0.92 (0.91 to 0.94)	<.001
Myocardial infarction (n = 24 951)	13.2	12.6	0.56 (0.13 to 0.98)	0.99 (0.97 to 1.03)	.94
Ischemic stroke (n = 35 630)	18.4	18.2	0.25 (−0.26 to 0.76)	0.98 (0.96 to 1.01)	.20
CABG surgery/PCI (n = 74 362)	35.2	39.2	−3.38 (−4.12 to −2.64)	0.89 (0.88 to 0.91)	<.001

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Secondary Outcomes

Outcome	No. of events/No. at risk: Statin user	Statin nonuser	Weighted incidence rate difference/1000 person-years (95% CI)	HR (95% CI)	Favors statin continuation	Favors statin discontinuation	P value for interaction
All-cause mortality							
Sex							
Men	35025/555622	166416/318244	-19.61 (-20.55 to -18.67)	0.75 (0.74-0.76)			.31
Women	941/1,556	4520/8737	-14.48 (-19.58 to -9.38)	0.78 (0.72-0.84)			
Race							
White	32541/51570	155658/296617	-19.51 (-20.48 to -18.53)	0.75 (0.74-0.76)			.71
Black	2853/4530	12699/24641	-20.32 (-23.78 to -16.87)	0.77 (0.74-0.80)			
Other	572/1028	2579/4645	-14.36 (-20.52 to -8.19)	0.77 (0.69-0.85)			
Age group, y							
75-79	13568/24092	69439/163178	-9.56 (-10.74 to -8.37)	0.78 (0.76-0.80)			.34
80-84	15966/24295	66281/115062	-16.63 (-18.14 to -15.13)	0.78 (0.77-0.80)			
85-89	5660/7826	28306/40186	-23.13 (-26.40 to -19.84)	0.80 (0.78-0.83)			
≥90	772/965	6910/8555	-35.90 (-47.31 to -24.50)	0.80 (0.74-0.86)			
Diabetes							
Yes	10917/15429	19108/42969	-16.59 (-18.85 to -14.32)	0.74 (0.72-0.76)			.59
No	25049/41749	151828/284012	-20.66 (-21.68 to -19.64)	0.74 (0.73-0.75)			
Dementia							
Yes	3614/4283	21675/27686	-44.02 (-49.07 to -38.98)	0.73 (0.70-0.76)			.01
No	32352/52895	149261/299295	-17.24 (-18.17 to -16.31)	0.76 (0.75-0.77)			
Arthritis							
Yes	16706/26274	64793/101909	-17.47 (-18.85 to -16.10)	0.76 (0.75-0.77)			.001
No	19260/30904	106143/16789	-20.30 (-21.55 to -19.04)	0.74 (0.73-0.76)			

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Impressions

- Strengths:
  - Large sample size
  - Inclusion of patients with various comorbidities
- Limitations:
  - Statins utilized in this study not necessarily reflective of current practice
  - Statin intensity not defined
  - Incidence of adverse effects not measured
  - Women and minorities highly underrepresented in the study population

Association of Statin Use With All-Cause and Cardiovascular Mortality in US Veterans 75 Years and Older. Orkaby, A. Dhr er, J. Ho, Y. et al. JAMA. 2020; 324(1):68-74.

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More to Come!

- STAREE (expected 2023)
  - Will include patients 70 years and older
  - Placebo vs atorvastatin 40mg QDAY
  - Outcomes:
    - Death, development of dementia, or development of disability
- PREVENTABLE (expected 2026)
  - Patients 75 years and older
  - Placebo vs atorvastatin 40mg QDAY
  - Primary outcome to be development of dementia and disability-free survival

https://www.clinicaltrials.gov

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Outline

- Statins for primary prevention
- Potential alternative indications for SGLT2 inhibitors

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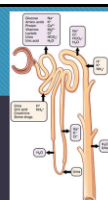
SGLT2 Inhibitors



- Medications in this class:
  - Empagliflozin (Jardiance)
  - Dapagliflozin (Farxiga)
  - Canagliflozin (Invokana)
  - Ertugliflozin (Steglatro)
- Lower glucose by inhibiting the sodium-glucose cotransporter 2 (SGLT-2) in the proximal tubule
  - Limits reabsorption of filtered glucose and lowers the renal threshold for glucose

SGLT2 inhibitors. UptoDate. Drug Information. Last updated 2020.
Image from: https://www.google.com/url?sa=i&url=https%3A%2F%2Fen.wikipedia.org%2Fwiki%2FNephron&psig=AOvVaw3SlloX-dry5HWoJzfCj07x&ust=1602883114834000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCLj64ZDDt-wCFQAAAAAdAAAAABAI

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Side Effects

- Orthostatic hypotension
- Increase in serum creatinine (SCr)
  - Discontinue if SCr >33% elevated from baseline after starting the medication
- Volume depletion
- Urinary tract infections

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Precautions and Contraindications

- **Consider avoiding in patients with:**
  - Frequent UTI's or genitourinary yeast infections
  - Significantly decreased renal function
- Not for patients with type 1 diabetes, history of DKA, or those with ESRD

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DAPA-HF

- Randomized controlled trial
- Patients with HFrEF (with or without type 2 diabetes)
  - Average age included was 66 years old
- Dapagliflozin 10mg daily compared to placebo

Mcmurray J, Solomon S, Inzucchi S, Kosiborod K, Kober L, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. The New England Journal of Medicine. 2019; 381:21; 1995-2008.

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Outcomes

- Primary outcome:
  - Worsening heart failure or cardiovascular (CV) mortality
- Secondary outcomes:
  - Cardiovascular death or heart failure hospitalization
  - Changes in Kansas City Cardiomyopathy Questionnaire (KCCQ) score
  - Worsening renal function
  - All-cause mortality

Mcmurray J, Solomon S, Inzucchi S, Kosiborod K, Kober L, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. The New England Journal of Medicine. 2019; 381:21; 1995-2008.

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DAPA-HF Results

- Statistical significance favoring dapagliflozin for all outcomes
  - No difference noted in renal outcomes
- For prevent of cardiovascular-related hospitalizations, NNT = 21

Mcmurray J, Solomon S, Inzucchi S, Kosiborod K, Kober L, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. The New England Journal of Medicine. 2019; 381: 21. 1995-2008.

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DAPA-HF Results

- No difference in adverse effects between dapagliflozin and placebo groups
  - Renal adverse events 1.6% in dapagliflozin vs 2.7% placebo (p=0.009)
- Diabetes status did not make a difference in the outcomes
  - Hypoglycemia and DKA only occurred in patients with diabetes

Mcmurray J, Solomon S, Inzucchi S, Kosiborod K, Kober L, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. The New England Journal of Medicine. 2019; 381: 21. 1995-2008.

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Overview of SGLT2 Inhibitors in HF

- Proposed mechanisms:
  - Reduction in preload
  - Improved cardiac metabolism
  - Reduction in sodium levels in the cytoplasm
- Dapagliflozin now FDA approved for management of HFrEF

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Summary of Evidence (Heart Failure)

Study	Reduction of CV deaths	MACE Reduction	Reduction in hospitalizations for HF	Slowed decline in renal function
DAPA-HF	✓		✓	—
DECLARE-TIMI	✓	—	✓	✓
EMPEROR-REDUCED	✓		✓	✓
CANVAS	✓	✓		✓

✓ Outcomes favored SGLT2-i use

— No difference in outcomes

Blank cells indicate outcome not assessed in study

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Summary of Evidence (CKD)

Study	Slowed decline of eGFR	ESRD	AKI	Reduction in renal/CV deaths
DAPA-CKD	✓	✓	—	✓
CREDENCE	✓	✓	—	✓
CANVAS	✓	✓	—	✓

✓ Outcomes favored SGLT2-i use

— No difference in outcomes

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Summary of SGLT2 Inhibitors

- Efficacy in CHF and CKD appears to be a class-effect
- More studies are underway
  - HFpEF
  - CKD
- Anticipate guideline updates as more evidence comes out

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A Critical Consideration…

September 14, 2020

Out-of-Pocket Costs for Novel Guideline-Directed Diabetes Therapies Under Medicare Part D

Colette DeJong, MD[1]; Camlyn Masuda, PharmD, BCACP, CDCES[2]; Randi Chen, MS[3]; et al

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Conclusions

- Consider using statins for primary prevention in older adults as they may likely still benefit
- SGLT2 inhibitors will likely be included in future revisions of heart failure and CKD guidelines
  - Decreased hospitalizations, death from renal or cardiovascular causes
  - No difference in development of AKI when compared to placebo

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Questions?

- Emily Harder (Emily.Harder@va.gov)

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References

- Ortman J, Velkoff V, Hoga H. An Aging Nation: The Older Population in the United States: Population Estimates and Projections. 2014.
- Arnett D, Blumenthal R, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. 2019; 74(10): e178-232.
- National Institute of Health. https://www.clinicaltrials.gov
- Mcmurray J, Solomon S, Inzucchi S, Kosiborod K, Kober L, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. The New England Journal of Medicine. 2019; 381; 21. 1995-2008.
- Wiviott S, Raz I, Bonaca M, Mosenzon O, et al. Dapagliflozin and Cardiovascular Outcomes (DECLARE-TIMI 58). New England Journal of Medicine. 2019; 380: 347-357.
- Perkovic V, Jardine M, Neal B, Bompoint S, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE). New England Journal of Medicine. 2019; 380:2295-2306.
- Neal B, Perkovic V, Mahaffey K, Zeeuw D, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS). 2017; 377:644-657.
- Heerspink H, Stefansson B, Correa-Rotter R, Chertow G, Greene T, et al. Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD). New England Journal of Medicine. 2020;383:1436-46.
- Packer M, Anker S, Butler J, Filippatos G, Pocock S, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. New England Journal of Medicine. 2020. DOI: 10.1056/NEJMoa2022190.

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