Case Presentation:
A 70 y/o female with PMHx of HTN, diabetes, hypercholesteremia was seen in the clinic for her routine visit. The patient was prescribed and started on Farxiga which she has been complaint on for 4 weeks. She is well controlled on the medication. During discussion with the doctor, she mentioned that Farxiga (an SGLT2 inhibitor) is a fairly new class of anti-diabetic medications and have been very beneficial for the patients whom they have prescribed it for.

I wanted to know if SGLT2 inhibitors (which like most drugs has its side effects) are safe for use in our patient population (Elderly > 65 y/o) short term or long term.

Clinical Question: Are SGLT2 inhibitors safe for use in Elderly patients with diabetes?

Question Type: What kind of question is this?
Prevalence Screening Diagnosis
Prognosis Treatment Harms

For my question I am looking for studies that explore the harms of SGLT2 inhibitors as a class and also any additional information on individual drugs within the class. As the population that is being explored are elderly it is important to know whether the harms of a medication class may outweigh the benefits of the drug and to note any potential contraindications or any other uncommon side effects that may not be noted frequently. Because of the importance of this question, I think because this is harms question observational studies may be ethically better. I think that retrospective, prospective cohort studies and case studies can be beneficial. Findings from randomized controlled trials that originally may have been investigating the effectiveness of the medication may also provide some information on the side effects of the drug class. Although these would all be good alternatives in the absence of Systematic reviews and Meta-analysis, these two if available would provide the highest standard of evidence.

PICO search terms:

P	I	C	O
Elderly patients	SGLT2 inhibitors	Placebo	Adverse outcomes
Male and Female patients older than 65 years old	Farxiga		Safety risks
Elderly patients with Type 2 diabetes mellitus	Dapagliflozin		Negative side effects

SEARCH TOOLS & LIMITS

Number of articles returned once relevant limits are added

Database	Filter	Terms Searched	Articles Returned

PubMed	1. English, Human studies, Age 65+ and 80+, 2012-2022 Clinical Trials/ Meta-analysis/ RCT/ Systematic review	"SGLT2 inhibitors safety in diabetic elderly"	• 196
PMC/NCBI	1. Open access/ 10 years	"Are SGLT2 inhibitors safe for use in elderly patients"	• 171
Cochrane library	1. Title, abstract, Keyword/ English 2012-2022	"SGLT2 inhibitors safety in elderly"	• Cochrane (0) • Reviews (0) • Trials (11)

For this study, my clinical question was a little more general in the sense that although I wanted to find out the safety profile of this drug class on the elderly population, my question does not focus on other criteria such as race, other underlying health conditions etc. I chose the 3 databases listed above because they usually provide an extensive list of search results (particularly PubMed). I used the few search phrases above because I wanted to try and narrow down my findings to my search topic and population as much as possible. PubMed was most helpful as it had many filters to help narrow down my results. I chose the following articles from these databases by first

i. Narrowing down the articles by finding systematic reviews and meta-analyses first
ii. Then eliminated articles that focused on race, ethnicity, drug combination therapies, age etc.
iii. I also tried to find articles that looked at the general class of medication first and then explored specific drugs.
iv. I then ranked articles based on most recent vs. older articles.

Once all this was done, I decided to read through the abstracts for articles I felt focused more on my study question before deciding which seemed to be the most resourceful to use for my Pico.

<u>Article 1:</u> SGLT2 inhibitors and cardiovascular and renal outcomes: a meta-analysis and trial sequential analysis

Citation: Barbarawi M, Al-Abdouh A, Barbarawi O, Lakshman H, Al Kasasbeh M, Chen K. SGLT2 inhibitors and cardiovascular and renal outcomes: a meta-analysis and trial sequential analysis. Heart Fail Rev. 2022 May;27(3):951-960. doi: 10.1007/s10741-021-10083-z. Epub 2021 Feb 23. PMID: 33620621.

Type of Study: Meta-Analysis & trial sequential analysis

Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce cardiovascular events and renal outcomes in patients with diabetes mellitus (DM). This meta-analysis aimed to provide a thorough evaluation regarding the efficacy and safety of SGLT2 inhibitors. Data search of MEDLINE/PubMed, Embase, and Cochrane Library databases and ClinicalTrials.com from inception through November 26, 2020. We included randomized trials, SGLT2 inhibitors compared with placebo, patients with or without diabetes at recruitment, and reporting the incidence of cardiovascular or renal outcomes. Two authors

extracted pertinent data into predefined data collection tables. Ten trials were included (71,553 patients). The mean age was 64.7 ± 8.4 years, with 65.1% male. Follow-up durations range 9-50 months. Inhibition of SGLT2 resulted in lower composite outcome of heart failure (HF) hospitalization or cardiovascular death (RR 0.76, 95% CI 0.73-0.81, P < 0.01) and lower risk of renal outcomes (RR 0.68, 95% CI 0.60-0.77, P < 0.01). Furthermore, SGLT2 inhibitors were associated with lower major adverse cardiovascular events (MACEs), HF hospitalization, cardiovascular mortality, all-cause mortality, myocardial infarction, and serious adverse events, compared with placebo (P < 0.05). Sensitivity analyses revealed lower MACE events also in patients with HF, and a lower HF hospitalization and cardiovascular mortality in non-diabetic patients (P < 0.05). While the amputation risk was comparable between the two groups, the risk of diabetic ketoacidosis was higher in the SGLT2 inhibitor group. Inhibition of SGLT2 in patients with DM and prevalent ASCVD reduces the risk of HF hospitalization, cardiovascular mortality, all-cause mortality, MACE, and renal outcomes without increasing the risk of serious adverse events or amputation.

Reason for Selection: I chose this article because it is meta-analysis and provides a higher level of evidence. It was one of the most recent articles amongst my search results. In comparison to another meta-analysis and systematic review I came across, this study had a mean age of 64.7 (+/- 8.4 years) which was closer to my study population (elderly patients) compared to the other meta-analysis. It also had a large study sample for the analysis.

Key points:

- The goal of the article was to evaluate the efficacy and safety of SGLT2 inhibitors particularly Canagliflozin, Empagliflozin, Dapagliflozin, Sota-gliflozin, Ertugliflozin
- The search databases included: MEDLINE/PubMed, Embase, and Cochrane Library databases and ClinicalTrials.com and included studies from inception up to November 26, 2020, and include a study population of 71,553 patients (of whom 39, 053 pts were on SGLT2 inhibitors)
- The study explores the efficacy of the medication in patients with or without diabetes (and included 8 large RCTs with study populations of at least 500 patients) in comparison to placebo
- SGLT2 inhibitors promote glycosuria (by blocking glucose re-absorption in the proximal kidney tubules). SGLT2 inhibitors are also associated with decreased arterial stiffness and weight reduction
- The American Diabetic Association (ADA) have recommended SGLT2 inhibitors for the treatment of patients with DM and established CVD (class IIa, level B).
- The primary outcome of the study was incidence of composite of HF hospitalization, Cardiovascular death and renal outcomes (AKI, renal death). Secondary outcomes were major adverse cardiovascular events (MACE), HF hospitalization, cardiovascular mortality, all-cause mortality, MI, all serious adverse events, amputation risk and DKA.
- Findings" Primary endpoint shows SGLT2 inhibitors were associated with lower composite rate of HF hospitalization (24% reduction) or cardiovascular death and renal outcome (32% reduction) compared with placebo. For secondary endpoints MACE was lower in the SGLT2 inhibitors group, lower rate of HF hospitalizations, cardiovascular mortality, MI, and all-cause mortality compared to placebo.
- Safety outcomes shows less serious adverse events with SGLT2 inhibitors but **higher risk of DKA,** comparable amputation risk except in the case of Canagliflozin which showed increase in amputation risk.
- Dapagliflozin was found to show remarkable results for treating HF regardless of presence or absence of T2DM.
- Although not discussed in the result section, for secondary outcomes, there was shown to be an increased risk for genital fungal infections with the use of SGLT2 inhibitors.

PDF Link: https://link.springer.com/content/pdf/10.1007/s10741-021-10083-z.pdf

<u>Article 2:</u> Inhibition of the sodium-glucose co-transporter 2 in the elderly: clinical and mechanistic insights into safety and efficacy

Citation: Cintra R, Moura FA, Carvalho LSF, Barreto J, Tambascia M, Pecoits-Filho R, Sposito AC. Inhibition of the sodium-glucose co-transporter 2 in the elderly: clinical and mechanistic insights into safety and efficacy. Rev Assoc Med Bras (1992). 2019 Jan;65(1):70-86. doi: 10.1590/1806-9282.65.1.70. PMID: 30758423.

Type of Study: Systemic Review and Meta-analysis

Abstract

The prevalence of type 2 diabetes mellitus (T2DM) in the elderly grew sharply over the last decade. Reduced insulin sensitivity and secretory capacity, weight gain, sarcopenia, and elevated adiposity are all common metabolic and body changes in the aging population that favor an increased risk of hypoglycemia, frailty syndrome, falls, and cognitive dysfunction. First line antidiabetic therapy is frequently not safe in older individuals because of its high risk of hypoglycemia and prevalent co-morbid diseases, such as chronic kidney disease, osteoporosis, cardiovascular disease, and obesity. Sodium-glucose cotransporter 2 inhibitor (SGLT2i) is a new class of antidiabetic therapy that inhibits glucose and sodium reabsorption on renal proximal convoluted tubule. Its effect is well demonstrated in various clinical scenarios in the younger population. This review and metanalysis describe particularities of the SGLT2i on the elderly, with mechanistic insights of the potential benefit and remaining challenges about the use of these drugs in this important age group. Further, we will present a meta-analysis of the main effects of SGLT2i reported in post-hoc studies in which the median age of the subgroups analyzed was over 60 years. Despite the absence of specific clinical trials for this population, our findings suggest that SGLT2i therapy on older individuals is effective to lower glucose and maintain its effect on systolic blood pressure and body weight.

Reason for article: I chose this article because it is a meta-analysis and a stronger source of evidence. It also focuses on SGLT2 inhibitors as a class and focuses on the effects this drug class can have on the elderly, including the safety profile of the drug class.

Key Points:

- SGLT2 inhibitors are able to lower blood pressure, lead to weight loss and cases of Acute kidney injury have been reported with SGLT2 inhibitors particularly Canagliflozin and dapagliflozin
- Safety events that were noted included Volume depletion events however the incidence of this adverse effect is low, but it can worsen kidney function. The incidence of volume depletion was also found to be dose dependent. Special attention should be paid for the occurrence of orthostatic hypotension in the elderly.
- Euglycemic Diabetic Ketoacidosis has also been noted too be slightly higher with SGLT2 inhibitors compared to other anti-diabetic therapies.
- SGLT2 use in the elderly was not seen to increase the risk of hypoglycemia
- Genitourinary tract infections were higher in incidence in older females. In the EMPAREG trial UTIs were noted more with empagliflozin use. Urosepsis and an increased risk of stroke was noted

Pdf link: https://www.scielo.br/j/ramb/a/RWqwfK4xzwscCqMV74wFTcD/?lang=en

Article 3: **Efficacy and Safety of Dapagliflozin in the Elderly: Analysis From the DECLARE–TIMI 58 Study**

Citation: Avivit Cahn, Ofri Mosenzon, Stephen D. Wiviott, Aliza Rozenberg, Ilan Yanuv, Erica L. Goodrich, Sabina A. Murphy, Deepak L. Bhatt, Lawrence A. Leiter, Darren K. McGuire, John P.H. Wilding, Ingrid A.M. Gause-Nilsson, Martin Fredriksson, Peter A. Johansson, Anna Maria Langkilde, Marc S. Sabatine, Itamar Raz; Efficacy and Safety of Dapagliflozin in the Elderly: Analysis From the DECLARE–TIMI 58 Study. *Diabetes Care* 1 February 2020; 43 (2): 468–475. https://doi.org/10.2337/dc19-1476

Type of Study: Randomized Controlled Trial

Objective: Data regarding the effects of sodium-glucose cotransporter 2 inhibitors in the elderly (age ≥65 years) and very elderly (age ≥75 years) are limited.

Research design and methods: The Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 assessed cardiac and renal outcomes of dapagliflozin versus placebo in patients with type 2 diabetes. Efficacy and safety outcomes were studied within age subgroups for treatment effect and age-based treatment interaction.

Results: Of the 17,160 patients, 9,253 were <65 years of age, 6,811 ≥65 to <75 years, and 1,096 ≥75 years. Dapagliflozin reduced the composite of cardiovascular death or hospitalization for heart failure consistently, with a hazard ratio (HR) of 0.88 (95% CI 0.72, 1.07), 0.77 (0.63, 0.94), and 0.94 (0.65, 1.36) in age-groups <65, ≥65 to <75, and ≥75 years, respectively (interaction *P* value 0.5277). Overall, dapagliflozin did not significantly decrease the rates of major adverse cardiovascular events, with HR 0.93 (95% CI 0.81, 1.08), 0.97 (0.83, 1.13), and 0.84 (0.61, 1.15) in age-groups <65, ≥65 to <75, and ≥75 years, respectively (interaction *P* value 0.7352). The relative risk reduction for the secondary prespecified cardiorenal composite outcome ranged from 18% to 28% in the different age-groups with no heterogeneity. Major hypoglycemia was less frequent with dapagliflozin versus placebo, with HR 0.97 (95% CI 0.58, 1.64), 0.50 (0.29, 0.84), and 0.68 (0.29, 1.57) in age-groups <65, ≥65 to <75, and ≥75 years, respectively (interaction *P* value 0.2107). Safety outcomes, including fractures, volume depletion, cancer, urinary tract infections, and amputations were balanced with dapagliflozin versus placebo, and acute kidney injury was reduced, all regardless of age. Genital infections that were serious or led to discontinuation of the study drug and diabetic ketoacidosis were uncommon, yet more frequent with dapagliflozin versus placebo, without heterogeneity (interaction *P* values 0.1058 and 0.8433, respectively).

Conclusions: The overall efficacy and safety of dapagliflozin are consistent regardless of age.

Reason for Selection:
I chose this article because it is also a more recent article and is a RCT which also provides a higher level of evidence. I also chose it because the study focused on Dapagliflozin (Farxiga) which is also the medication that was used to treat the specific patient used for this PICO presentation. I also wanted an article that focuses on elderly patients.

Key Points:

- They explored the effects of SGLT2 inhibitors in pts >/= 65 y/o and >/= 75 y/o with diabetes mellitus (Type 2) and established atherosclerotic cardiovascular disease or risk factors in comparison to placebo. Participants were 17,160 patients.
- The primary composite efficacy end points were CVD or hospitalization for HF and adverse cardiovascular events (MACE: composite of CV death, MI or Ischemic stroke). Other safety outcomes such as amputations, fractures and malignances were also assessed.
- Dapagliflozin was found to reduce composite cardiovascular death or hospitalization for HF in all age groups (<65, >/= 65, <75 and >/= 75). Sustained dec. of 40% or more in GFR to <60 ml/min/1.73 m2, new ESRD or death from renal or CV causes was reduced with Dapagliflozin compared to placebo.
- Dapagliflozin yielded greater weight reduction in comparison to placebo in all age groups.
- In terms of safety outcomes, major hypoglycemia events were increased with an inc. with age in all groups. However, the hypoglycemia was less frequent with dapagliflozin versus placebo. Fractures were also more common in elderly and very elderly and increasing with age. Volume depletion was increased with increasing age. AKI was also at higher rates with increasing age with higher incidence in the very elderly population (>75). However, Volume depletion was balanced between the Dapagliflozin and Placebo groups while AKI events were fewer with the Dapagliflozin group compared to placebo.
- Diabetic Ketoacidosis was rare, but more events were noted with Dapagliflozin compared to placebo. Genital infections leading to discontinuation of Dapagliflozin was also common compared to the placebo group.

PDF link: https://diabetesjournals.org/care/article/43/2/468/36100/Efficacy-and-Safety-of-Dapagliflozin-in-the

Article 4: Urinary tract infections in patients with diabetes treated with dapagliflozin

Citation: Johnsson, Ptaszynska, A., Schmitz, B., Sugg, J., Parikh, S. J., & List, J. F. (2013). Urinary tract infections in patients with diabetes treated with dapagliflozin. Journal of Diabetes and Its Complications, 27(5), 473–478. https://doi.org/10.1016/j.jdiacomp.2013.05.004

Type of Study: Meta-Analysis

Abstract:

Aims: Urinary tract infection is common in patients with type 2 diabetes. Possible causative factors include glucosuria, which is a result of treatment with sodium glucose cotransporter 2 (SGLT2) inhibitors. Dapagliflozin is an investigative SGLT2 inhibitor with demonstrated glycemic benefits in patients with diabetes. Data from dapagliflozin multi-trial safety data were analyzed to clarify the association between glucosuria and urinary tract infection.

Methods: Safety data from 12 randomized, placebo-controlled trials were pooled to evaluate the relationship between glucosuria and urinary tract infection in patients with inadequately controlled diabetes (HbA1c N6.5%–12%). Patients were treated with dapagliflozin (2.5, 5, or 10 mg) or placebo once daily, either as monotherapy or add-on to metformin, insulin, sulfonylurea, or thiazolidinedione

for 12–24 weeks. The incidence of clinical diagnoses and events suggestive of urinary tract infection were quantified**.**

Results: This analysis included 3152 patients who received once-daily dapagliflozin (2.5 mg [n = 814], 5 mg [n = 1145], or 10 mg [n = 1193]) as monotherapy or add-on treatment, and 1393 placebo-treated patients. For dapagliflozin 2.5 mg, 5 mg, 10 mg, and placebo, diagnosed infections were reported in 3.6%, 5.7%, 4.3%, and 3.7%, respectively. Urinary glucose levels, but not the incidence of urinary tract infection, increased progressively with dapagliflozin dosage. Most identified infections were those considered typical for patients with diabetes. Discontinuations due to urinary tract infection were rare: 8 (0.3%) dapagliflozin-treated patients and 1 (0.1%) placebo-treated patient. Most diagnosed infections were mild to moderate and responded to standard antimicrobial treatment.

Conclusions: Treatment of type 2 diabetes with once daily dapagliflozin 5 or 10 mg is accompanied by a slightly increased risk of urinary tract infection. Infections were generally mild to moderate and clinically manageable. This analysis did not demonstrate a definitive dose relationship between glucosuria and urinary tract infection.

Reason for Selection:
I chose this article because it is a Meta-Analysis and although it is an older article it is one that focuses on urinary tract infections which seemed to be rarely discussed in the other articles I had come across. It also focuses on the role of Dapagliflozin which was mentioned in article 3 as having a potential to cause UTIs as a side effect and Dapagliflozin is also a medication that was prescribed in the case study for my Pico.

Key Points:

- The study includes 12 randomized placebo-controlled trials and a total population of 4545 patients of which 3152 patients received once a day dapagliflozin and 1393 placebo treated patients.
- Patients in the dapagliflozin groups with higher doses (5 mg or 10 mg) experience events suggestive of UTI more than these in the 2.5mg and placebo groups. The event was also more common in women. Dysuria and UTI were reported in >/= 1% of men in the one or more of the dapagliflozin groups but not in the placebo group. More **suggestive events of UTI were also documented in patients >/= 65 y/o vs younger patients treated with dapagliflozin.**
- In total 230 patients were diagnosed with UTI (56 for placebo, 35 for dapagliflozin 2.5mg, 76 for dapagliflozin 5mg and 63 for 10 mg). In the dapagliflozin 2.5mg group 2 patients experienced Urinary tract events which were one UTI and one malacoplakia vesicae. One episode of urosepsis was reported in the dapagliflozin 10 mg group.

PDF link: https://pdf.sciencedirectassets.com/271280/1-s2.0

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
1. Mahmoud Barbarawi, Ahmad Al-abdouh, Owais Barbarawi, Harini Lakshman, Mariam Al kasasbeh (2021)	Meta-Analysis & trial sequential analysis	- They had 2 autors independently retrieve RCTs from MEDLINE/PUBMED, Embase, Cochrane Library & Clinical trilas.com from inception to November 26, 2020. Any discrepancies or disputes was resolved by an independent third author. - The 10 RCTs (in total 71,553 Patients of which 39,053 received SGLT2 inhibitors and 32,500 received placebo) included in the final analysis had to have a population of at least 500 pts each and include any SGLT2 inhibition agents compared with placebo, patients with or without diabetes and reports of cardiovascular or renal outcomes. - The search terms used included SGLT, SGLT2, sodium-glucose co-transporter, canagliflozin, dapagliflozin, ertugliflozin, sotagliflozin, empagliflozin, cardiovascular, and renal without language restrictions. - The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)	- Primary outcome: Incidence of the composite of HF hospitalization or cardiovascular death and renal outcomes. Secondary Outcomes: Major adverse cardiovascular events (MACE), HF hospitalization, cardiovascular mortality, all-cause mortality, myocardial infarction. All serious adverse events, amputation risk, and DKA.	- Primary endpoint: Inhibition of the SGLT2 was associated with lower composite rates of HF hospitalization or cardiovascular death and renal outcomes compared to placebo (6,594 cases, RR 0.76, 95% CI 0.73–0.81, P < 0.01, I2 = 25%, and 2,950 cases, RR 0.68, 95% CI 0.60–0.77, P < 0.01, I2 = 62%, respectively) - Secondary endpoint: Incidence of major adverse cardiovascular events (MACE) was lower in patients receiving SGLT2 inhibitors. There was lower rate of HF hospitalization (RR 0.69. 95% CI 0.65–0.74, P < 0.01; I2 = 0%) with SGLT2 use. There was also a lower rate of any hospitalization, cardiovascular mortality, and all-cause mortality (RR 0.87; 95% CI 0.81–0.93, P < 0.01; I2 = 42%) with SGLT2 use. - In terms of Safety outcomes: SGLT2 was associated with less serious adverse events (RR 0.93; 95% CI 0.90–0.95, P < 0.01; I2 = 0%) but a higher risk for DKA (RR 2.29; 95% CI 1.49–3.53, P < 0.01; I2 = 9%), and amputation in comparison to Placebo.	- The studies were trials mainly studying the effect of SGLT2 inhibitors in pts with DM and in a much small group of non-diabetic pts which does not allow for generalizability of results.
2. Cintra R, Moura FA,	Systemic Review and	- Uses methods recommended by	- Assessing the challenges and	- Some SGLT2 inhibitors reduced systolic BP	-

Carvalho LSF, Barreto J, Tambascia M, Pecoits-Filho R, Sposito AC. (2019)	Meta-analysis	Cochrane guidelines according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).	benefits of SGLT2 inhibitors with a focus on Blood pressure reductions, Weight loss, Effects on kidney and renal disease progression, Safety profile, Diabetes Ketoacidosis risk, Hypoglycemia, Genital Urinary tract infections, bone metabolism and Effect on mortality and Stroke.	particularly seen with Canagliflozin compared to placebo over 104 weeks treatment which is consistent with studies on individuals >5 years old treated with Empagliflozin. - SGLT2 inhibitors in elderly may cause some weight loss -Effect on Kidney and Kidney progression. Patients' kidney function should be assessed prior to starting school. - Safety concern: Volume depletion was observed to be 5.9% on canagliflozin but the incidence of Volume depletion related AE is low and can be dependent on dose and increase with time. - DKA (Euglycemic DKA): they found that the incidence of eDKA with SGLT2 inhibitor is low - Hypoglycemia: SGLT2 inhibitor therapy in the elderly does not seem to increase the risk of hypoglycemia. -Genitourinary tract infections: The incidence is higher in older TSDM females especially in pts with poorly controlled diabetes. -Bone metabolism: Patients > 65 but the incidence of factures was higher on the placebo branch	
3. Avivit Cahn, Ofri Mosenzon, Stephen D. Wiviott, Aliza Rozenberg, Ilan Yanuv, Erica L.	Randomized Control Trial	- The DECLARE-TIMI 58 trial had a total of 17,160 of which for this study 6,811 were age >/= 65 years to < 75 years, 9253 were < 65 years in age and 1,096 were >/= 75 years old with T2DM and	- The primary outcome/composite efficacy endpoints were CV death or Hospitalization for HF and Major adverse cardiovascular events (MACE: the	- Dapagliflozin reduced the composite CVD/HHF consistently with HR 0.88 (95% CI 0.72, 1.07), 0.77 (0.63, 0.94), and 0.94 (0.65, 1.36) in age-groups < 65, >/=65	- As part of the exclusion criteria participants with a creatinine clearance of < 60 ml/min were excluded from the study which may have led to the

Goodrich, et.al. (2020)		ASCVD (atherosclerotic cardiovascular disease) or risk factors. -Participants were randomized to receive Dapagliflozin or placebo in addition to standard care and were followed for a median of 4.2 years - Participants were at least 40 years old with HbA1c 6.5%-12%.	composite of CV death, MI or Ischemia stroke). - The secondary outcomes/ secondary cardiorenal composite outcome was a sustained decrease of 40% or more of eGFR to < 60 ml/min/1.73 m^2, new end stage renal disease, or death from renal or CV causes. - Renal specific composite outcomes were for a 40% decrease of eGFR to < 60 ml/min/1.73 m^2, ESRD or death from renal causes. Safety endpoints were assessed in patients who received at least one dose of the Dapagliflozin. Things like amputations, fracture, hypoglycemia, UTIs, genital infections and malignancies were assessed.	to <75, and >/= 75 years, respectively (Interaction P value 0.5277). - Rates of HHF were reduced with Dapagliflozin, with HR 0.88 (95% CI 0.68, 1.15), 0.60 (0.46, 0.79), and 0.81 (0.50, 1.30), respectively, in age-groups <65, >/=65 to <75 and >/= 75years (interactionPvalue0.1402). - Dapagliflozin yielded a greater reduction in weight versus placebo, and this was maintained in all age-groups during the entire study period (all P, 0.0001) - Safety: (severe adverse events) SAEs in the overall safety population were more common in the elderly and very elderly compared with the younger patients, with incidence rates of 107.3, 131.2, and 191.1 cases per 1,000 person years in age-groups <65, >/=65 to <75, and >/=75 years, respectively (P, 0.0001). - Major hypoglycemia events increased with increasing age in the overall safety population, with incidence rates of 1.7, 2.6, and 6.5 cases per 1,000 person-years in age-groups, <65, >/=65 to <75, and >/=75 years, respectively (P, 0.0001). However major hypoglycemia was less frequent in the Dapagliflozin vs placebo group, but more predominant in the elderly and very elderly group. - Overall fractures were more common in the elderly and very elderly, with	exclusion of more frail elderly patients that would be more prone to volume depletion, AKI, fractures, and other worse outcomes.

				incidence rates of 11.2, 15.8, and 17.4 cases per 1,000 person years, in age-groups, <65, >/=65 to <75, and >/=75 years, respectively (P, 0.0001). -Volume depletion in the overall safety study population increased with increasing age, with incidence rates of 5.6, 7.8, and 14.9 cases per 1,000 person-years in age-groups ,65, <65, >/=65 to <75, and >/=75 years, respectively (P, 0.0001) however it was balanced between the Dapagliflozin vs placebo group. - AKI was also reported overall, at higher rates with increasing age, with incidence rates of 4.2, 5.4, and 9.3 cases per 1,000 person-years in age groups <65, >/=65 to <75, and >/=75 years, respectively (P 5 0.0001). - Amputation rate did not differ by age (P 5 0.3201) and was balanced between Dapagliflozin and placebo, with no age-based treatment interaction. - Diabetic ketoacidosis was rare, but more events were observed with dapagliflozin versus placebo, consistently across age-groups. - Genital infections that led to the discontinuation of the study drug were more common with dapagliflozin versus placebo, and there were two SAE genital infections in each treatment arm, with no heterogeneity. - There was no statistically significant increase in urinary tract infections (serious or leading to drug	

				discontinuation) between the Dapagliflozin vs Placebo groups.	
4. Kristina M. Johnsson, Agata Ptaszynska, Bridget Schmitz, Jennifer Sugg, Shamik J. Parikh, James F. List (2013)	Meta-Analysis	- Data was from 12 randomized, placebo-controlled trials and pooled. - A total of 4545 patients from 12 clinical trials of which 1393 were in the placebo group, 814 were in the 2.5mg group, 1145 were in the 5mg group and 1193 were in the 10mg group for Dapagliflozin. - Patients included in the trials were between 18-79 y/o old with inadequately controlled T2DM (Baseline mean HbA1c was 8.1%- 8.4%) BMI <45 kg/m^2. - In these studies patients received Dapagliflozin (1mg -50 mg daily) or placebo for 12 weeks or 24 weeks. Patients with prior history or risk factors for genital infection were excluded from participation. Patients with a history of or risk factor for UTIs were not excluded. -In the Dapagliflozin group the exposure ranged from 148.2 - 150.5days.	- To evaluate the relationship between pharmacologically induced urinary glucose excretion and UTIs in patients with T2DM treated with Dapagliflozin.	Majority of patients in the Dapagliflozin 5 and 10 mg group experience events suggestive of UTI. (7.3% and 6.5%) than patients in the 2.5 mg group and placebo group (4.2% and 4.5% respectively) -Most episodes were mild or moderate in intensity across all groups. - The events appeared to be more common in women than men in all treatment groups. - Dysuria and UTI were reported in > or = 1% of men in the Dapagliflozin group but not in the placebo group - A total of 230 patients were diagnosed with a UTI: 56 from the Placebo group. 35 for the 2.5 Dapagliflozin, 76 for Dapagliflozin 5mg group and 63 for Dapagliflozin 10mg. -Overall rate of UTI in the dapagliflozin group was more than in the Placebo group. - Cases of Recurrent UTI were also reported in 22.9% of dapagliflozin-treated patients vs 13.6% in the placebo-treated patients, however, the frequency of recurrence did not seem to be dose dependent. -Cases of Pyelonephritis were also noted but rarely and with a similar pattern as was the case with the incidence of UTIs in the Dapagliflozin group.	There may have been risk for confounding as the study included patients that have had a history or risk for UTIs (although there were only few patients). This may make the results non-generalizable.

Summary of the Evidence

Article 1:
This article as mentioned earlier is a Meta-Analysis which is a higher level of evidence. The studies used to compile the analysis for this was based on solely large scale Randomized controlled trials (RCTs) which were a total of 10 RCTs. Of the 10 trials 3 trials use dapagliflozin, 2 trials used empagliflozin, 2 trials used canagliflozin, 2 trials used sotagliflozin, and 1 trial used ertugliflozin. The outcomes studied in this analysis were the incidence of composite of HF hospitalization or cardiovascular death and renal outcomes primarily, and the secondary outcomes were the major adverse cardiovascular events (MACE), HF hospitalization, cardiovascular mortality, all-cause mortality, myocardial infarction. In terms of the safety profile of SGLT2 inhibitors all serious adverse events, amputation risk, and DKA were also included. My clinical question for my PICO concentrates on the safety of SGLT2 inhibitor use so I am mostly focusing on the findings of the safety outcomes which in this case showed that SGLT2 inhibitors were associated with less serious adverse cardiovascular and renal effects but did have an increased risk of DKA and amputation as shown in the table above.

Article 2:
This article is a Systematic review as listed above and is another good source of data. This analysis focuses more on the effects of SGLT12 inhibitors with more focus Elderly populations as they can be more frail and likely to have worse outcomes under certain stress or under hospitalization etc. The study explores the benefits and harms of the SGLT2 inhibitors particularly in the areas of blood pressure reductions, weight loss, effects on kidney and renal disease progression, safety profile, diabetes ketoacidosis risk, hypoglycemia, genital urinary tract infections, bone metabolism and Effect on mortality and stroke. Again, for my Pico I am focusing on the safety of this class of antidiabetic medications and the findings of this study showed that SGLT2i such as Canagliflozin and Empagliflozin may reduce systolic BP, it can also cause weight loss which may or may not be a wanted goal in elderly patients. It was also seen that although volume depletion may be low it can occur in patients as seen with canagliflozin. They found no increased risk for hypoglycemia in elderly patients. They also found that Euglycemic DKA is possible, however rare in patients and that female participants were at more risk for Genito-urinary infections although also low incidences were noted.

Article 3:
This study is from a Large RCT that focused more on the SGLT2 inhibitor Dapagliflozin and also focused more on the elderly and very elderly populations (>65). In terms of safety profile of the SGLT2 inhibitor (also in relation to elderly participants), it was seen that there is a higher risk for DKA in elderly patients that are taking Dapagliflozin, there was also increased incidence of Genito-urinary infections in the Dapagliflozin group compared to Placebo. Here there was an overall increase in volume depletion and its most effects were seen in the elderly and very elderly participants. There was also an increase in major hypoglycemia events with increase in age in the overall study population, but it was less frequent in the Dapagliflozin group particularly. However, most of the adverse side effects noted with Dapagliflozin use seen in the overall study group.

Article 4:
This study is a Meta-analysis that focuses on the negative side effect of SGLT2 inhibitors, particularly on Dapagliflozin, and its effects on the incidence of UTIs. The study found that overall Dapagliflozin had higher incidence of UTIs in patients overall in comparison to patients that were on placebo (but the patients that did have placebo also did have incidence of UTIs). It was also noted that there was some dose related effect as well as it was seen that at a lower dose of 2.5mg there was less incidence of UTIs compared to the 5mg and 10 mg doses which had higher incidences of UTIs. There was also a higher

recurrence rate of UTIs in the Dapagliflozin group, but this was not a dose related finding. Lastly, there were 2 cases of Pyelonephritis noted in the Dapagliflozin group.

Conclusion:
As with many medications there are negative adverse effects that may occur with the use of SGLT2 inhibitors as seen in the discussions and tables above such as risk of volume depletion, hypoglycemia, fractures, diabetic ketoacidosis, genitourinary infections, UTIs, etc. But it is important to note that the occurrence of these adverse effects have been shown to be rare, and do not have very significant risk of being more common or severe in the elderly population. Considering the benefits that have also been noted with the use of SGLT2 inhibitors such as a renal protective effect and positive outcomes in patients with HF it is a medication that proffers reasonable benefits to patients. From the data from my sources and findings I think that SGLT2 inhibitors can be safe for use in elderly patients, but it is important to counsel patients on the possibility of adverse events and the signs and symptoms to be aware of and look out for that should prompt patients to seek immediate medical assistance when needed.

PICO Question: Are SGLT2 inhibitors safe for use in Elderly patients with diabetes?

Clinical bottom line

Based on the findings I obtained during the review of the articles I was able to choose between 2 meta-analysis, 1 systematic review and 1 randomized controlled study to support my conclusions. In response to the question of safety of SGLT2 inhibitor use in elderly patients, it seems that this class of anti-diabetics are fairly safe for use and infact three were FDA-approved which are canagliflozin (Invokana) dapagliflozin (Farxiga) and empagliflozin (Jardiance). As the studies above showed, SGLT2 inhibitors have a significant role and benefit in treatment of patients with T2DM and cardiovascular disease. It has shown to be effective in reducing the rate of Hospitalization due to heart failure. However, in terms of the safety profile, which is the basis for this assignment, there are safety concerns that exist with this drug class such as the risk of developing DKA, UTI, volume depletion, hypoglycemia, Genito-urinary infections etc. in comparison to placebo. Although these adverse effects have been noted to rarely occur and, in most cases, they can be reversed/ treated. With the significant findings and benefits of SGLT2 inhibitors that have been found I think that this class of medication was a whole would be safe for use in the elderly (> 65 y/o) as long as patients are being carefully monitored and observed for signs of adverse effects from the medications.

Weight of Evidence:
Article 1 > Article 4 > Article 2 > Article 3

I chose article one as having the greatest evidence as the sources were al RCTs, the SGLT2 inhibitors studied in the RCT was not just one (e.g., Dapagliflozin) but other including Dapagliflozin, Empagliflozin, Canagliflozin, Sotagliflozin, and Ertugliflozin. Article 4 I chose next as it is a meta-analysis which is also a higher level of evidence and focuses on Dapagliflozin which was the drug given to the patient in my case scenario and appears to be commonly used. Article 2 I chose because it a systematic review and next in the hierarchy followed lastly by article 3 which is a RCT.

Magnitude of Effects:

Article 1: Mahmoud Barbarawi, Ahmad Al-abdouh, Owais Barbarawi, Harini Lakshman, Mariam Al kasasbeh (2021)

Serious adverse effects as mentioned in article include things such as symptoms of volume depletion, renal events, major hypoglycemia, bone fractures, and these were found to be low with SGLT2 inhibitor use ($p < 0.01$) however DKA risk (higher by 2.7-fold, but overall risk was <0.17%) and risk of amputation was higher with SGLT2 inhibitor use compared to placebo.

Article 2: Cintra R, Moura FA, Carvalho LSF, Barreto J, Tambascia M, Pecoits-Filho R, Sposito AC. (2019)

On a pooled analysis, eDKA frequency was overall low but slightly higher on SGLT2i (2-3 times) than with other anti-diabetic therapies. "SGLT2 inhibitors in the elderly population did not increase the risk of hypoglycemia. The RR of hypoglycemia was 1.11 (95% CI: 0.84, 1.45; p=0.554; I2=0%) across SGLT2 inhibitors. "The RR of uncomplicated and complicated UTI on SGLT2i therapy was respectively 1.04 (0.95, 1.14; p=0.186; I2=24.9%) and 0.93 (0.66, 1.31. p=0.745; I2=0%)." SGLT2 inhibitor, females had a higher risk of genitourinary infection, with a RR of 4.13 (2.96, 5.76; p<0.001; I2=32.6%), and males had a RR of 4.02 (2.91, 5.57; p<0.001; I2=0%).

Article 3: Avivit Cahn, Ofri Mosenzon, Stephen D. Wiviott, Aliza Rozenberg, Ilan Yanuv, Erica L. Goodrich, et.al. (2020)

Incidence rates of CVD/HHF were 10.9, 14.8, and 26.7 (P, 0.0001) and those of MACE were 20.9, 24.7, and 37.4 cases per 1,000 person-years in age-groups < 65, >/= 65 to <75, and >/=75 years, respectively (P,0.0001). Dapagliflozin reduced the composite CVD/HHF consistently with HR 0.88 (95% CI 0.72, 1.07), 0.77 (0.63, 0.94), and 0.94 (0.65, 1.36) in age-groups < 65, >/=65 to <75, and >/= 75 years, respectively (Interaction P value 0.5277). Rates of HHF were reduced with Dapagliflozin, with HR 0.88 (95% CI 0.68, 1.15), 0.60 (0.46, 0.79), and 0.81 (0.50, 1.30), respectively, in age-groups <65, >/=65 to <75 and >/= 75years (interactionPvalue0.1402). Major hypoglycemia events increased with increasing age in the overall safety rates of 1.7, 2.6, and 6.5 cases per 1,000 person-years in age-groups, <65, >/=65 to <75, and >/=75 years, respectively (P, 0.0001). However, major hypoglycemia was less frequent in the Dapagliflozin vs placebo group, however its effect was more predominant in the elderly and very elderly group. Volume depletion in the overall safety study population increased with increasing age, with incidence rates of 5.6, 7.8, and 14.9 cases per 1,000 person-years in age-groups <65, >/=65 to <75, and >/=75 years, respectively (P, 0.0001) however it was balanced between the Dapagliflozin vs placebo group. AKI was also reported overall, at higher rates with increasing age, with incidence rates of 4.2, 5.4, and 9.3 cases per 1,000 person-years in age groups <65, >/=65 to <75, and >/=75 years, respectively (P 5 0.0001) but was less in the Dapagliflozin group.

Article 4: Ptaszynska, Bridget Schmitz, Jennifer Sugg, Shamik J. Parikh, James F. List (2013)

Majority of patients in the Dapagliflozin 5 and 10 mg group experience events suggestive of UTI. (7.3% and 6.5%). Dysuria and UTI were reported in > or = 1% of men in the Dapagliflozin group but not in the placebo group. a total of 230 patients were diagnosed with a UTI: 56 from the Placebo group. 35 for the 2.5 Dapagliflozin, 76 for Dapagliflozin 5mg group and 63 for Dapagliflozin 10mg. Recurrent UTIs were also reported in 22.9% of dapagliflozin-treated patients vs 13.6% in the placebo-treated patients, however, the frequency of recurrence did not seem to be dose dependent.

Clinical Significance

There is risk for negative side effects from SGLT2 inhibitor use such as UTIs (which may be attributed to the glycosuria from the use of SGLT2 inhibitors.), volume depletion, genitourinary infections etc. But as shown in the articles we can see that SGLT2 inhibitors have positive outcomes and benefits for many patients (including the elderly) with heart failure and kidney disease. I think counseling on the awareness of these side effects of some SGLT2 inhibitors may be of more benefits to patients as mentioned previously in my conclusion.

Other considerations important in weighing this evidence to guide practice

It seems that the studies do have varying findings and data which may be as a result of the different protocols used for each study. It may be hard to make solid conclusion about the safety and risk of SGLT2 inhibitors without individual studies on the different kinds of SGLT2 inhibitors. For my PICO, I chose to focus particularly on Dapagliflozin in the last 2 articles. The findings from studies on Dapagliflozin showed similar side effects like increased risk of DKA, volume depletion etc. I think would not be best to generalize these findings to all SGLT2 inhibitors. I also think that dosage may be important to consider when conducting future studies on an SGLT2i. It can help create some form uniformity in the data obtained from the studies and may provide stronger evidence to for any dose dependent effect of SGLT2i on patients.