Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: A 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension

BACKGROUND:

- The study was funded by AstraZeneca and Bristol-Myers Squibb to look at efficacy and safety of dapagliflozin when added to usual care in individuals with inadequately controlled T2DM with a history of documented CVD which included elderly patients (>65 and >75 years old).
- This study is needed because when doing clinical trials these 2 populations are often underrepresented.
    - The drug is already on the market at time study was published, therefore their focus was on sub-populations.
- Dapagliflozin is an oral selective inhibitor of sodium glucose co-transporter 2 which is the kidney transporter chiefly responsible for glucose reabsorption from the glomerular filtrate.
- The drug has shown decreases in A1c, body weight, and blood pressure in type 2 diabetes patients in previous studies.

OBJECTIVE:

- Primary endpoint looked at mean change in HbA1c from baseline and proportion of participants achieving a three-item outcome measure combined clinical benefit: simultaneous HbA1c decrease of 0.5% or more, total body weight reduction of atleast 3%, and SBP reduction atleast 3 mmHg from baseline.

METHODS

- **Design**: 24 week, multicenter, randomized, double-blind, age-stratified, placebo-controlled phase III study with additional 28 and 52 week extensions.
- **Inclusion**: patients with type 2 diabetes with an additional diagnosis of some form of cardiovascular disease
- **Exclusion**: type 1 diabetes, use of rosiglitazone or three or more antihyperglycemic drugs, symptoms of poorly controlled diabetes such as polyuria, polydipsia, and/or >10% weight loss, FPG >270 mg/dl; cardiovascular events within 2 months of enrollment; New York Association class IV CHF; unstable or acute CHF, systolic blood pressure >160 mmHg and/or diastolic >100 mmHg at randomization, CrCl <60 ml/min urine albumin: creatinine ratio >1800 mg/g, history of unstable or rapidly progressing renal disease.
- # patients enrolled: 964 participants (482 patients in the placebo group and 480 in the treatment group)
- Drug regimens/dosages used: placebo once daily, dapagliflozin 10 mg once daily
- **Primary outcome measure**: Looked at mean change in HbA1c from baseline and proportion of participants achieving a three-item outcome measure combined clinical benefit: simultaneous HbA1c decrease of 0.5% or more, total body weight reduction of atleast 3%, and SBP reduction atleast 3 mmHg from baseline.
- Power: Power for the study was not reported
- Data handling method used: intent-to-treat

RESULTS

- Number of patients who completed study: discontinuation included 39 in placebo group and 45 in dapagliflozin group, all other patients completed the study.
- **Primary end point**
    - Participants in the dapagliflozin group had a significant reduction in mean placebo-adjusted HbA1c at 24 weeks (-0.4%) that was maintained through 52 weeks (-0.5%).
    - Decreases in total body weight greater in dapagliflozin than placebo group at week 24 (-1.9%) and maintained through week 52 (-2.1%).
    - More participants with a baseline BMI >27 kg/m2 achieved 5% or greater reduction in BW in the dapagliflozin than placebo at 24 and 52 weeks.
    - Patients taking dapagliflozin showed a significant decrease in placebo-corrected seated BP at week 24 (-3.0 mmHg) and maintained it through week 52.
    - There were 5 times as many participants that reached the 3-item outcome goal in dapagliflozin group vs placebo.

- Adverse effects
    - Incidence of adverse events leading to discontinuation of the study was higher in the dapagliflozin group than in the placebo group
    - There were 4 deaths in placebo and 5 deaths in dapagliflozin groups, none determined to be caused by the treatment; similar discontinuation in each group occurred
    - Most adverse effects were mild or moderate in intensity
    - The most common adverse effects occurring more frequently in the dapagliflozin group were fungal genital infection/vulvovaginal mycotic infection/balanitis, (10.7% women and 5.9% men), urinary tract infection (8.3%), and events of renal impairment and failure (9.5%).

Authors Conclusions

- Dapagliflozin, when added to normal care, was well tolerated and superior to placebo for HbA1c reduction at 24 weeks in an older population of individuals with T2DM with documented CVD.
    - >90% of the population had hypertension and >80% were taking a lipid lowering medication
- Safety has been proven to be acceptable and tolerable
- Author states there needs to be further research as this study does not assess frail or very old individuals and physicians should use discretion when prescribing to this population – including those with poor renal function.

STRENGTHS

- Real life practice involves patients on many medications so this was a good patient population
- The study design was appropriate for what their goals were looking at.
- Looked at effect on all three components combined (glucose, body weight, and blood pressure) this is beneficial because many of the targeted patients need help in all three areas.
- Supplemental material lays out specifically the process used, for example: body weight measurements using the same scales where at all possible with light clothing, no shoes, and fasting stomach.

LIMITATIONS

- Not consistent with data representation (some places will give a percent reduction difference between the two groups where others give percentage of patients who experienced the effect. Ex page 1254 last paragraph
- The data they state is clinically significant may be misrepresented. A 3 mmHg drop in blood pressure or 2 kg weight loss for these patients is probably not going to prevent a cardiovascular event.
- Conflict of interest with authors and drug company, the article states this conflict at the end.
    - The authors/editors all were either employees of the company or had stock/interest in the company that caused a biased approach.
- The dose used in the study was 10mg, even though the initial dose for dapagliflozin in practice is 5 mg, I believe they should have started everyone at 5mg and if "rescue" criteria was met, then increase to 10mg.

CONCLUSIONS

• State your conclusion regarding the study (use 3rd person, not 1st)

- I believe this study does represent the population that will be receiving this therapy, but there were many limitations that make the article unreliable. There were also statistical parameters lacking such as a p-value and some standard deviations that I would have liked to see to know how much error was likely and how concrete the results actually proved to be. Altogether this therapy has already proven to be safe and effective and this study looked at use in elderly and patients with CVD. The results that I held most weight on were the adverse effects, because in this population you worry more about increased adverse effects and risks, therefore I believe because it showed no more increase risk in this patient population than with others, it can be taken away from that study that this medication is safe for elderly and patients with cardiovascular disease.

• State how results related to actual practice

- I believe this drug has a huge impact in practice and is already being used in the general population with success, though many patients are weary of adding a new medication without knowing more facts about it.

• Future Research:

- Future research should involve third parties that have less biases. It should also be performed using 5mg, because that is the initiation dose of this medication.
- Other studies that have more controlled parameters are also needed to show results with less biased involvement from the authors.

Leiter LA, Cefalu WT, Bruin TW, Gause-Nilsson I, Sugg J, Parikh SJ. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind placebo-controlled study with a 28-week extension. JAGS. 2014. 62:1252-1262.

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