Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

SGLT2 Inhibitors

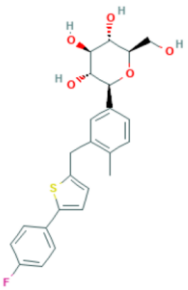
Evidence Summary

SGLT2 inhibitors effectively reduce HbA1c, cardiovascular complications from diabetes, and improve heart function in those with heart failure.

Neuroprotective Benefit: SGLT2 inhibitors may be beneficial for neurodegenerative diseases in diabetics, but there is currently little rationale for their direct neuroprotective effects.

Aging and related health concerns: SGLT2 inhibitors are effective at reducing cardiovascular risks in diabetics and are possibly beneficial in non-diabetic patients with heart failure.

Safety: SGLT2 inhibitors are associated with an increased risk of genital infections, though most studies are less than one year in duration.

Availability: Available with a prescription (as brand name drugs, not generics)	**Dose**: Canagliflozin (100 or 300mg); Dapagliflozin (5 or 10mg); Empagliflozin (10 or 25mg); Ertugliflozin (5 or 15mg). Each drug taken daily and orally in the morning	**Molecular Formula:** $C_{24}H_{25}FO_5S$ **Molecular weight:** 444.5g/mol  Source: PubChem (for Canagliflozin)
Half-life: ~10-14 hours for each	**BBB**: Possibly penetrant (though it has not been explicitly examined)	
Clinical trials: SGLT2 inhibitors have been tested in at least 27 clinical trials (n = 14,074 patients) for diabetes; at least four clinical trials (n = 29,270 patients) for cardiovascular disease; six clinical trials (n = 9,550) in heart failure patients; and seven studies (n = 2,381) for blood pressure.	**Observational studies**: One case control study (n = 176,250 patients) for dementia	

What is it?

Sodium-glucose Cotransporter-2 (SGLT2) inhibitors (gliflozins) are glucose lowering drugs recommended for diabetics with cardiovascular or kidney disease who have not reached their glycemic target. SGLT2 is a protein in the kidneys that plays a role in the reabsorption of glucose from the glomerular back into circulation. It is responsible for ~90% of the kidney's glucose reabsorption. SGLT2 inhibitors can prevent glucose reabsorption thus releasing more glucose into the urine and preventing its uptake into the blood stream. Although SGLT2 inhibitors appear to be beneficial for diabetics, there is little indication they are beneficial for non-diabetics, except possibly for heart failure patients. However, they are a new class of diabetes drugs (the first, canagliflozin, was approved in 2013), and other beneficial mechanisms of action have not been fully explored. Theoretically canagliflozin and dapagliflozin may act as acetylcholinesterase inhibitors, though this has not been shown (Wicinski et al, 2020). They may also

have an effect in Alzheimer's disease by increasing ketone levels (an alternative energy source for the brain), though this might only be effective for patients with type 2 diabetes (Jobori et al, 2017).

There are several SGLT2 inhibitors on the market:

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)
- Ipragliflozin (Suglat) (approved in Japan)
- Luseogliflozin (Lusefi) (approved in Japan)

Neuroprotective benefit: SGLT2 inhibitors may be beneficial for neurodegenerative diseases in diabetics, but there is currently little rationale for their direct neuroprotective effects.

Types of evidence:

- One randomized controlled trial in patients with type two diabetes
- Once case-control observational study
- One preclinical study in an AD/diabetes mouse model
- Two preclinical studies in diabetes mouse models

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

In a randomized controlled trial, 39 elderly individuals with type 2 diabetes on a stable dose of metformin were treated with either GLP-1 agonists or SGLT2 inhibitors over one year. There was no change in cognition in either group after treatment. Patients on the SGLT2 inhibitors saw a decrease in weight and an increase in HDL-c (Perna et al, 2018).

In a case-control observational study of 176,250 patients with diabetes from the Danish National Diabetes Register, the use of both GLP-1 agonists and SGLT2 inhibitors was associated with the greatest reduced risk of dementia compared to other diabetes medications (**OR for both ~0.58**). However, the study did not control for how well diabetes was controlled, and SGLT2 inhibitors are a newer class of anti-diabetics, so it is not yet clear whether they are a superior class of anti-diabetics (Wium-Andersen et al, 2019).

Human research to suggest benefits to patients with dementia:
None reported

Mechanisms of action for neuroprotection identified from laboratory and clinical research
Hierro-Bujalance et al (2020) tested the effect of empagliflozin (10mg/kg) in a mouse model of Alzheimer's disease and type 2 diabetes (APP/PS1 with db/db) over 22 weeks (from 4 to 26 weeks of age). Empagliflozin treatment improved cognition, prevented brain atrophy and neuronal death, reduced the number of activated microglia, reduced brain hemorrhage burden, and reduced the number of amyloid plaques.

In a mouse model of diabetes (db/db mice) empagliflozin treatment over 10 weeks reduced cardiac fibrosis and thickening, oxidative stress, and prevented cognitive dysfunction (Lin et al, 2014). In a rat model of diabetes (high fat diet fed rats) both a GLP-1 agonist (vildagliptin) and an SGLT2 inhibitor (dapagliflozin) improved cognition. However, an increase in synaptic plasticity was most pronounced with the SGLT2 inhibitor (Sa-nguanmoo et al, 2017).

In addition, canagliflozin and dapagliflozin are predicted to be potential acetylcholinesterase inhibitors based on molecular docking experiments (Wicinski et al, 2020).

APOE4 Interactions:
None reported

Aging and related health concerns: SGLT2 inhibitors are effective at reducing cardiovascular risks in diabetics and are possibly beneficial in non-diabetic patients with heart failure.

Types of evidence:

- One network meta-analysis of RCTs for mortality
- Seven meta-analyses of RCTs for cardiovascular disease (CVD) outcomes
- Two meta-analyses for diabetes
- One meta-analysis for neuropathy
- One meta-analysis for cancer risk
- Preclinical studies for lifespan and neuropathy

Mortality

Palmer et al (2020) conducted a systematic review and network meta-analysis of 764 RCTs (421,346 patients) at least 24 weeks in length comparing the effectiveness of SGLT2 inhibitors or GLP-1 agonists in patients with diabetes. RCTs could either include monotherapy trials or drugs added as background therapy to other glucose lowering drugs. Trials also had to compare the treatments with other glucose lowering drugs, placebo, or standard of care. The study also compared patients at very low risk (no CVD risk factors), low risk (three or more CVD risk factors), moderate risk (CVD), high risk (chronic kidney disease) or very high risk (CVD and kidney disease).

Compared to placebo, SGLT2 inhibitors reduced all-cause mortality (**OR = 0.77; 95%CI 0.71-0.83**), cardiovascualr mortality (**OR = 0.84; 95%CI 0.76-0.92**), non-fatal myocardial infarction (**OR = 0.87; 95%CI 0.79-0.97**), kidney failure (**OR = 0.71; 95%CI 0.57-0.89**), and admission to the hospital for heart failure (**OR = 0.70; 95%CI 0.63-0.77**). These effects were more pronounced in patients with higher risk factors. They had no effect on non-fatal stroke. SGLT2 inhibitors also reduced HbA1c (-0.6%).

Overall, SGLT2 inhibitors were anticipated to be more effective than GLP-1 agonists for every outcome except for non-fatal stroke. However, they were associated with a greater risk of genital infections than GLP-1 agonists.

An interactive summary of the results can be found at https://magicevidence.org/match-it/200820dist/#!/.

Another study reported that empagliflozin reduced the number of cardiac senescence cells and cardiac fibrosis in a mouse model of diabetes (streptozotocin injection) (Madonna et al, 2020).

Cardiovascular disease (CVD)

Qiu et al (2020) conducted a meta-analysis (11 RCTs) of SGLT2 inhibitors and GLP1 agonists in diabetics for their effects on CVD outcomes. SGLT2 inhibitors reduced the risk of major adverse cardiovascular events (MACE) in Caucasian participants (**HR = 0.88; 95%CI 0.81-0.95**). They did not significantly reduce the risk of MACE in Black or Asian individuals with type 2 diabetes (although in Asian populations the results were almost significant: **HR = 0.81; 95%CI 0.61-1.06**) Similar results were reported for GLP1 agonists. Ghosh-Swaby et al (2020) reported similar results (same trials) with GLP1 agonists and SGLT2 inhibitors being equally effective for the reduction of MACE (but they did not break out different ethnic groups).

In a meta-analysis of three studies, Patoulias et al (2020) reported that SGLT2 inhibitors (dapagliflozin and empagliflozin) reduced left ventricular (LV) mass but had no effect on LV systolic or diastolic volume. In both diabetic and non-diabetic patients with heart failure and reduced ejection fraction (n = 8474), treatment with either dapagliflozin or empagliflozin reduced mortality (**HR = 0.87; 95%CI 0.77-0.98**) and cardiovascular mortality (**HR = 0.75; 95%CI 0.68-0.84**) (Zannad et al, 2020).

Another meta-analysis of six studies in 9,550 patients with preexisting heart failure (with or without diabetes), SGLT2 inhibitors reduced heart failure hospitalization (**HR = 0.69; 95%CI 0.57-0.84**), cardiovascular death (**HR = 0.79; 95%CI 0.68-0.92**), and any mortality (**HR = 0.80; 95%CI 0.70-0.92**) compared to placebo. Notably, only dapagliflozin studies included non-diabetics (Kumar et al, 2020).

A meta-analysis of seven studies (n = 2,381 patients) suggested that SGLT2 inhibitors could reduce 24-hour systolic blood pressure by ~3.62mm Hg. These results were relatively consistent between different SGLT2 inhibitors and dose. Although the exact mechanisms of blood pressure reduction with SGLT2 inhibitors are not currently known, the authors suggest they could have a diuretic effect (Panagiotis et al, 2019).

Finally, meta-analysis of 36 studies suggested that SGLT2 inhibitors had no effect on total cholesterol levels compared to placebo, but they reduced triglycerides, increased HDL-c, and reduced liver alanine aminotransferases. However, they also increased levels of LDL-c (Chen et al, 2021).

Diabetes

A systematic review and meta-analysis from Chen et al (2020) compared the efficacy of five SGLT2 inhibitors (dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, and sotagliflozin) on the reduction of HbA1c (a measure of the three-month average blood glucose level) over 24 weeks. All the SGLT2 inhibitors reduced HbA1c levels compared to placebo.

In a sub-group analysis (drug-naïve patients, duration of diabetes, BMI, and the region of the study), there were few significant differences between the drugs except that canagliflozin was more effective in drug-naïve patients and those with a shorter duration of disease (<5 years).

In a meta-analysis of studies greater than two years (three studies; one for empagliflozin, dapagliflozin, and saxagliflozin) in patients with diabetes who had not responded to metformin, empagliflozin was reported to be the most effective (23% of patients responded – i.e., maintained lower HbA1c – vs. ~5-7% for the other two drugs) (Zilli et al, 2020).

Neuropathy

One study reported that empagliflozin had no effect on peripheral neuropathy in type 2 diabetic mice (db/db mice) but did improve neuropathy outcomes (sensory nerve conduction velocity) in type 1 diabetic mice (streptozotocin injection) (Eid et al, 2020). One meta-analysis said that no trial had reported on peripheral neuropathy outcomes for SGLT2 inhibitors in diabetic patients (Dorsey-Trevino et al, 2020).

Cancer

Pelletier et al (2020) reported that in general SGLT2 inhibitors were not associated with an increased risk of cancer. When looking at individual cancers, they reported that empagliflozin was associated with an increased risk of bladder cancer (**OR = 4.49; 95%CI 1.21-16.73**) and canagliflozin was associated with a decreased risk of gastrointestinal cancer (**OR = 0.15; 95%CI 0.04-0.60**). However, they caution that SGLT2 inhibitors are associated with well-known risks for genital infections, and empagliflozin's association with bladder cancer may be due to detection bias. In addition, most of the trials of SGLT2 inhibitors have been less than one year. Since cancer takes a long time to develop, it is not clear that these two drugs are truly associated with different risks of cancer.

Safety: SGLT2 inhibitors are associated with an increased risk of genital infections, though most studies are less than one year in duration.

Types of evidence:

- Five meta-analyses of RCTs
- One review

The most common adverse effect with the use of SGLT2 inhibitors is genital infections (which can increase up to four-fold). This could be due to the increased levels of glucose in the urine. Rare cases of ketoacidosis and bone fracture have also been reported and added to FDA labels (Hsia et al, 2017). However, it does not appear that SGLT2 inhibitors are less safe than other diabetes medications.

A systematic review and network meta-analysis reported that SGLT2 inhibitors did not increase the risk of hypoglycemia or diabetic ketoacidosis. They did increase the risk of genital infection (e.g., urinary tract infections, genital mycotic infection) and gastrointestinal events (Palmer et al, 2020). Another meta-analysis of 16 studies (n = 12,749) reported that SGLT2 inhibitors did not increase the risk of orthostatic hypotension (Rong et al, 2020).

A meta-analysis of 109 studies reported that, compared to placebo, SGLT2 inhibitors reduced the risk of acute kidney injury. There were no differences in diabetic ketoacidosis, urinary tract infections, or bone fractures. In a subgroup analysis, they reported that dapagliflozin increased the risk of urinary tract infections. One study reported that canagliflozin was associated with a greater risk of lower limb amputation, though more research is needed (Donnan et al, 2018).

A meta-analysis of 51 RCTs (n = 24,371 patients) reported no differences in adverse events between low-dose or high-dose use of SGLT2 inhibitors with the exception of high-dose canagliflozin (**RR = 1.17; 95%CI 1.05=1.30**). When examining the difference between SGLT2 inhibitors, the meta-analysis reported a reduced risk of infections with empagliflozin (**RR = 0.92; 95%CI 0.86-0.98**) and an increased risk for back pain with dapagliflozin (**RR = 1.83; 95%CI 1.13-2.95**) (Shi et al, 2020).

Pelletier et al (2020) reported that empagliflozin has been associated with an increased risk of bladder cancer in RCTs. However, the authors caution that SGLT2 inhibitors are associated with well-known risks for genital infections, and empagliflozin's association with bladder cancer may be due to detection bias. Few long-term (greater than one year) studies of the gliflozins have been conducted.

Drug interactions:
Canagliflozin is associated with one major drug interaction (gatifloxacin – an ophthalmic solution used to treat bacterial conjunctivitis) and 335 moderate drug interactions (for a full list, see drugs.com). It should also not be taken by patients with renal dysfunction, hyperkalemia, hyperlipidemia, or hypotension.

Dapagliflozin is also associated with one major drug interaction (gatifloxacin) and 320 moderate drug interactions (drugs.com). It should also not be taken by patients with bladder cancer, renal dysfunction, hyperlipidemia, or hypotension.

Empagliflozin is also associated with one major drug interaction (gatifloxacin) and 356 moderate drug interactions (drugs.com). It should not be taken by patients with renal dysfunction, hyperlipidemia, or hypotension.

Ertugliflozin is also associated with one major drug interaction (gatifloxacin) and 321 moderate drug interactions (drugs.com). It should not be taken by patients with liver dysfunction, renal impairment, hyperlipidemia, hypoglycemia, hypotension, infections, ketoacidosis, or urinary tract infections.

Sources and dosing:
The SGLT2 inhibitors are usually given at a low dose or high dose once per day in the morning, depending on the needed reduction in HbA1c. The dose may also be adjusted if a patient is being treated for heart failure or has renal issues.

- Canagliflozin (100 or 300mg)
- Dapagliflozin (5 or 10mg)
- Empagliflozin (10 or 25mg)
- Ertugliflozin (5 or 15mg)

Research underway:
There are 225 ongoing studies in clinicaltrials.gov for SGLT2 inhibitors (link), mostly for diabetics or diabetics with heart conditions.

Other notable studies include:

- One study testing canagliflozin in 100 patients with type 2 diabetes to test its effect on cognitive function (NCT04304261).
- One study testing dapagliflozin in 48 Alzheimer's patients (excluding diabetics unless they are on metformin monotherapy) looking at FDG-PET, cerebral N Acetyl-Aspartate (NAA) levels, and cognition (NCT03801642).
- One study testing empagliflozin in 100 non-diabetic healthy patients looking at plasma ketone levels (NCT03852901).

Search terms:

- sglt2 inhibitor + diabetes (meta-analysis), cardiovascular (meta-analysis), safety (meta-analysis), Alzheimer, lifespan, aging, neuropathy, cancer, apoe4
- Alzheimer + canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, sotagliflozin

Websites visited:

- Clinicaltrials.gov
- Pubmed
- Drugs.com

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