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.

Angiotensin II receptor blockers (ARBs)

Evidence Summary

ARBs may reduce the risk of Alzheimer's disease and other indications more than other antihypertensives, but some data is conflicting.

Neuroprotective Benefit: There is some evidence that ARBs may reduce the risk of Alzheimer's disease, but the evidence is conflicting. Whether they would be beneficial in normotensive patients is not clear.

Aging and related health concerns: ARBs are cardioprotective in hypertensive subjects and possibly normotensive subjects. The risk for cancer is conflicting.

Safety: ARBs are generally safe with few side effects reported. Long-term effects have conflicting results for some indications.

Availability: Available w/prescription; e.g. Telmisartan (Micardis) Candesartaan (Atacand)	**Dose**: Telmisartan: 40-80mg/day; Candesartan: 16-32mg/once or twice daily	**Chemical formula:** Telmisartan: $C_{33}H_{30}N_4O_2$ **MW**: 514.617g/mol
Half life: Telmisartan, 24hrs; candesartan, 9 hrs	**BBB**: Yes (in animals) for telmisartan and candesartan	
Clinical trials: 5 for cognitive function.	**Observational studies**: 14 for reduced risk of Alzheimer's. 4 in Alzheimer's patients.	

What is it?

The renin angiotensin system (RAS) has important roles in blood pressure, systemic vascular resistance, water and electrolyte balance, and cardiovascular homeostasis. However, components of the RAS systems are also present in non-vascular tissues, including the brain. The classical RAS receptors are angiotensin receptor type 1 (AT1R) and AT2R. On endothelial cells, AT1R has a role in vasoconstriction while AT2R has a role in vasodilation.

RAS functions through several enzymatic reactions. A precursor peptide, angiotensinogen, is cleaved by renin creating angiotensin I (Ang I), which is then processed by angiotensin-converting enzyme (ACE) to angiotensin II (Ang II). Ang II binds to AT1R and AT2R leading to downstream effects. Most drugs targeting RAS act to either inhibit ACE (ACE inhibitors - ACEi) and prevent the conversion of Ang I to Ang II, or they inhibit AT1R while sparing AT2R activation (ARBs).

In addition to systemic effects, angiotensinogen is expressed in the brain where it is processed into Ang II. Hyperactivation of AT1R in the brain can lead to cognitive impairment, cell death, and inflammation, with opposing effects occurring with AT2R activation. Adding to the complexity, in addition to AT1R/AT2R expression on the membrane of most cell types in the brain, these receptors may also be expressed in intracellular organelles, such as mitochondria and the nucleus (Kehoe, 2018).

In addition to inhibiting AT1R, some ARBs (e.g. telmisartan, and to a lesser degree, irbesartan) are also partial PPARγ agonists, another target that was of interest for Alzheimer's disease (e.g. pioglitazone and

rosiglitazone, two PPARγ tested for Alzheimer's) (Clasen et al, 2005). Data on whether ARBs cross the blood-brain barrier are mixed, with radiography studies suggesting poor penetration. However, whether they get into the brain under chronic dosing in humans is unknown. Generally, telmisartan is thought the be the ARB with the greatest brain penetration due to its high lipophilicity (Michel et al, 2013). However, blood brain barrier penetration may not be required for the potential beneficial effects.

ARBs are thought to be preferential to ACEi for Alzheimer's prevention, as *in vitro* studies suggest that ACE may degrade Aβ – although this is not confirmed in humans (Kehoe, 2018). Thus, ARBs may retain this ACE/Aβ degrading activity. Also, inhibiting the production of Ang II reduces the beneficial effects of AT2R activation. Finally, although hypertension in mid-life is associated with Alzheimer's disease, the relationship between hypertension in those over 60 and Alzheimer's disease is unclear (e.g. Gabin et al, 2017; Corrada et al, 2017).

ARBs are a class of numerous drugs that all end in sartan.

Neuroprotective Benefit: There is some evidence that ARBs may reduce the risk of Alzheimer's disease, but the evidence is conflicting. Whether they would be beneficial in normotensive patients is not clear.

Types of evidence:

- 1 network meta-analysis for cognitive function
- 3 additional RCTs on cognitive function
- 1 meta-analysis of 10 observational studies for risk of Alzheimer's disease
- 4 additional observational studies on risk for Alzheimer's disease
- 4 neuropathology studies in Alzheimer's patients
- 2 observational studies in Alzheimer's patients
- 8 preclinical studies
- 1 review

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

Clinical Trials: In 53 elderly (>60) hypertensive individuals (on previous anti-hypertensives) with executive dysfunction but not dementia, candesartan was superior to lisinopril (ACEi) or hydrochlorothiazide (diuretic) in improving executive function over 12 months (Hajjar et al, 2012) and in

increasing cerebral blood flow velocity (BFV) in individuals with low BFV at baseline (Hajjar et al, 2013). In a network meta-analysis of RCTs, ARBs were significantly superior to placebo (effect size 0.6), B-blockers (0.67), diuretic (0.54), and ACEi (0.47) on cognition in hypertensive subjects (Levi Marpillat et al, 2012) (though this could be due to methodological issues since ARBs were approved more recently when more precise cognitive tests were available).

Two RCTs, ONTARGET and TRANSCEND, compared telmisartan to either an ACEi (ramipril), telmisartan+ramipril or a placebo for 56 months in elderly patients (>55) with controlled hypertension and evidence of vascular disease. Telmisartan had no effect on cognitive decline or cognitive impairment in either study (Anderson et al, 2011). However, in the SCOPE trial, testing the effects of candesartan or placebo in elderly patients (70-89) with mild to moderate hypertension over 3.7 years, candesartan led to better cognitive outcomes for individuals with low baseline cognitive function but no changes in individuals with high cognitive function (Zanchetti and Elmfeldt, 2006).

Observational studies: In a meta-analysis of 10 studies, Zhuang et al (2016) reported a 31% reduced risk for Alzheimer's disease in patients taking ARBs (compared to a 13% reduced risk with ACEi – though there was no significant difference between the groups) and a 60% reduced risk of cognitive impairment with aging.

(Li et al, 2010 was in the previous meta-analysis but is included here as it is the largest observational study to date). In an observational study over 4 years in 819,491 patients (mostly males, > 65 – from the VA database) with cardiovascular disease, ARBs were associated with a decreased risk for Alzheimer's disease compared to lisinopril (an ACEi that is not brain penetrant) (HR = 0.81; 95%CI 0.68-0.96) and a cardiovascular comparator (any non-ARB, non-ACEi, or non-statin) (HR = 0.84; 95%CI = 0.71-1.00). Switching from lisinopril to an ARB mid-study was also associated with a decreased risk of dementia compared to staying on lisinopril throughout (HR = 0.28; 95%CI 0.24-0.32). Besides lisinopril not being brain-penetrant, other confounding factors are that lisinopril also is not as effective for stroke prevention or for diabetes (Li et al, 2010).

In another observational study over 4.25 years in 426,089 individuals over the age of 18, ARBs were associated with a slightly reduced risk of dementia (HR = 0.92; 95%CI 0.85-1.00) compared to those using an ACEi, a result that was only slightly better for centrally acting ARBs (HR = 0.84; 95%CI 0.71-1.00). Only 50% of the study participants were over the age of 65, possibly diluting the results (Goh et al, 2014). Another nested case-control study in the UK suggested that patients with Alzheimer's were less likely to be prescribed ARBs than other anti-hypertensives (OR = 0.47; 95%CI 0.37-0.58) (suggesting they

may be protective), even when measuring exposure 8 years prior to the study (Davies et al, 2014). Additionally, Kuan et al (2016) reported that in patients with hypertension and type 2 diabetes, ARBs reduced dementia risk by 40% (compared to 26% for ACEi) compared with non-ARB/ACEi patients, with a dose-dependent effect.

Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, Ho et al (2017) reported that over 3 years cognitive performance in hypertensive subjects taking ARBs did not differ from normotensive subjects (except decline in a test of executive function) while those taking other anti-hypertensives declined. Users of ARBs that cross the blood brain barrier performed better than those taking other antihypertensives on most cognitive measures and had fewer white matter hyperintensities (WMH) than the other antihypertensive group and the non-blood brain barrier crossing ARB group.

Human research to suggest benefits to patients with dementia:
Neuropathological data suggests Alzheimer's disease is associated with overactivation of RAS. Savaskan et al (2001) reported an increased expression of ACE, Ang II, and AT1R in the cortex of Alzheimer's patients. Similarly, Miners et al (2008) reported increased perivascular levels of ACE in Alzheimer's patients with cerebral amyloid angiopathy (CAA – amyloid accumulation around blood vessels).

In the above observational study from Li et al (2010) in patients with pre-existing Alzheimer's disease, ARB use non-significantly reduced the risk of death compared to lisinopril (an ACEi) (HR = 0.85; 95%CI 0.72-1.00) and a CVD comparator (0.83; 95%CI 0.71-0.97). In another observational study in 6,290 patients with dementia (AD, vascular, other types), ACEi prescription at diagnosis of dementia, but not ARB prescription was associated with an increased mortality risk compared to other anti-hypertensives over a 10-year follow up (Kehoe et al, 2013). The authors speculate that, based on preclinical data, ACE may degrade Aβ, and reducing the activity of ACE (via ACEi) may have a detrimental impact on neuropathology, while inhibiting AT1R (via ARBs) may be beneficial.

In a post-mortem study of hypertensive patients who had been diagnosed with dementia, Hajjar et al (2012) reported that taking ARBs (compared to other anti-hypertensives) reduced the risk of amyloid accumulation (CERAD criteria) (OR = 0.47; 95%CI 0.27-0.81), tau pathology (Braak and Braak stage) (OR = 0.52; 95%CI 0.31-0.85), but increased the risk of stroke and vascular pathology (OR = 2.37; 95%CI 1.15-4.89). The authors speculate this could be due to confounding by indication (i.e. those with greater vascular risk were prescribed ARBs), though whether this is true is unclear. Additionally, Hoffman et al (2009) reported that hypertensive patients taking anti-hypertensives had better cognition, less amyloid,

and less tau (except in the hippocampus) than normotensive subjects or hypertensive individuals not taking any medication.

In a small study of 20 Alzheimer's patients over 6 months, Kume et al (2012) reported that individuals taking amlodipine (a calcium channel blocker) (but not telmisartan) declined in cognition, while individuals taking telmisartan had improved cerebral blood flow in a number of brain regions.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Animal studies suggest that ARBs may improve cognition, increase CBF, and reduce inflammation.

Preclinical studies for telmisartan and cadesartan
Telmisartan
In a model of ICV injection of Aβ, pretreatment with low-dose telmisartan improved cognition, increased cerebral blood flow (CBF), and reduced levels of TNFα (though not MCP-1). Telmisartan is also a Peroxisome Proliferator-Activated Receptor-γ (PPARγ) activator, and these results were attenuated with coadministration of a PPARγ inhibitor (Tsukuda et al, 2009). Likewise, 5-month intranasal telmisartan treatment in an Alzheimer's animal model was reported to reduce cortical neuronal loss, reduce astrogliosis, slightly reduce amyloid burden and microglial accumulation, reduce iNOS levels, and improve cognition (Torika et al, 2017). Similar amyloid and microglia results were observed after two months of intranasal telmisartan (Torika et al, 2016). Telmisartan also improved cognition and reduced TNFα expression in rats subjected to ischemia and ICV injections of Aβ, results that were also attenuated with coadministration of a PPARγ inhibitor (Shindo et al, 2012).

Candesartan
In a mouse model of Alzheimer's disease, 5-month treatment of candesartan mostly failed to improve cognition, did not increase CBF, or reduce amyloid; despite improving cerebrovascular reactivity, reducing astrogliosis and microgliosis, increasing neurogenesis, and increasing BDNF levels. The authors speculate the vasodilatory effect due to an increase in AT2R and the lack of benefit to cognition a reduction in AT4R levels in the hippocampus, an angiotensin receptor important for memory (Trigiani et al, 2018). On the other hand, 2-month treatment with intranasal candesartan reduced hippocampal, but not cortical, amyloid levels (Torika et al, 2017).

An *in vitro* study suggested that telmisartan increased both Aβ40 and Aβ42 but decreased the Aβ42/40 ratio, while candesartan had no effect on Aβ generation (Liu et al, 2014). Additionally, in an *in vitro* study of glutamate toxicity in primary neurons, candesartan, when given before (but not after)

glutamate, prevented the change in gene expression of most genes altered with glutamate toxicity, including many genes involved in Alzheimer's disease (Elkahloun et al, 2016).

APOE4

No studies have reported interactions between ARBs and APOE genotype.

Aging and related health concerns: ARBs are cardioprotective in hypertensive subjects and possibly normotensive subjects. The risk for cancer is conflicting.

Types of evidence:

- 3 genetic studies on longevity
- 2 preclinical studies for lifespan
- 1 meta-analysis for CVD risk in normotensive subjects
- 4 meta-analyses for CVD risk
- 2 meta-analyses in diabetes
- 2 meta-analyses of RCTs for cancer
- 2 meta-analyses of observational studies for cancer

Lifespan

One study reported that the use of anti-hypertensives accelerated DNAmAge, but this may be driven by the strong, positive association of beta blockers (the most commonly used anti-hypertensive) with accelerated DNAmAge, as ARBs were associated with a weak, non-significant reduction in DNAmAge (Gao et al, 2018).

Interestingly, in a meta-analysis of genetic polymorphisms associated with exceptional longevity, the ACE-D allele, which leads to increased ACE activity (thus more Ang II), was associated with exceptional longevity (OR = 1.11; 95%CI 1.01-1.22). The ACE-D allele is associated with a 10% increased risk for CVD, and the authors speculate this may be a case of antagonistic pleiotropy, whereby having the ACE-D allele may be detrimental earlier in life but protective later in life (Revelas et al, 2018). Another small study reported that an AT1R allele, that leads to reduced expression of AT1R on PBMCs and lower blood pressure, is over-represented in Italian and Japanese centenarians (conducted by the same group that performed the AT1R KO study below) (Benigni et al, 2013).

AT1R knockout (KO) mice lived approximately 26% longer than control animals, and at 29 months, when all the control animals had died, 85% of the AT1R KO animals were still alive. This was accompanied by improved heart, pancreas, and liver morphology, less atherosclerosis, reduced oxidative damage in multiple tissues, and increased mitochondria number in the kidneys. mRNA of *sirt3* and *nampt* (but not *sirt1*) was increased in the kidneys AT1R KO animals. *In vitro* studies suggested that Ang II reduced *sirt3* and *nampt* mRNA, an effect that was reversed by coincubation with candesartan (Benigi et al, 2009). These results are echoed in a study of male rats chronically treated with losartan. Losartan treated rats had no age-associated increase in blood pressure, a 19% increase in lifespan, retained aortic NOS signaling, and reduced cardiac remodeling (Basso et al, 2007).

Normotensive patients at risk for Cardiovascular disease

McAlister et al (2013) combined the data from 13 RCTs testing the effectiveness of ARBs or ACEi in patients at risk for atherosclerotic vascular disease and separated the group by baseline blood pressure. Normotensive patients (SBP < 130 at baseline) taking ARBs or ACEi were at a decreased risk of cardiovascular mortality (OR = 0.83; 95%CI 0.75-0.91), all-cause mortality (OR = 0.89; 95%CI 0.82-0.96), fatal/non-fatal MI (OR = 0.84; 95%CI 0.73-0.97), and a trend for fatal/non-fatal stroke (OR = 0.88; 95%CI 0.78-1.01). Unfortunately, ARBs and ACEi were not examined separately, and only 45% of the patients in the trial were taking ARBs, so it is not clear how effective ARBs specifically are in normotensive subjects.

Cardiovascular disease

In 2004, a study showed that valsartan was equally effective as amlodipine with regards to a composite of cardiovascular mortality and morbidity but increased the risk of myocardial infarction by 19%. Therefore, ARBs were mired in controversy for a time as researchers questioned whether the class of drugs might increase the risk of myocardial infarction. Bangalore et al (2011), conducted a meta-analysis of 37 RCTs that compared ARBs with either a placebo or a comparator drug. ARBs were not associated with an increased risk of myocardial infarction, all-cause mortality, cardiovascular mortality, or angina pectoris. However, ARBs may be associated with a reduced risk of stroke (RR = 0.90; 95%CI 0.84-0.98), heart failure (RR = 0.87; 95%CI 0.81-0.93), and new onset diabetes (RR = 0.85; 95%CI 0.78-0.93). Another meta-analysis of 17 ARB and ACEi clinical trials reported that ACEi were associated with a 15% and 23% reduced risk of mortality and cardiovascular mortality, respectively, while ARBs were not associated with a reduced risk of death. However, both drugs reduced the risk of acute myocardial infarction (ARBs – 9%), stroke (ARBs – 11%), and heart failure/hospitalization (ARBs – 20%) (Salvador et al, 2017). However, another meta-analysis of 11 RCTs reported that ARBs were associated with a significant 21% reduction in stroke risk, but no significant effects on myocardial infarction, hospitalization for heart failure, or mortality (Akioyamen et al, 2016).

Diabetes/Chronic kidney disease

In a network meta-analysis of 157 anti-hypertensive trials in patients with type 2 diabetes and chronic kidney disease, no drug reduced all-cause mortality. However, ARB monotherapy was associated with a reduced risk of end-stage renal disease (OR = 0.77; 95%CI 0.65-0.92) and myocardial infarction (OR = 0.70; 95%CI 0.53-0.94) but not stroke (Palmer et al, 2015). Another meta-analysis of anti-hypertensive clinical trials reported that both ACEi and ARBs reduced the risk of new onset diabetes by ~20-27% while beta-blockers and calcium channel blockers increased risk (Li et al, 2017).

Cancer

An increased risk for cancer with ARB use was first noted in the 2003 study Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM). In 2010, a meta-analysis of 9 ARB RCTs reported that ARB use was associated with an increased risk of new cancer incidence (RR = 1.08; 95%CI 1.01-1.15) but not cancer death. In an analysis of solid organ cancers, ARB use was associated with a 25% increased risk of lung cancer, but not prostate or breast cancer. This lung cancer effect was only significant in patients on a background of ACEi therapy (Sipahi et al, 2010). Most of the patients in the previous meta-analysis come from two studies of telmisartan. However, in 2011, a network meta-analysis of 70 RCTs reported no increased risk of cancer with the use of ARBs (OR = 1.01; 95%CI 0.93-1.09), but an increased cancer risk in patients taking both ARBs and ACE (OR = 1.14; 95%CI 1.02-1.28). Like the previous study, there was no increase in cancer-related deaths. There was also no increased cancer risk using telmisartan versus other ARBs (Bangalore et al, 2011).

Some differences between the two studies: Sipahi et al (2010) included 9 ARB RCTs while Bangalore et al (2011) included 21 ARB trials. Bangalore et al (2011) treated those taking an ARB and an ACEi as a separate category, and when Sipahi et al (2010) separated out the two groups the relative risk for ARBs was slightly attenuated (13% increased risk for ARB+ACEi, p=0.011; 8% for ARB only, p=0.041).

Yang et al (2015) reported that ARB use was associated with a decreased risk of cancer in a meta-analysis of 6 observational cohorts with more than 3 million individuals (RR = 0.80; 95%CI 0.55-0.95). Individual ARBs were associated with similar, albeit non-significant, 10-15% decreased cancer risk. In individual cancers, ARBs were associated with a 19% decreased risk of lung cancer. The strongest anti-cancer effect was in Asian populations (31% risk reduction), with Caucasian populations being non-significant. These results were replicated in another meta-analysis of largely overlapping observational studies with reduced lung cancer risk in Asian but not Caucasian populations (Zhang et al, 2015).

Safety*:* ARBs are generally safe with few side effects reported. Long-term effects have conflicting results for some indications.

Types of evidence:

- Evidence from multiple clinical trials

ARBs are generally well-tolerated and safe, with the most common adverse events including headache, respiratory infection, dizziness, and fatigue. In clinical trials side effects are generally not significantly greater than placebo (except potentially for hypotension, renal dysfunction, and hyperkalaemia) (Abrahams et al, 2014). Drugs.com list rare side effects including changes in vision, dizziness, fast heartbeats, hives, painful urination, and swelling in the extremities. Other potential side effects include myalgia, insomnia, anxiety, and hypotension. ARBs are generally better tolerated than ACEi. The potential long-term side effect with cancer is still unclear.

Drug interactions:
ARBs increase the renal absorption of lithium, so use of lithium with ARBs should be avoided. Telmisartan taken with digoxin increases digoxin levels, so the combination should be avoided (Abraham et al, 2014).

There are many other drug interactions for ARBs, including most of the other anti-hypertensives. More information here on telmisartan and candesartan.

Precision medicine considerations:
Many SNPs are associated with different responses to ARBs and ACEi. *Flaten and Monte (2017)* provide information on pharmacogenomic effects of particular SNPs.

Additionally, there may be different effects based on race. For example, in the cancer studies above, most of the anticancer benefits were seen in Asian populations. Additionally, African Americans may not respond as well to drugs that target the RAS (e.g. ACEi and ARBs) and generally respond better to diuretics and calcium channel blockers (Musemwa and Gadegbeki, 2017).

Sources and dosing:
Starting doses for ARBs vary depending on the type of dose (e.g. telmisartan 20-80mg/day, candesartan 8-32mg/day). Dosing are titrated based on side effects and blood pressure achieved.

Research underway:

There are five ongoing clinical trials testing ARBs for Alzheimer's disease (2 funded by ADDF – SARTAN-AD and CEDAR).

- SARTAN-AD – comparing telmisartan and perindopril in Alzheimer's disease to see which can reduce brain atrophy.
- Candesartan's Effects on Alzheimer's Disease and Related Biomarkers (CEDAR) – testing candesartan in normotensive individuals with MCI for the number of hypotensive incidents and changes in Alzheimer's biomarkers.
- Health Evaluation in African Americans Using RAS Therapy (HEART) – testing the effect of telmisartan in African Americans at risk for Alzheimer's disease.
- CALIBREX – comparing candesartan to lisinopril in patients with hypertension and MCI.
- rrAD – testing losartan and amlodipine in hypertensive adults with subjective cognitive decline.

Search terms:

Pubmed

angiotensin receptor blocker + Alzheimer, apoe4, hypotension, cancer [meta-analysis], [meta-analysis]

angiotensin + lifespan

Google

angiotensin receptor blocker + normotensive

Websites visited:

- Clinicaltrials.gov (3)
- Examine.com (0)
- DrugAge (0)
- Drugs.com
- DrugBank.ca
- Labdoor.com (0)

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