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.

Acarbose

Evidence Summary

Acarbose is effective in treating diabetes, preventing cardiovascular events in diabetics, and extends lifespan in mice, but does not cross the blood-brain-barrier.

Neuroprotective Benefit: Since acarbose has poor blood-brain-barrier penetrance, any neuroprotective benefit will be secondary to improvement in blood glucose control.

Aging and related health concerns: While effects in healthy adults are unknown, acarbose prevents diabetes in people with prediabetes and decreases the incidence of cardiovascular events in diabetics. In mice, acarbose extends lifespan.

Safety: Most reported side effects are mild and are gastrointestinal in nature (diarrhea, flatulence, bloating), but the majority of studies on safety have been carried out in diabetics and long-term effects in healthy adults are unknown.

What is it? Acarbose is a generic drug for the treatment of type 2 diabetes. It inhibits α-glucosidase, an enzyme in the small intestines that digests starches and disaccharides into glucose. It also inhibits α-amylase in the pancreas, which breaks down complex starches into oligosaccharides. The net effect of acarbose is decreased blood glucose levels.

Neuroprotective Benefit: Since acarbose has poor blood-brain-barrier penetrance, any neuroprotective benefit will be secondary to improvement in blood glucose control.

Types of evidence:

- 1 clinical trial in patients with hepatic encephalopathy and type 2 diabetes
- 1 laboratory study on pharmacokinetics and blood-brain-barrier permeability
- 1 review on pharmacologic therapies for hepatic encephalopathy

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

No studies have tested acarbose for dementia or age-related cognitive decline. The only literature available for cognitive outcomes is from studies in hepatic encephalopathy, which is a common neuropsychiatric condition associated with cirrhosis, resulting in impaired cognition and level of consciousness. Common dysfunctions are seen in attention, visual perception, visuospatial accuracy, and motor functions (Weissenborn et al., 2003; McCrea et al., 1996). In a randomized controlled trial of 107 patients with hepatic encephalopathy and type 2 diabetes, 8 weeks of acarbose treatment (100 mg, 3 times daily) significantly decreased blood ammonia levels, improved cognitive function (Reitan's number connection test), and improved intellectual function score compared with placebo (Gentile et al., 2005). Acarbose also decreased fasting and postprandial glucose levels and significantly lowered glycated hemoglobin values compared to control. The positive effects on cognitive function are likely secondary to improvement in peripheral pathology that is specific to hepatic encephalopathy.

Human research to suggest benefits to patients with dementia. None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research: In a pharmacokinetic study in rats and dogs, permeability of acarbose through the blood-brain-barrier was very low (Ahr et al., 1989). Neuroprotective benefits of acarbose, if any, are likely to be secondary to improvement in peripheral pathology, such as improved glucose control and decreased cardiovascular events. Type 2 diabetes and Alzheimer's disease share certain characteristics, including impaired insulin

signaling and oxidative stress (Sebastiao et al., 2014). Diabetics have up to 73% increased risk of dementia and a 100% higher risk of developing vascular dementia than non-diabetics (Deckers et al., 2015; Gudala et al., 2013; Vagelatos and Eslick, 2013; Chatterjee et al., 2016).

APOE4 interactions: None available.

Aging and related health concerns: While effects in healthy adults are unknown, acarbose prevents diabetes in people with prediabetes and decreases the incidence of cardiovascular events in diabetics. In mice, acarbose extends lifespan.

Types of evidence:

- 8 meta-analyses in people with diabetes (6) and prediabetes (2)
- 2 randomized controlled trials examining cardiovascular events and hypertension in people with impaired glucose tolerance
- 1 review on cardiovascular benefits
- 2 mouse studies on lifespan

Type 2 diabetes: BENEFIT. Multiple meta-analyses show that acarbose can help to manage type 2 diabetes. A Cochrane meta-analysis reported that insulin combined with acarbose decreases glycated hemoglobin levels more significantly than insulin monotherapy (Vos et al., 2016). Acarbose also reduces the necessary dose of daily insulin. The glucose-lowering effects of acarbose and metformin are comparable (Gu et al., 2015). In a meta-analysis comparing different anti-hyperglycemic drugs, all agents reduced glycated hemoglobin levels but by differing magnitudes (Mearns et al., 2015). Acarbose showed the lowest magnitude of change in glycated hemoglobin (- 7mM/mol, or -0.6%) and liraglutide produced the greatest change (-13 mM/mol, or -1.2%). Canagliflozin, GLP-1 analogues, insulin glargine, and thiazolidinediones (TZDs) fell in the middle (around -1%).

Some studies have examined the effects of acarbose in prediabetic people. A meta-analysis of 8 RCTs including 2,628 people reported that the preventive effect of acarbose on the development of diabetes seems superior in Eastern populations with prediabetes compared with Western populations. Compared with the control (placebo and/or lifestyle intervention), the incidence of type 2 diabetes was significantly lower in the Eastern group treated with acarbose (number needed to treat=5.9) than in the Western group (number needed to treat=11.1) (Hu et al., 2015). This difference may be due to the relatively high proportion of carbohydrates in Asian diets. In a double-blind randomized controlled trial

of 1,429 people with prediabetes (impaired glucose tolerance), acarbose treatment (100 mg, 3 times/day) for ~3.3 years resulted in a 25% relative risk reduction in the development of type 2 diabetes (HR=0.75, 95% CI, 0.63 to 0.90) (Chiasson, 2006).

Cardiovascular disease: BENEFIT. A Cochrane meta-analysis of 5 RCTs including a total of 2,360 subjects reported that acarbose decreases cardiovascular events in people with impaired glucose tolerance (prediabetes) (Van de Laar et al., 2006). But no statistically significant effects were observed on mortality, lipid indices, or blood pressure. In a double-blind randomized controlled trial not included in the above meta-analysis, acarbose treatment (100 mg, 3 times daily) for ~3.3 years resulted in a 34% risk reduction in the development of new cases of hypertension (HR, 0.66; 95% CI, 0.49 to 0.89; P = 0.0059), and in a 49% risk reduction in the development of cardiovascular events (HR, 0.51; 95% CI, 0.28 to 0.95; P = 0.03) (Chiasson, 2006).

A meta-analysis of 18 clinical trials reported that while acarbose treatment did not alter total cholesterol levels, a significant reduction in triglycerides and a significant increase in HDL were observed (Monami et al., 2012).

Reactive hypoglycemia: BENEFIT. Acarbose reduces the early rise in blood glucose by inhibiting the breakdown of starches/disaccharizes into glucose in the intestine—this, in turn, prevents the spike in insulin that can induce hypoglycemia. Many of the studies are old, but they consistently show that acarbose is beneficial. A double-blind study in reactive hypoglycemia used a dose of 100 mg during a sucrose tolerance test and the insulin response to oral sucrose was reduced (Gerard et al., 1984). In another study in people with postprandial hypoglycemia, 3 months of acarbose treatment significantly reduced the frequency of hypoglycemic attacks, from 4 times a week to once a week (Ozgen et al., 1998). A smaller study in people with idiopathic reactive hypoglycemia showed that after 4 weeks of acarbose therapy, all 6 patients were asymptomatic on a regular diet (Peter, 2003). They used a dose of 25 mg for each meal the first 2 weeks and 50 mg per meal the last 2 weeks. There are other case studies of very old people and the results were similar. For example, an 89-year old experienced a severe hypoglycemic episode and was given acarbose for the next 4 years (50 mg, 3 times a day)(Deliens et al., 2014). She had no further episodes.

Weight loss: MIXED/BENEFIT. One meta-analysis of 20 RCTs in patients with diabetes showed that acarbose does not affect body weight when compared to placebo/control (Mearns et al., 2015). However, in a meta-analysis that compared Eastern versus Western populations, the acarbose group achieved a significantly larger absolute weight loss of (change from baseline) 1.35 kg in Eastern

populations (weighted mean difference; WMD = -2.26 kg, 95% CI -2.70 to -1.81) than in Western populations (WMD = -0.91 kg, 95% CI -1.36 to -0.47), though some risks of bias have been noted in Eastern studies (Li et al., 2014). The magnitude of weight change is unlikely to be clinically meaningful.

Lifespan: BENEFIT. No evidence in humans yet. The National Institute on Aging Interventions Testing Program (NIA ITP) was designed to test compounds such as acarbose that are purported to extend lifespan and/or delay onset of age-related diseases. This collaborative program uses 1) parallel studies in males and females at 3 different sites, 2) genetically heterogeneous mice to guard against conclusions based on a single inbred genotype, and 3) enough samples to provide statistical power.

In the 2014 report, mice were fed acarbose mixed in the diet (1000 mg of acarbose in 1 kg of diet; 1000 ppm) from 4 months of age and onward (Harrison et al., 2014). Acarbose increased male median lifespan by 22% but increased female medial lifespan by only 5%, based on data pooled across 3 sites (statistically significant for both sexes). This sex effect of acarbose could not be accounted for by differences in weight changes--acarbose reduced body weights considerably more in females (15, 22, 23, 22% lighter) than in males (15, 14, 11, 9% lighter). One possible reason for this sex effect is the unusually short lifespan of the male controls at 2 out of 3 test sites, magnifying the apparent effect of acarbose in males. Maximum lifespan (90th percentile) increased 11% in males and 9% in females. Acarbose did not affect HbA1c levels, but fasting blood glucose levels were higher in acarbose-fed males and females. This counterintuitive effect may be due to acarbose delaying the digestion of complex carbohydrates and absorption of sugars from the GI tract. Acarbose also reduced fasting insulin in males, but not females, suggesting that males may have achieved greater insulin sensitivity. In both males and females, acarbose significantly reduced plasma levels of insulin-like growth factor 1 (IGF1), a hormone that has been associated with shorter lifespan (Teumer et al., 2016; Suh et al., 2008). FGF21, a hormone produced by the liver in response to fasting (extends lifespan in mice), was elevated by acarbose, but was greatly reduced with dietary restriction in the same study. Thus the mechanisms of action for life extension are not entirely the same for acarbose and dietary restriction.

In a follow-up study published in 2016, mice were fed the same dose of acarbose but started much later in life, at 16 months of age, to test whether acarbose is effective in extending lifespan if started at middle-age (Strong et al., 2016). Acarbose significantly increased median longevity in males and 90th percentile lifespan in both sexes. When data were pooled across sites, there was a significant increase in survival for male mice treated with acarbose, with a 6% increase in median lifespan and a significant 12% increase in maximal lifespan. Acarbose started at this late age only had a small effect on median lifespan in females (2%, p=0.07), but led to a significant (6%) increase in maximal lifespan. The previous

study showed a greater magnitude of lifespan extension, suggesting that acarbose treatment appears to be optimal when initiated earlier in life. The authors are currently testing different doses with treatment initiated at an intermediate time (12 months) and also looking at effects on age-sensitive changes in multiple tissues in hopes to understand the mechanisms of action of acarbose on lifespan and healthspan. It is currently unknown whether acarbose is extending longevity by retarding basic mechanisms of aging, by postponing death from multiple forms of neoplasia, or by a combination of these two.

Safety: Most reported side effects are mild and are gastrointestinal in nature (diarrhea, flatulence, bloating), but the majority of studies on safety have been carried out in diabetics and long-term effects in healthy adults are unknown.

Types of evidence:

- 2 meta-analyses based on 41 RCTs (diabetes) and 5 RCTs (prediabetes)
- 1 clinical trial in hepatic encephalopathy and diabetes
- 2 short-term studies in healthy men
- 2 reviews
- 1 mouse lifespan study

Details. Ample evidence for safety exists for patients with diabetes and prediabetes. A Cochrane meta-analysis of type 2 diabetic patients that included 41 randomized controlled trials and a total of 8,130 subjects reported that adverse effects were mostly of gastrointestinal origin and dose-dependent (Van de Laar et al., 2005). No significant effects on total mortality or mortality due to cardiovascular causes were found, but this is because only one study included mortality as an outcome. Acarbose use did significantly reduce the incidence of cardiovascular disease. Common side effects include diarrhea, flatulence, bloating, and nausea, but the majority of these disappear after 1-2 months (Hanefeld and Schaper, 2008). Similar results were obtained from a Cochrane meta-analysis of people with prediabetes or impaired glucose tolerance that included 5 randomized controlled trials and 2,360 subjects, which reported that acarbose caused more GI side effects than placebo (RR=1.40, 95% CI, 1.31-1.50) (Van de Laar et al., 2006). Acarbose may also be safe and effective in cirrhotic patients with low-grade hepatic encephalopathy and diabetes (Gentile et al., 2005).

No studies have examined whether acarbose is safe in healthy people other than a few small short-term pharmacokinetic studies (Kageyama et al., 1997; Aoki et al., 2010). Acarbose administered alone should

not cause hypoglycemia. Side effects (gastrointestinal) were similar to those reported in diabetes studies.

In the mouse lifespan study, there were no significant differences between control and acarbose-treated mice in the proportion of mice dying with any cause of death, likely because many different causes were represented (Harrison et al., 2014). The incidence of liver degeneration was reduced by acarbose from 42% to 3% in males, but did not have a similar effect in females, with 17% liver degeneration in acarbose-treated and 13% in controls. Improved liver function in acarbose-treated males may have contributed to their improved survival, though the mechanisms are unknown. Hepatic lipidosis ("macro lipidosis") is diminished significantly by acarbose (27% to 4%) and this effect is significant in males (incidence is lower in females but not statistically significant).

Drug interactions: Acarbose should not be used with anticoagulants (e.g., warfarin), because the risk of side effects (e.g., bleeding) may be increased by acarbose (drugs.com). Acarbose should also not be used with drugs that cause hyperglycemia, which may lead to loss of blood glucose control. These drugs include calcium channel blockers (e.g., verapamil), corticosteroids (e.g., prednisone), diuretics (e.g., hydrochlorothiazide), isoniazid, nicotinic acid, estrogens, oral contraceptives, phenothiazines (e.g., chlorpromazine), phenytoin, or thyroid hormones (e.g., levothyroxine).

Sources and dosing: Acarbose is an anti-diabetic drug that is sold as Precose (Bayer Pharmaceuticals) in the US. Acarbose is often used with other anti-diabetic medications (e.g., insulin, metformin, sulfonylureas) to control diabetes as the mechanism of action is distinct. Acarbose is taken orally 3 times a day at the start of each meal. Daily doses are determined based on the doses and combinations of other anti-diabetic drugs, but typically range from 50 to 300 mg daily. Maximum dose for people under 60 kg is 50 mg orally 3 times a day (drugs.com). For people over 60 kg, the maximum dose is 100 mg orally 3 times a day.

While many studies have been carried out in people with diabetes or impaired glucose control, it is currently unknown whether people without these conditions would benefit from improved blood sugar control. In a prospective study of 78 women with polycystic ovarian syndrome, acarbose treatment (300 mg/day) improved insulin and fasting glucose levels to greater extents in overweight patients compared to non-overweight patients (Tugrul et al., 2008). These differences can be explained in part by the higher insulin and fasting glucose levels at baseline in overweight patients. For healthy people with normal insulin and glucose levels, or for those who eat low-carb diets, acarbose may not be beneficial.

The mouse lifespan studies did not measure the doses consumed by the mice as acarbose was mixed in their diet (1000 ppm). Generally, mice consume 10-15 g of chow per 100 g of body weight daily (Huerkamp and Dowdy, 2008). Based on their body weights, it is roughly estimated that the mice consumed ~100 mg/kg/day of acarbose. The human equivalent dose after taking into account differential body surface area is 8.13 mg/kg/day (or 487.8 mg daily for a person weighing 60 kg). Thus the approximate dose used in mice is much higher than the maximum dose recommended for patients with diabetes (300 mg daily).

Research underway: Several clinical trials are underway. One clinical trial is examining whether blocking carbohydrate intake in the small intestine with acarbose may be therapeutic in older people with postprandial hypotension (a drop in blood pressure after eating) (NCT01914133). Two clinical trials are testing the anti-aging effects of acarbose: one is examining changes in gene expression in muscle and adipose tissue (NCT02953093) and the other is an open-label trial in elderly subjects testing before-and-after effects of endothelial function, physical function, cognitive function, immune parameters, and gut microbiome composition (NCT02865499). Clinical trials in type 2 diabetes patients are comparing the effects of acarbose treatment against gemigliptin (NCT02500329), saxagliptin (NCT02315495), vildagliptin (NCT02999841), and metformin (NCT02605772).

Search terms:

Pubmed, Google: acabose

- + meta-analysis, + clinical trial, + Cochrane, + dementia, + Alzheimer's, + cognitive, + ApoE, + lifespan, + cardiovascular, + hypertension, + safety

Clinicaltrials.gov: acarbose