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.

Carvedilol

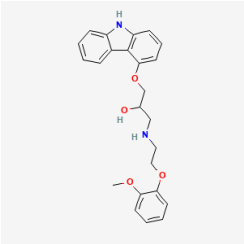
Evidence Summary

Carvedilol is a beta blocker with significant benefit for specific cardiac conditions. Some preclinical and observational work suggests potential benefit for dementia prevention, but this work is preliminary.

Neuroprotective Benefit: Preclinical work suggests a benefit for dementia and observational studies suggests a potential prevention benefit. However, there is also a theoretical mechanism for memory impairment. More clinical work is needed.

Aging and related health concerns: Carvedilol provides significant reductions in morbidity and mortality for specific cardiovascular indications; it is one of the first-line treatments for these indications. There is no indication of benefit for other populations.

Safety: Carvedilol is generally well-tolerated. Common side effects include hypotension, bradycardia, shortness of breath, and weight gain. There are several serious disease contraindications, including asthma.

Availability: By prescription	**Dose**: Carvedilol dosing is specific to indication and should be individualized. There are immediate-release (3.125 to 25 mg, twice daily) and extended-release formulations available (10 to 80 mg, once daily); both are taken orally. Maximum dose is generally 50 mg (immediate-release) or 80 mg (extended-release) daily.	**Chemical formula:** $C_{24}H_{26}N_2O_4$ **MW**: 406.5 g/mol  Source: PubChem
Half-life: 7 to 10 hours	**BBB**: Penetrant	
Clinical trials: The largest review referenced RCTs of carvedilol with a total of 9,120 patients.	**Observational studies**: The largest meta-analysis identified included 30,943 patients who used carvedilol.	

What is it?

As part of the autonomic nervous system, the sympathetic nervous system (SNS) plays a role in regulating a variety of involuntary and necessary physiological processes such as heart rate and contractility, blood pressure, and airflow. The actions of the SNS are mediated in part through catecholamine neurotransmitters such as epinephrine and norepinephrine acting on adrenergic receptors. Adrenergic receptors are G-protein coupled receptors. The family of adrenergic receptors can be divided into two groups: α-adrenergic receptors and β-adrenergic receptors. These groups can be further divided into different subtypes, with two subtypes of α-adrenergic receptors, α_1 and α_2, and three subtypes of β-adrenergic receptors, β_1, β_2, and β_3. Each receptor subtype has different G protein(s) associated with it as well as tissue-type expression differences, which lead to various downstream effects. Modulating the different adrenergic receptors, whether alone or in combination, can lead to significant effects on cardiovascular function (Alshak & Das, 2023).

Beta blockers are a class of drugs that antagonize one or multiple β-adrenergic receptors. There are a variety of beta blockers on the market. Carvedilol (brand name Coreg®) is a nonselective β-adrenergic antagonist as well as an α-adrenergic antagonist; it is a racemic mixture of equal parts R-carvedilol, an α-

adrenergic blocker, and S-carvedilol, which antagonizes both α- and β-adrenergic receptors. This receptor antagonism leads to vasodilation and slower heart rate, which can improve blood flow and decrease blood pressure. Carvedilol is approved for use for heart failure, hypertension, and left ventricular dysfunction following myocardial infarction. Carvedilol is used off label for a variety of conditions, including as a prevention strategy for cirrhotic esophageal variceal bleeding, stable angina, and management of heart arrhythmias. Carvedilol is often prescribed as one of multiple medications for any given indication (Yao & Chen, 2022; Heidenreich et al., 2022; Singh & Preuss, 2024).

Cardiovascular disease is a risk factor for dementia (Livingston et al., 2024). Appropriate management of this and other risk factors may help prevent dementia. Preclinical work has suggested that carvedilol may have direct neuroprotective benefits, and observational studies have suggested that carvedilol use may be associated with lower incidence of dementia (See 'Neuroprotection' section).

Neuroprotective Benefit: Preclinical work suggests a benefit for dementia and observational studies suggests a potential prevention benefit. However, there is also a theoretical mechanism for memory impairment. More clinical work is needed.

Types of evidence:

- 1 Lancet report
- 1 randomized controlled trial
- 2 clinical trials
- 4 observational studies
- 5 reviews
- 7 laboratory studies

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

No clinical trial has directly tested whether carvedilol can prevent dementia or decline or explored in depth what effects, if any, carvedilol has on cognitive function.

One small randomized, unblinded study enrolled 40 elderly individuals with chronic heart failure who were already receiving treatment for their condition and randomized them to additionally receive either

placebo or carvedilol for 12 weeks. The goals of the study were to compare the clinical status as well as cognitive and functional abilities of the patients over the course of the 12 weeks. The authors found no difference in cognitive function as measured by MMSE or daily functioning between the placebo and carvedilol group at any timepoint in the study (Luparini et al., 1999).

There is some observational evidence that suggests a potential association between carvedilol usage and incidence of dementia.

A retrospective observational study by Beaman et al., 2023 utilized data from the Danish national registers to assess the association between certain beta blockers and incidence of AD in patients with hypertension. Specifically, the researchers were interested in whether there was a difference in incidence of AD based on the blood-brain barrier (BBB) permeability of the beta blocker a patient received. The study included a cohort of 69,081 individuals with primary hypertension who were prescribed a beta blocker and one other hypertension medication; the median age was 64, and the median follow-up period was 9.8 years. The authors classified beta blockers as either high BBB penetrance, moderate BBB penetrance, or low BBB penetrance; carvedilol and propranolol were classed as beta-blockers with high BBB penetrance. The researchers found that the 10-year standardized absolute risk of AD was 24% lower in the group that received one of the two highly penetrant beta-blockers compared to those who received a beta-blocker with low permeability (RR=0.76; 95% CI: 0.61 to 0.95, $p<0.040$). This association was significant starting from 1.5 years after inclusion into the study, and the association was specific to AD diagnosis; there was no difference in absolute risk of any dementia diagnosis between low and high BBB penetrance beta blockers. There was also a trend towards a significant decrease in dementia incidence in the group that received moderately penetrant beta blockers compared to those who received low penetrance beta blockers. In sensitivity analyses, the authors did not detect a difference in effect between carvedilol and propranolol, suggesting that the effect is not specific to carvedilol alone. It should be noted that the authors reported an increased incidence of death in the group receiving a moderate or high penetrance beta blocker compared to a low penetrance beta blocker, though this effect was not significant in sensitivity analyses that removed all events in the first year of the study, leading the authors to posit that there was an increased unmeasured comorbidity burden in the groups receiving more BBB penetrant beta blockers.

As this study was an observational study, it is not possible to assign a cause-and-effect relationship. There were several baseline characteristic differences between the three groups that could influence the results. If the results reflect an underlying biological truth, these data could stem from multiple

underlying mechanisms of action. While one possible explanation is that highly BBB penetrant beta blockers can provide directly neuroprotective effects, the high penetrance beta blockers included in this study are also nonselective for β adrenergic receptors, whereas the low and moderate penetrance beta-blockers are selective for β_1 adrenergic receptors; this pharmacological discrepancy opens other possibilities for mechanisms of action. Further work is needed to clarify the relationship between beta blockers and incidence of AD (Beaman et al., 2023).

Two case-control studies using Medicare claims data assessed the relationship between medication usage and diagnosis with either AD, Parkinson's disease (PD), or amyotrophic lateral sclerosis (ALS) (Song et al., 2023), or Lewy body dementia (LBD) (Scholz et al., 2023); both reported reduced incidence of dementia in patients who received carvedilol in the years before their dementia diagnosis.

Song et al., 2023 examined data from 42,885 patients with dementia and 334,387 randomly selected controls who were not diagnosed with dementia, using covariates to control for differences. They found that carvedilol was associated with a significantly lower incidence of dementia (mean OR=0.80; adjusted PD OR= 0.81; 95% CI 0.77 to 0.86; adjusted AD OR=0.90; 95% CI 0.81 to 0.99; adjusted ALS OR=0.78; 95% 0.59 to 1.01; mixed dementia OR=0.72; 95% CI 0.62 to 0.82). In a replication cohort, the authors compared incidence of dementia in patients who received carvedilol compared to other beta blockers and found a significantly lower incidence of AD/PD/ALS in patients who received carvedilol compared to those who received a non-carvedilol beta blocker (HR=0.81; 95% CI 0.67 to 0.99). Scholz et al., 2023 included 148,170 LBD cases and 1,253,043 matched controls. Unlike Song and colleagues, Scholz and colleagues looked at classes of drugs rather than specific drugs and found consistent reduction of LBD incidence in patients who received any class of anti-hypertensive, including beta blockers. While the authors did not report the individual odds ratios or p-values of each drug, carvedilol was marked as a particularly significant association with reduced incidence of dementia. It should be noted that the authors hypothesize that the high OR of propranolol is due to reverse causation; propranolol can be prescribed for tremor, and the association may reflect LBD patients seeking treatment for their neurological symptoms (Figure 3, Scholz et al., 2023).

However, there are contradictory results as to the effects of beta blockers on cognition. For instance, Holm et al., 2020 report that use of beta blockers was associated with an increased incidence of vascular dementia, though not other dementias (Holm et al., 2020). Other studies find no effects of beta blockers on cognitive function. These finding are complicated by the differences between beta blockers, the challenges inherent in observational studies, and that beta blockers are rarely prescribed as

monotherapies in older populations, making it difficult to tease apart the effects of individual drugs (Yang et al., 2021).

Human research to suggest benefits to patients with dementia:

An RCT (NCT01354444) assessed whether a 6-month treatment with carvedilol improved memory as measured by the Hopkins Verbal Learning Test (HVLT) or biomarkers of AD in patients with AD. The study enrolled 29 patients and randomized them to either 25 mg carvedilol or matching placebo. The results were published on clinicaltrials.gov and also reported in a media article (Alzheimer's News Today). The authors did not identify any statistical difference in cognitive performance or AD biomarkers between groups after 6 months of treatment, though it should be noted that only 6 of the 14 participants in the carvedilol group and 11 of the 15 patients in the placebo group completed the study, leaving small sample sizes for comparison.

Other studies have looked at the effects of beta-blockers as a class, which may or may not reflect the action of carvedilol. Rosenberg et al., 2008 report the results of an observational study that longitudinally followed patients with dementia and assessed the cognitive, functional and neuropsychiatric trajectories of the patients, as well as modifiers of those trajectories. In this analysis, they examined the effects of cardiovascular medications on the rate of functional decline as measured by CDR-SB. This part of the study included 216 individuals who were followed for a median of 3 years. The authors found that patients who used beta-blockers at baseline experienced a 40% decrease in rate of functional decline; this was a significant effect ($p=0.04$). There was also a significant slowing of decline with use of statins compared to those who did not use statins. No other cardiovascular medication (ACE inhibitors, calcium channel blockers, nitrates, digoxin) was associated with a change in CDR-SB trajectory.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Cardiovascular conditions like hypertension can increase the risk of dementia (Livingston et al., 2024). Use of medications like carvedilol that can treat these underlying health conditions could therefore indirectly reduce the risk of dementia.

There are several hypotheses for directly neuroprotective mechanisms of action of carvedilol. Carvedilol has both antioxidant and anti-inflammatory effects, and has been reported for cardiovascular disease

(Book, 2002; Dandona et al., 2007; Chen-Scarabelli et al., 2012; Uche et al., 2023), type 1 diabetes (Diogo et al., 2017), ulcerative colitis (Nasser et al., 2022), and in neuronal cell models (Ouyang et al., 2013). There are at least some studies in humans that indicate an antioxidant effect in patients with chronic heart failure (Toyoda et al., 2020). Studies of ischemic injury animal models have suggested that carvedilol may have anti-apoptotic and therefore neuroprotective actions (Lysko et al., 1992; Book, 2002).

Carvedilol crosses the blood-brain barrier (BBB) and can therefore directly affect different cell populations and processes in the brain. One preclinical study of animal models of AD reported that treatment with carvedilol reduced levels of oligomeric Aβ in both in silico assays as well as in vivo animal experiments. They also found that carvedilol attenuated cognitive decline and improved neuroplasticity in the AD animal models compared to control treatment (Wang et al., 2011). Other studies have also reported cognitive benefits of R-carvedilol treatment in animal models of AD (Yao & Chen, 2022). Yao & Chen, 2022 propose that the effects of carvedilol are via modulation of the ryanodine receptor and concomitant calcium release by carvedilol (Yao & Chen, 2022; Hori et al., 2024).

Another theory is that proposed by Beaman et al., 2023. Norepinephrine is a regulator of CSF-dependent clearance; this process may help clear protein aggregates such as Aβ and tau. As beta-blockers reduce norepinephrine signaling, and reductions in norepinephrine signaling are thought to improve clearance in the central nervous system, the authors suggest that BBB-penetrant beta blockers may promote CSF-dependent clearance via modulation of β-adrenergic receptors in the brain.

β-adrenergic receptors in the central nervous system are thought to play an important role in a variety of AD-relevant processes, including sleep, glial function, synaptic plasticity, and memory consolidation (Beaman et al., 2023). It should be noted that antagonism of adrenergic receptors may have negative consequences for cognitive function, with some studies reporting memory impairment from use of beta blockers in animal models. As described above, other papers find cognitive benefits of beta blocker use in animal models. Discrepant results may be due to a variety of factors, including use of different beta blockers with varying receptor sensitivities or what specific assessment of memory was used in the study. As an example of the latter possibility, human studies have suggested that another beta blocker, propranolol, can impair memory of emotionally-charged stories, but not emotionally-neutral ones (O'Dell et al., 2015; Gao et al., 2016; Beaman et al., 2023). Yao & Chen, 2022 posit that use of just R-carvedilol instead of the racemic mixture may provide more benefit by more selectively antagonizing

specific receptors only. Significant work is needed to further explore the impacts of modulation of adrenergic receptors by specific beta-blockers, including in humans.

APOE4 interactions:

It is not known whether there is any interaction between carvedilol and APOE status.

Aging and related health concerns: Carvedilol provides significant reductions in morbidity and mortality for specific cardiovascular indications; it is one of the first-line treatments for these indications. There is no indication of benefit for other populations.

Types of evidence:

- 5 meta-analyses or systematic reviews, including 2 Cochrane meta-analyses
- 3 randomized controlled clinical trials
- 2 clinical trials
- 2 professional resources such as clinical practice guidelines
- 6 reviews
- 3 laboratory studies

Heart Failure and Complications, Including Mortality: BENEFIT

Carvedilol is one of the three beta blockers recommended for heart failure with reduced ejection fraction (HFrEF); treatment with carvedilol has been shown to reduce hospitalizations and mortality in this patient population. The reduction in mortality is specific to those three beta blockers and is not considered a class effect. Treatment with carvedilol or other beta blockers can improve left ventricular ejection fraction, reduce symptoms of heart failure, and improve clinical status. Clinical practice guidelines state that beta blockers should be prescribed to all patients when HFrEF is diagnosed, unless beta blockers are not tolerated or are contraindicated. The benefits of carvedilol and other beta blockers has been reported in patients with and without diabetes or coronary artery disease, in both men and women, in older adults, and across racial and ethnic groups. To reduce the risk of major cardiovascular events, treatment with carvedilol or other beta blocker should continue even if symptoms do not appear to improve. Beta blockers are typically prescribed alongside other medications

(Heidenreich et al., 2022: American College of Cardiology / American Heart Association Clinical Practice Guideline).

Hypertension: BENEFIT, BUT NOT TYPICAL FIRST LINE TREATMENT

Carvedilol, like other beta blockers, reduces blood pressure (Wong et al., 2015). However, they are generally not first line treatments for hypertension unless there is a specific relevant indication such as heart failure. For patients with primary hypertension, carvedilol and other beta blockers are thought to be less effective in adults older than 60 compared to younger adults at reducing major cardiovascular events, including mortality (Khalil & Zeltser, 2023). A Cochrane meta-analysis found that beta blockers as a class were inferior to other antihypertensives such as calcium channel blockers for a variety of outcomes, such as cardiovascular death and stroke. The authors caveat that newer beta blockers such as carvedilol were underrepresented in the studies available for meta-analysis (Wiysonge et al., 2017).

Carvedilol and other beta blockers are also used for other cardiovascular indication. This includes patients who experienced a heart attack and have left-ventricular dysfunction (Dargie et al., 2001) atrial fibrillation (Joglar et al., 2023: American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines), and stable angina (Oh et al., 2016). Carvedilol is used in patients with cirrhosis and portal hypertension; carvedilol can prevent variceal bleeding and is the preferred choice among beta blockers (Turco et al., 2023). Studies are also exploring the use of carvedilol as a treatment for cardiac toxicity stemming from chemotherapy (Avila et al., 2018; Attar et al., 2022; Farooq et al., 2024; see also 'Research Underway').

Safety: Carvedilol is generally well-tolerated. Common side effects include hypotension, bradycardia, shortness of breath, and weight gain. There are several serious disease contraindications, including asthma.

Types of evidence:

- 2 meta-analyses or systematic reviews
- 2 clinical trials
- 2 observational studies, including one pharmacovigilance study
- 3 professional resources

Carvedilol can cause hypotension with its associated symptoms of dizziness, fatigue, and headaches (Singh & Preuss, 2024). Other adverse events can include weight gain, shortness of breath, and nausea (Cohn et al., 1997; Singh & Preuss, 2024).

A post-hoc meta-analysis of two RCTs of carvedilol compared to placebo assessed safety in two groups: patients with chronic kidney disease (CKD), and those without. The analysis indicated there were significantly more adverse events and more serious adverse events in the carvedilol group compared to the placebo group. However, compared to placebo, both CKD and non-CKD carvedilol groups had significant decrease in the risk of all-cause mortality, cardiovascular mortality, and composite of cardiovascular mortality or heart failure hospitalization, among other significant decreases in types of death. Certain adverse events were significantly more frequent in both CKD and non-CKD patients who received carvedilol compared to their placebo counterparts: bradycardia, dizziness, syncope, and hypotension. Orthostatic hypotension, hyperkalemia, and hyperglycemia were more frequent only in CKD patients who received carvedilol compared to those who received placebo (Wali et al., 2011).

In studies of patients with heart failure, carvedilol is generally reported to be well-tolerated. One RCT of 2,289 patients with severe chronic heart failure randomized to either placebo treatment or carvedilol reported that there were significantly fewer serious adverse events in the carvedilol group, including heart failure and sudden death (Packer et al., 2002). A Cochrane meta-analysis assessing the use of dual α- and β-adrenergic receptor blockers (carvedilol and labetalol) compared to placebo in patients with primary hypertension found no significantly increased withdrawal due to adverse events between the dual beta blocker group and placebo group (RR=0.88; 95% CI 0.54 to 1.42) (Wong et al., 2015). Carvedilol has also not been associated with more adverse events than other beta blockers such as metoprolol (Poole-Wilson et al., 2003). A 2019 systematic review assessed the efficacy and safety of carvedilol and another beta blocker, bisoprolol, as initial therapy for hypertension, comparing both drugs to placebo. They reported that there were no differences in frequency of withdrawal due to adverse events in the carvedilol groups compared to placebo group, though the safety data was from just two studies with a total of 286 participants (Kishi & Fujii, 2019).

The effects of carvedilol on patient populations without a cardiovascular indication is not as well understood. One RCT assessed the effects of carvedilol on cardiac toxicity in 200 patients receiving chemotherapy. There were no differences in overall incidence of adverse events between groups and no serious adverse events. Blood pressure and heart rate were lower in the carvedilol group compared to

placebo group. Symptomatic hypotension was the most common adverse event in the carvedilol group (Avila et al., 2018).

One small 6-month RCT compared the effects of carvedilol to placebo in 29 patients with AD. The study was not published, but the researchers did make their results public on clinicaltrialsgov. Due to the small size the results are difficult to generalize, but the safety results are as follows:

Adverse Event	Placebo (n=15)	Carvedilol (n=14)
Serious Adverse Event	1 of 15; 6.7%	2 of 14; 14.3%
Adverse Event	12 of 15 (80%)	12 of 14 (85.71%)

Overall, there were no striking differences in frequency of events by organ system by group; there were numerically more instances of psychiatric events (1 in carvedilol vs. 5 in placebo) and arthritis (0 n carvedilol vs. 4 in placebo) in placebo as compared to carvedilol. Fewer people in the carvedilol group completed the trial compared to placebo (8/14 did not complete in carvedilol; 4/15 did not complete in placebo). The reasons for discontinuation were not given.

There are several patient populations for whom carvedilol is contraindicated or who require careful monitoring if treated with carvedilol. Patients with severe hypotension and certain cardiac rhythm abnormalities should not take carvedilol. Carvedilol is metabolized in the liver, and so patients with severe hepatic impairment should not use this drug. As carvedilol and other nonselective beta blockers can cause bronchoconstriction, carvedilol is typically not recommended for patients with asthma. Given these effects on the airway and the interference with adrenergic signaling, carvedilol can render epinephrine less effective, which can be important for people with anaphylactic allergies to discuss with their doctor. The vasodilating effects of carvedilol can be contraindicated with peripheral vascular disease such as Reynaud's syndrome. Carvedilol can also mask symptoms of hypoglycemia, necessitating careful monitoring of blood sugar in people with diabetes (Singh & Preuss, 2024, Drugs.com).

Drug interactions:

Carvedilol is known to interact with 547 drugs. Of these interactions, 20 are major, 462 are moderate, and 33 are minor. Some notable interactions include that with nondihydropyridine calcium channel blockers such as verapamil or diltiazem; certain antidepressants such as fluoxetine, duloxetine, and bupropion which inhibit an enzyme that metabolizes carvedilol, thus potentially increasing

concentration of carvedilol and associated adverse events; and medications such as clonidine that decrease levels of catecholamines. All three of these drugs or drug classes can increase risk of adverse events, including serious adverse events, and so require careful monitoring if administered together. Carvedilol also can blunt the effects of epinephrine administered as a treatment for allergic reaction (Drugs.com, Singh & Preuss, 2024).

Taking carvedilol and a multivitamin with minerals at the same time can decrease the effects of carvedilol; these medications may need to be taken at least 2 hours apart. It is recommended to take carvedilol with food (Drugs.com).

As a beta-blocker, carvedilol is contraindicated or should be used with caution in several diseases, including bradyarrhythmia / AV shock, cardiogenic shock/hypotension, patients requiring hemodialysis, ischemic heart disease, peripheral arterial disease, peripheral vascular disease, liver disease, asthma or COPD, and psoriasis. A full list can be seen on Drugs.com.

Research underway:

There are approximately 50 trials registered on clinicaltrials.gov that are exploring the uses of carvedilol. Almost all of these trials are assessing the efficacy of carvedilol for cardiac efficacy or cardiac protection, such as for patients receiving chemotherapy. Some trials are exploring the use of carvedilol in patients with cirrhosis. Two trials involve neurodegenerative diseases.

NCT05794997 is an observational study that aims to use healthcare claims data to evaluate the comparative incidence of dementia / AD between patients treated with different medications for the same indication. It is part of the Data Analysis for Drug Repurposing for Effective Alzheimer's Medicines (DREAM) study. This specific study compares the risk of dementia/AD onset between patients who received propranolol/carvedilol vs. atenolol / bisoprolol / sotalol. The primary outcome is time to dementia outset; the secondary outcome is time to AD onset.

NCT03775096 is a study of carvedilol in patients with early Parkinson's disease (PD). PD patients often have non-motor symptoms including autonomic dysfunction and increased sympathetic tone, and exhibit impairment on an assessment of cardiac sympathetic innervation known as iodine-123 metaiodobenzylguanidine (123I-MIBG) myocardial scintigraphy; 123I-MIBG is a synthetic analog of

norepinephrine. This open label pilot study in 15 PD patients is exploring whether 6 months of carvedilol treatment can affect 123I-MIBG uptake. Patients will start with a dose of 3.125 mgs twice daily and will increase to a maximum of 25 mgs twice a day over the course of 4 weeks. Other outcomes include safety information, heart rate variability, or measures of both motor and non-motor PD symptoms.

Search terms:

Pubmed, Google: carvedilol

- Alzheimer's disease, dementia, hypertension, cardiovascular, stroke, safety, neuroprotective, antioxidant

Websites visited for carvedilol:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma: Carvedilol; Coreg