



*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.*

## Ticagrelor (Brilinta)

### Evidence Summary

Ticagrelor is superior to other anti-coagulants in several cardiovascular indications, but it comes with some side effects. Cognitive effects are unknown.

**Neuroprotective Benefit:** P2Y<sub>12</sub> is expressed on microglia and oligodendrocytes in the human brain, but its function is still unclear, as is the effect inhibition will have or whether ticagrelor would reach the brain.

**Aging and related health concerns:** Large clinical trials suggest ticagrelor is superior to other anti-coagulants in some indications. Additional clinical trials are examining its anti-inflammatory effects.

**Safety:** Common side effects of ticagrelor include dyspnea and bleeding. Generally, bleeding is not worse than current standard of care.

### What is it?

Ticagrelor is a P2Y<sub>12</sub> antagonist approved for the prevention of thrombotic events in patients with acute coronary syndrome (ACS) or myocardial infarction (MI). Phase 3 clinical trials were also conducted for peripheral artery disease (PAD) and stroke. P2Y<sub>12</sub> is a purinergic receptor primarily expressed on platelets. However, it is also expressed on endothelial cells, vascular smooth muscle cells, dendritic cells, leukocytes, neurons, and microglia. Other P2Y<sub>12</sub> antagonists include the thienopyridines (ticlopidine, clopidogrel and prasugrel), also approved for cardiovascular indications.

Ticagrelor has many pharmacokinetic (PK) and pharmacodynamics (PD) properties that may make it superior to the thienopyridines in many indications. Thienopyridines are pro-drugs that must first be metabolized by the liver. Their systemic concentration is reportedly low, below their *in vitro* IC50 concentration, meaning their effects may be limited to inhibition of P2Y<sub>12</sub> on platelets and not at other cells (e.g. endothelial cells or VSMCs) ([Nylander and Schulz, 2016](#)). In addition, their metabolites bind irreversibly to the P2Y<sub>12</sub> receptor. Ticagrelor, on the other hand, is a direct acting, reversible P2Y<sub>12</sub> inhibitor, providing faster and more consistent P2Y<sub>12</sub> inhibition than the thienopyridines.

In addition, ticagrelor binds to equilibrative nucleoside transporter 1 (ENT1), an adenosine reuptake transporter. Adenosine has a very short half-life in the circulation, but inhibition of ENT1 may increase local extracellular levels of adenosine. Increased local adenosine may provide anti-inflammatory effect and increase coronary vasodilation ([Nylander and Schulz, 2016](#); [Wittfeldt et al, 2013](#)).

As with all anti-thrombotic drugs, ticagrelor is associated with an increased risk of bleeding, which in certain situations – especially during surgery and percutaneous coronary interventions (PCI) – may be worse than aspirin or clopidogrel ([Nylander and Schulz, 2016](#)).

**Neuroprotective Benefit:** P2Y<sub>12</sub> is expressed on microglia and oligodendrocytes in the human brain, but its function is still unclear, as is the effect inhibition will have or whether ticagrelor would reach the brain.

#### Types of evidence:

- Several post-mortem studies

Human post-mortem studies suggest that P2Y<sub>12</sub> is specifically expressed on parenchymal microglia but not perivascular or meningeal macrophages (as opposed to Iba1 and CD68 which can be expressed on all



myeloid cells). Its expression is stable throughout adult life, suggesting a stable parenchymal microglia population, but P2Y<sub>12</sub> expression decreases on microglia around amyloid plaques or in multiple sclerosis lesions (P2Y<sub>12</sub> is also expressed on human oligodendrocytes) ([Mildner et al, 2016](#)).

The function of the P2Y<sub>12</sub> receptor is less clear. Pre-clinical studies suggest that it may mediate migration of microglia and extension of microglia processes toward damage and the release of inflammatory cytokines. It was also implicated as a mediator of blood brain barrier closure in response to injury ([Moore et al, 2015](#); [Tozaki-Saitoh et al, 2017](#); [Charolidi et al, 2015](#); [Lou et al, 2016](#)). None of the P2Y<sub>12</sub> inhibitors have been studied for Alzheimer's disease or dementia, and we don't know what effect they would have (e.g. detrimental effects by preventing BBB closure or beneficial anti-inflammatory effects).

**Aging and related health concerns:** Large clinical trials suggest ticagrelor is superior to other anti-coagulants in some indications. Additional clinical trials are examining its anti-inflammatory effects.

Types of evidence:

- 4 phase 3 RCTs in various cardiovascular indications
- Smaller RCTs in other indications
- 2 pre-clinical studies

Longevity

None specifically for longevity.

Cardiovascular indications

Clopidogrel or aspirin were generally standard of care for many cardiovascular indications. Ticagrelor + aspirin or ticagrelor monotherapy has been studied in large Phase 3 trials against clopidogrel or aspirin. Unless stated otherwise, the ticagrelor studies used 90mg twice per day (bid).

Acute Coronary Syndrome (ACS): POTENTIAL BENEFIT

A 12-month RCT for the prevention of cardiovascular events in 18,624 patients hospitalized with ACS compared ticagrelor + aspirin to clopidogrel + aspirin. Ticagrelor was superior to clopidogrel in the prevention of death from vascular causes, myocardial infarction, or stroke (9.8% vs 11.7%; HR 0.84; 95%CI 0.77-0.92). It was also more effective at preventing death from any cause (4.5% vs 5.9%) ([Wallentin et al, 2009](#)). Since in patients with CYP2C19 and ABCB1 mutations, clopidogrel's efficacy is

decreased, [Wallentin et al, 2010](#) performed a subgroup analysis of these patients and found that ticagrelor was still superior regardless of genotypes analyzed ([Wallentin et al, 2010](#)).

Myocardial infarction (MI): POTENTIAL BENEFIT

A 3-year RCT for the prevention of cardiovascular events in 21,162 patients with previous MI compared ticagrelor + aspirin (60 or 90 mg bid) to aspirin. Ticagrelor + aspirin significantly reduced cardiovascular death, myocardial infarction, or stroke (60mg bid 7.77% vs placebo 9.04%; HR 0.84; 95%CI 0.75-0.95). Although 90mg bid and 60mg bid were not statistically compared, 60mg bid was generally just as good as 90mg bid with fewer side effects ([Bonaca et al, 2015](#)).

Stroke: NO BENEFIT

A 90-day RCT for the prevention of cardiovascular events in 13,199 patients with ischemic stroke compared ticagrelor + aspirin to aspirin + placebo. Ticagrelor + aspirin did not significantly reduce the incidence of a new stroke, myocardial infarction or death (6.7% vs 7.5%, n.s.) or ischemic stroke (5.8% vs 6.7%, n.s.) ([Johnston et al, 2016](#)).

Symptomatic Peripheral Artery Disease (PAD): NO BENEFIT AS MONOTHERAPY, POTENTIAL BENEFIT WITH ASPIRIN

A 3-year RCT for the prevention of cardiovascular events in 13,885 patients with PAD compared ticagrelor monotherapy to clopidogrel monotherapy. Ticagrelor monotherapy did not significantly reduce the risk of cardiovascular death, myocardial infarction or ischemic stroke (10.8% vs 10.6% n.s.) ([Hiatt et al, 2017](#)). However, a network meta-analysis of anti-platelet therapies reported that ticagrelor + aspirin was the superior treatment for the prevention of major adverse cardiovascular events (MACE) (RR 0.67; 95%CI 0.46-0.96), albeit with a non-significant increased risk of bleeding (see more in safety section below) ([Katsanos et al, 2015](#)).

Inflammation: POTENTIAL BENEFIT

Ticagrelor is associated with a decrease in inflammation compared to other anti-platelet drugs. A 7-day RCT in 107 patients undergoing percutaneous coronary intervention (PCI) reported that ticagrelor significantly decreased the post-surgery increase in inflammation (hs-CRP and ESM-1, a protein regulated by cytokines) compared to clopidogrel ([Wei et al, 2017](#)). In a human model of systemic inflammation where healthy individuals are injected with LPS, the effect of ticagrelor was compared to clopidogrel or placebo; ticagrelor reduced the pro-inflammatory cytokines TNF $\alpha$ , G-CSF, IL-6, IL-8, and CCL2 by half (and generally more so than clopidogrel) and slightly increased the anti-inflammatory cytokine IL-10. It also decreased fibrin aggregation by-products – another marker of inflammation; however, there were no effects on CRP ([Thomas et al, 2015](#)).



*Atherosclerosis: POTNETIAL BENEFIT (pre-clinical)*

Treatment of mice (ApoE<sup>-/-</sup>) with advanced atherosclerotic lesions with ticagrelor (compared to placebo) tended (non-significantly) to reduce lesion size. Ticagrelor did not change apoptotic cells or macrophage number in the lesion site; however, it did significantly reduce the size of the necrotic core and increased the fibrous cap (suggesting increased plaque stability) ([Preusch et al, 2016](#)).

*Myocardial Reperfusion Injury: POTENTIAL BENEFIT (pre-clinical)*

In a rat model of ischemia-reperfusion injury, ticagrelor, but not clopidogrel, dose-dependently reduced infarct size and increased myocardial adenosine and eNOS levels. After 4 weeks, ticagrelor improved left ventricular ejection fraction, decreased pro-inflammatory cytokines (TNF $\alpha$ , IL-1 $\beta$  and IL-18), and increased the anti-inflammatory cytokine 15-epi-lipoxin-A4 ([Ye et al, 2015](#)).

**Safety:** Common side effects of ticagrelor include dyspnea and bleeding. Generally, bleeding is not worse than current standard of care.

*Types of evidence:*

- Multiple large clinical trials

Dyspnea (shortness of breath) is the most common side effect of ticagrelor. In large clinical trials it occurs in 5-19% of patients (19% in patients with prior myocardial infarction). It is hypothesized to occur due to binding of neuronal P2Y<sub>12</sub> receptors or because ticagrelor increases local concentrations of adenosine. The dyspnea is reported to be mild or moderate in intensity but does lead to discontinuation in about 5% of patients.

Major bleeding is another potential side effect, but it varies widely depending on the patient population (e.g. 2.3% in myocardial infarction patients, 0.5% in ischemic stroke patients, and 11.6% in ACS patients). It occurs more often in patients undergoing cardiac surgery (such as percutaneous coronary intervention). Generally, though, major bleeding does not occur much more often than a comparator drug (such as clopidogrel).

Other potential side effects from [Drugs.com](#) include tightness in the chest and fast or irregular heartbeat.



### **Drug Interactions:**

[Drugs.com](#) lists 73 major drug interactions with ticagrelor. Many of these include other anti-coagulants as well as other drugs that may increase or decrease blood levels of ticagrelor. Care should be taken with other anti-coagulant drugs, although sometimes ticagrelor is given with aspirin. In clinical trials, most patients were also taking other cardiovascular drugs (statins, beta-blockers, ACEi, etc.) and they are not listed as drug interactions, so they are probably fine. Caffeine is an adenosine receptor antagonist, and the interaction between ticagrelor and caffeine is not clear. However, a clinical trial is underway to see if caffeine can prevent ticagrelor-induced dyspnea ([Lindholm et al, 2015](#)).

### **Sources and dosing:**

Ticagrelor is available by prescription from AstraZeneca. Most clinical trials use a 180mg loading dose on day 1 followed by 90mg bid thereafter. In one clinical trial, 60mg bid provided the same benefit as 90mg bid, and it will be interesting to see if further clinical trials are conducted with lower doses.

### **Research underway:**

There are [142 active clinical trials](#) underway including cardiovascular indications, cerebral vascular disease, stroke, microvascular dysfunction, inflammation, and migraines.

### **Search terms:**

Pubmed: **ticagrelor + atherosclerosis, cardiovascular, alzheimer, dementia, inflammation, longevity, peripheral neuropathy, osteoarthritis**

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