Rev Port Cardiol. 2015;34(4):279–285

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

REVIEW ARTICLE

# Cardiovascular effects of fingolimod: Relevance, detection and approach

**Carlos Aguiar**[a,*], **Sónia Batista**[b], **Ricardo Pacheco**[c]

[a] *Cardiology Department, Hospital Santa Cruz, CHLO, Carnaxide, Portugal*
[b] *Multiple Sclerosis Outpatient Clinic, Coimbra University, Coimbra, Portugal*
[c] *Medical Department, Novartis Farma S.A., Porto Salvo, Portugal*

Received 6 November 2014; accepted 15 November 2014
Available online 3 April 2015

**KEYWORDS**
Multiple sclerosis;
Fingolimod;
Bradycardia;
Atrioventricular block;
Heart rate

**Abstract** Fingolimod, a structural analogue of sphingosine, is the first oral treatment available for multiple sclerosis. The presence of sphingosine-1-phosphate receptors in the sinus and atrioventricular nodes, myocardial cells, endothelial cells and arterial smooth muscle cells is responsible for fingolimod's cardiovascular effects. We provide a comprehensive review of the mechanisms of these effects and characterize their clinical relevance.


**PALAVRAS-CHAVE**
Esclerose múltipla;
Fingolimod;
Bradicardia;
Bloqueio auriculoventricular;
Frequência cardíaca

**Efeitos cardiovasculares do fingolimod: relevância, deteção e abordagem terapêutica**

**Resumo** O fingolimod, um análogo estrutural da esfingosina, é o primeiro tratamento oral disponível para a esclerose múltipla. A presença de recetores esfingosina-1-fosfato no nódulo sinusal e auriculoventricular, miócitos cardíacos, células endoteliais e células do músculo liso arterial possibilita a ocorrência de efeitos cardiovasculares com o fingolimod. Neste artigo, faz-se uma revisão dos mecanismos dos efeitos cardiovasculares do fingolimod e a caracterização da sua relevância clínica.


## Introduction

The treatment of multiple sclerosis (MS) has seen remarkable progress in the last two decades, with increasingly effective disease control, particularly of its

* Corresponding author.
*E-mail address:* ctaguiar@sapo.pt (C. Aguiar).

**List of abbreviations**

| | |
|---|---|
| AVB | atrioventricular block |
| bpm | beats per minute |
| CNS | central nervous system |
| DMD | disease-modifying drug |
| ECG | electrocardiogram |
| EMA | European Medicines Agency |
| eNOS | nitric oxide synthase |
| EPOC | Evaluate Patient OutComes Study |
| GIRK | G protein-coupled inwardly-rectifying potassium channel |
| HR | heart rate |
| IFN beta-1a | interferon beta-1a |
| MS | multiple sclerosis |
| NO | nitric oxide |
| S1P | sphingosine-1-phosphate |
| S1PR1 | sphingosine-1-phosphate receptor type 1 |

relapsing-remitting forms. Several disease-modifying drugs (DMDs) have been approved and some new molecules are reaching the market, expanding the range of available therapeutic options. Treatment selection is therefore becoming more tailored to the patient's clinical profile and necessarily more complex, requiring a thorough knowledge of the relevant pharmacology on the part of the MS-treating physician.

Fingolimod, a structural analogue of sphingosine, is the first oral DMD approved for MS treatment. Its mode of action is innovative. Its active metabolite, formed by in vivo phosphorylation, modulates sphingosine-1-phosphate (S1P) receptors and induces their downregulation on the surface of lymphocytes. This leads to sequestration of primarily naive and memory T lymphocytes within lymph nodes, potentially reducing trafficking of these pathogenic cells into the central nervous system (CNS).[1,2] Moreover, as it is highly lipophilic, fingolimod readily crosses the blood-brain barrier and penetrates the CNS,[3] and there is increasing evidence of a direct effect on S1P receptors in oligodendrocytes, astrocytes, and neurons.[1,4]

In the European Union, fingolimod is approved for use as a single-agent DMD in selected patients with highly active relapsing-remitting MS, defined by the European Medicines Agency (EMA) as a second-line therapy after the failure of interferon beta-1a (IFN beta-1a), or as a first-line therapy for patients with rapidly evolving severe disease.[5]

Fingolimod's efficacy has been established in three phase III clinical trials,[6–8] showing not only superior efficacy in reducing relapse rates and improved MRI measures of disease activity compared to placebo and intramuscular IFN beta-1a, but also reduced risk of disability progression compared to placebo. Regarding its safety profile, fingolimod was generally safe and well tolerated, with most adverse events being of mild to moderate severity, including bradycardia and atrioventricular block (AVB), infections, increased liver enzyme levels, hypertension and macular edema.

Nevertheless, in clinical settings, concerns remain about its cardiovascular effects, particularly after the first dose. Further clarification of fingolimod's effects on the cardiovascular system and its underlying mechanisms will enable practicing clinicians to initiate fingolimod in appropriately selected and screened MS patients, maximizing its effectiveness and safety.

## Cardiovascular effects of fingolimod: mechanisms

S1P is a bioactive lysophospholipid that mediates several physiological functions.[4,9] Although the main source of S1P is the erythrocyte, other sources include activated platelets, mast cells, endothelial cells, fibroblasts and the central nervous system.[10–13] S1P regulates various cellular responses such as proliferation, differentiation, survival, cytoskeletal reorganization, formation of cytoplasmic prolongations, chemoattraction and motility, intercellular adhesion and formation of cell junctions. It is thus involved in numerous physiological processes, including immunity, vascular and pulmonary smooth muscle tone, endothelial barrier function, and cardiovascular and nervous system function and morphogenesis. Extracellular S1P exerts its effects by binding to five receptors (S1PR1–5) belonging to the family of G protein-coupled receptors.[1,14,15]

Fingolimod, a structural analogue of sphingosine, is a prodrug that is phosphorylated by platelet sphingosine kinase type 2, in a reaction that does not require platelet stimulation.[16–18] The active drug, fingolimod-phosphate, is an agonist of S1PR1, S1PR4 and S1PR5, and at concentrations ten times higher, it is also an agonist of S1PR3.[19,20] Binding of fingolimod-phosphate to the receptor has an initial agonist effect, but prolonged receptor internalization and subsequent proteasomal degradation results in a functional antagonism effect. Therefore, in the long term, the drug is an inhibitor of receptor function.[21–23]

The presence of S1PR1 and S1PR3 in the heart and blood vessels is responsible for the cardiovascular effects of fingolimod.[24,25] Specifically, S1PR1 is predominant in the sinus node, atrioventricular node, myocardial cells and endothelial cells, while S1PR2 is predominant in arterial smooth muscle cells, in which S1PR1 and S1PR3 are present in similar concentrations.[26–29]

In the heart, activation of S1PR1 causes dissociation of the G protein, thus activating acetylcholinergic G protein-coupled inwardly-rectifying potassium channels (GIRKs).[30] Activation of these channels leads to potassium efflux, which hyperpolarizes the cell membrane, hindering its depolarization and decreasing automation and excitability.[31] In brief, bradycardia occurs by a mechanism similar to the binding of acetylcholine to the muscarinic receptor and to the mechanism of atrioventricular conduction delay. Internalization of S1PR1 is responsible for the transient nature of fingolimod-induced negative chronotropic and dromotropic effects. Both atropine (a muscarinic receptor antagonist) and isoprenaline (a beta-1 and -2 adrenergic receptor agonist) reverse these side effects of fingolimod.[32,33]

In endothelial cells, activation of S1PR1 induces phosphorylation of protein kinase B and activates nitric oxide synthase (eNOS), both leading to increased nitric oxide (NO) production.[34–36] NO relaxes smooth muscle cells, causing vasodilation. Activation of S1PR1 in arterial smooth muscle cells releases calcium from intracellular stores, increasing its intracellular concentration, and leading to myocyte contraction and vasoconstriction. Thus, blood pressure does