Cardiol Ther (2025) 14:249–265
https://doi.org/10.1007/s40119-025-00405-9

ORIGINAL RESEARCH

Effectiveness and Tolerability of Trimetazidine 80 mg Once Daily in Patients with Chronic Coronary Syndrome in Brazil: The V-GOOD Observational Study

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Received: January 6, 2025 / Accepted: March 19, 2025 / Published online: April 29, 2025

ABSTRACT

***Introduction*:** The V-GOOD study evaluated the effectiveness of trimetazidine modified-release (MR) 80 mg once daily (OD) in patients with chronic coronary syndrome (CCS) who remained symptomatic despite antianginal therapies in routine clinical practice.

***Methods*:** This prospective, observational study involved 1026 adult outpatients with symptomatic CCS from 70 sites in Brazil who were prescribed trimetazidine MR 80 mg OD plus background antianginal treatment. Data on number of angina attacks, short-acting nitrate consumption, prevalence of angina-free patients, severity of angina, patient-reported daily physical activity impairment, treatment adherence, tolerability, and cardiologist and patient satisfaction were collected at baseline (V1), then at 1 month (V2) and 3 months (V3).

***Results*:** Following the addition of trimetazidine MR 80 mg OD, the mean ± standard deviation number of angina attacks per week decreased from 3.1 ± 2.8 at V1 to 1.0 ± 2.1 at V2, and 0.7 ± 1.7 at V3, with concurrent reductions in short-acting nitrate consumption, patient-reported daily physical activity impairment and the proportion of patients with limiting angina (Canadian Cardiovascular Society class III or IV), and increases in the proportion of angina-free patients (all $p<0.001$ vs. V1). Most cardiologists rated trimetazidine MR 80 mg OD as satisfactory/very satisfactory (90.7% for effectiveness and 94.8% for tolerability); most patients rated the treatment schedule as convenient/very convenient (97.2%) and satisfactory/very satisfactory (97.1%). Treatment was well tolerated.

***Conclusions*:** These data support the symptomatic benefits and good tolerability associated with adding trimetazidine MR 80 mg OD to other antianginal therapies in patients with persistent symptoms.

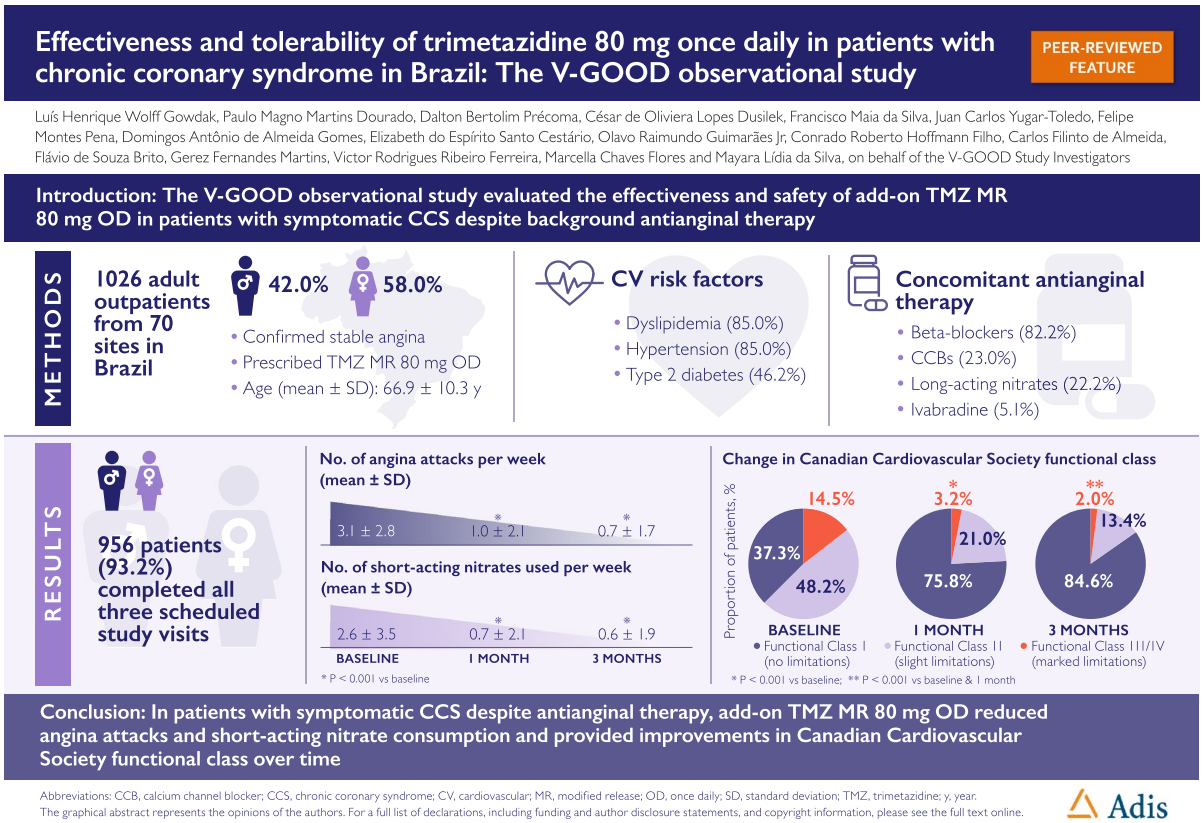
Graphical abstract available for this article.

***Trial registration number*:** NCT06464276.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40119-025-00405-9.

Extended author information available on the last page of the article

Graphical Abstract:



Keywords: Angina pectoris; Chronic coronary syndrome; Stable angina; Trimetazidine

Key Summary Points

Why carry out this study?

Patients with chronic coronary syndrome experience angina pectoris as the most common symptom.

Trimetazidine is a drug known to have anti-ischemic and antianginal effects when used alone or in combination with other first- or second-line antianginal agents.

The V-GOOD study was a large-scale, prospective, observational, non-interventional multicenter study that evaluated the effectiveness and tolerability of adding trimetazidine modified-release 80 mg once-daily to patients with chronic coronary syndrome who remained symptomatic despite antianginal therapies, in a real-world clinical setting in Brazil.

What was learned from the study?

Angina symptom control improved and exercise tolerance increased after trimetazidine was initiated; 90.7% of cardiologists and 97.1% of patients rated trimetazidine treatment as 'satisfactory' or 'very satisfactory'.

Trimetazidine was well tolerated for treating angina when added to current background antianginal therapy.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.28625555.

INTRODUCTION

Angina pectoris is the most common symptom experienced by patients with chronic coronary syndrome (CCS) [1]. This symptom can have a significant adverse impact on the patient's quality of life [2] and lead to mood disturbances [3] if not optimally controlled. Therefore, reducing angina symptoms and exercise-induced ischemia is one of the primary treatment goals for patients with CCS. According to the latest Joint Committee clinical practice guidelines from the American Heart Association (AHA)/American College of Cardiology (ACC), medical treatment of symptomatic patients with CCS usually involves a combination of agents with complementary modes of action, including oral anticoagulants and/or antiplatelet therapy, beta-blockers, and renin–angiotensin–aldosterone inhibitors, to prevent cardiovascular events and management symptoms associated with angina or ischemia [4]. However, optimal control of angina (i.e., the absence of symptoms, with maintenance of physical activity and no functional limitations) is rarely achieved in randomized trials and observational studies of medical and interventional treatments. For example, it is estimated that 20–40% of patients experience persistent or recurrent angina after a percutaneous coronary intervention (PCI) during short- to medium-term follow-up [5]. In the ORBITA trial, even after 6–12 weeks of optimizing a combination of hemodynamic agents (beta-blockers, calcium channel blockers [CCBs] and long-acting nitrates), approximately 50% of patients remained symptomatic [6]. Therefore, a different approach is required that can offer an effective, safe, and easy-to-use medical regimen to treat patients with symptomatic CCS [7].

Trimetazidine is known to have anti-ischemic and antianginal effects by shifting energy production from free fatty acid oxidation to glucose metabolism in ischemic cardiac cells [8, 9]. The efficacy and safety of trimetazidine were demonstrated in several randomized and observational clinical studies using different dosing regimens (20 mg three times daily or 35 mg twice daily) [10–13]. According to the 2024 European Society of Cardiology (ESC) [14] and 2014 Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia [SBC]) [15] guidelines, trimetazidine should be considered as second-line treatment to manage patients

who are intolerant of or remain symptomatic despite treatment with beta-blockers or CCBs. As patients with CCS are usually also affected by multiple comorbidities, such as hypertension, dyslipidemia, or diabetes [16], the associated high pill burden in these populations can lead to poor medication adherence and increased risk for adverse clinical outcomes and poor symptom control. Once-daily treatment regimens for cardiovascular disease were created to reduce the pill burden and improve adherence to evidence-based therapies [17]. One such regimen is a modified-release (MR) formulation of trimetazidine 80 mg, which was developed for once-daily administration to simplify treatment [18]. In real-world studies, trimetazidine MR 80 mg once daily (OD) has been shown to effectively reduce angina attacks and short-acting nitrate consumption, and improve adherence to antianginal medications, with good tolerability [19, 20]. In Brazil, 7.6% of adults aged ≥ 18 years have mild angina and 4.2% have moderate/severe angina [21]. The very high levels of genomic diversity in the Brazilian population, due to the genetic admixture of sub-Saharan Africans, native Amerindians, and Europeans, make it inappropriate to extrapolate pharmacogenetic or pharmacogenomic data from well-defined ethnic groups, such as Europeans or North Americans, to the majority of Brazilians [22]. Evaluating whether treatment strategies from other countries are effective in Brazil is therefore essential. In particular, the impact of using trimetazidine MR 80 mg OD in the real-world setting for managing Brazilian patients with CCS needs further assessment.

This study aimed to assess the effectiveness and tolerability of trimetazidine MR 80 mg OD in a large cohort of adult Brazilian patients with symptomatic CCS despite previous antianginal treatment consisting of hemodynamic agents alone or in combination, including first-line antianginal beta-blockers and/or CCBs and second-line antianginal agents such as long-acting nitrates.

METHODS

Study Design

The V-GOOD study (NCT06464276) was a large-scale, prospective, observational, non-interventional multicenter study performed in a real-world clinical setting in Brazil. CCS diagnostic techniques, the choice of antianginal treatments as well as the monitoring of CCS or any comorbidity were exclusively determined by the decision of each treating cardiologist and independently of study participation. The study was conducted from October 2021 to June 2022 and included 70 healthcare facilities across various regions of Brazil.

Study Population

Before inclusion in the study, all patients were receiving treatment according to the Brazilian guideline for the management of stable CCS [15]. The study enrolled adults aged ≥ 18 years with stable CCS (defined as Canadian Cardiovascular Society functional class II–III angina) who were prescribed trimetazidine MR 80 mg OD because of persistent symptoms despite previous antianginal treatment, which could include beta-blockers, CCBs, long-acting nitrates or other antianginal agents, as well as guideline-recommended secondary prevention agents (including angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], statins and antithrombotic agents).

The study excluded patients who were intolerant to any of the active ingredients in the trimetazidine formulation or had any contraindications to the use of trimetazidine MR 80 mg OD, such as Parkinson's disease, tremors, parkinsonian movement disorders, or restless leg syndrome. The exclusion criteria also specified the following: moderate or severe renal dysfunction (glomerular filtration rate < 60 ml/min); a history of myocardial infarction or cerebrovascular accident within

the past 3 months; unstable angina within the past 6 months; uncontrolled hypertension (blood pressure [BP] > 180/100 mmHg) despite ongoing antihypertensive therapy; pregnant or breastfeeding women; and individuals unable to understand the nature of the study protocol and follow the study instructions.

Treatment

Study participants were prescribed one capsule of trimetazidine MR 80 mg (Vastarel® liberação prolongada [LP] 80 mg; Laboratórios Servier do Brasil), to be taken orally OD after breakfast as advised by the cardiologist. During the 3-month follow-up, cardiologists could adjust the prescription of antianginal agents based on their clinical judgement to optimize symptom relief or control risk factors. Patients who were previously taking trimetazidine 35 mg twice daily could switch to trimetazidine MR 80 mg OD if the attending cardiologist deemed it appropriate. Any changes in antianginal therapy during the study were carefully documented to ensure that any differences in symptoms and patient-reported daily physical activity impairment could be attributed to trimetazidine MR 80 mg OD, rather than additional or increased dosages of other antianginal agents.

Data Collection and Outcomes

Clinical data were collected at baseline and during two other study visits following the addition of trimetazidine MR 80 mg OD: baseline (V1), 1 month after study inclusion (V2) and 3 months after study inclusion (V3). Cardiologists collected the following information during these visits: the mean number of angina attacks and mean number of short-acting nitrates used per week (primary outcomes), angina severity as measured by the Canadian Cardiovascular Society classification as class I to IV (with higher classes corresponding to increasing symptom burdens), patient-reported daily physical activity impairment, patient adherence and tolerability of trimetazidine MR 80 mg OD and cardiologist and patient treatment satisfaction (secondary outcomes). Daily physical activity impairment was patient self-assessed using a visual analog scale (VAS) graded from 0 to 10, where 0 indicated 'no limitations', 5 indicated 'moderate limitations', and 10 indicated 'severe limitations'. Global antianginal treatment adherence was measured using the validated Compliance Evaluation Test (CET), a six-item patient self-reporting questionnaire containing yes/no questions (yes = 1; no = 0), that defined a patient as 'good compliant' when all six items were answered "no", 'minor noncompliant' when 1 or 2 items were answered "yes", and as 'noncompliant' when ≥ 3 items were answered "yes" [23]. At each study visit, the treating cardiologists also asked their patients about their adherence to trimetazidine MR 80 mg OD. The cardiologists rated the effectiveness and tolerability of trimetazidine MR 80 mg OD as 'very satisfactory', 'satisfactory', 'not sufficiently satisfactory' or 'unsatisfactory', while the patients rated the convenience of treatment with trimetazidine MR 80 mg OD as 'very convenient', 'convenient' or 'inconvenient', and treatment satisfaction as 'very satisfied', 'satisfied' or 'dissatisfied'. In accordance with international guidelines, systolic blood pressure (SBP), diastolic blood pressure (DBP) and resting heart rate (HR) were collected in a quiet room using standard protocols and an auscultatory method [24].

Information on spontaneously reported adverse drug reactions (ADRs) or adverse events (AEs) was collected by treating cardiologists at V2 and V3. For each reported AE, the cardiologist assessed the potential causal relationship with trimetazidine MR 80 mg OD, as well as the seriousness of the case. Serious ADRs or serious AEs (SAEs) were defined as events resulting in any of the following outcomes: death; a life-threatening AE; in-patient hospitalization, or prolongation of existing hospitalization; persistent or significant disability or incapacity; or a congenital anomaly/birth defect.

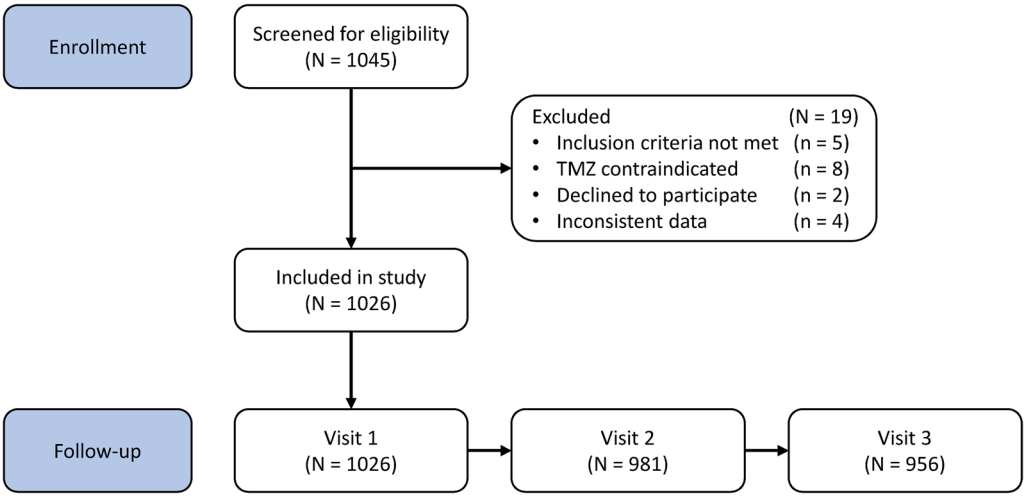


Fig. 1 Flow diagram of the study population. *TMZ* trimetazidine

Statistical Analysis

The study used descriptive statistics to summarize the data, including means, standard deviations (SDs), medians and interquartile ranges for continuous variables, and numbers and percentages of patients for categorical variables. Friedman's nonparametric test was employed to analyze the continuous variables, followed by Wilcoxon paired comparisons with Bonferroni correction, where necessary. For categorical variables (binary outcomes), Cochran's *Q* and McNemar tests for paired comparisons at two timepoints were used, as appropriate.

To determine the sample size, the study assumed that patients would experience an average of 3.1 weekly angina attacks at the initial visit, with a SD of 3.5 weekly angina attacks, and that the addition of trimetazidine would result in a reduction of at least 0.5 weekly angina attacks after 3 months of treatment. Based on these assumptions, and with a 95% power at a 0.05 significance level, the study required 830 patients. Given the longitudinal nature of the study, a 20% loss to follow-up was assumed, bringing the final number of patients included to at least 996. The study considered a p value of less than 0.05 statistically significant, and all statistical analyses were performed using R software (version 4.2.2).

Ethics

The study was performed in accordance with good clinical practice and the ethical principles derived from the revised Declaration of Helsinki. The Institutional Review Board of the National Coordinator Centre (Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil [4.884.990, approved on August 4, 2021]) approved the study protocol before the start of the study. All patients provided written informed consent prior to their enrollment. The STROBE guidelines were used in reporting this study [25].

RESULTS

Study Population

The V-GOOD study screened a total of 1045 patients, of whom 19 were excluded due to not meeting the inclusion criteria ($n = 5$) or having any exclusion criteria ($n = 14$; Fig. 1). Of the 1026 patients included in the study, 956 patients (93.2%) completed all scheduled study visits. The baseline demographic and clinical characteristics of the patients are presented in Table 1. The mean ± SD age of the patients

was 66.9 ± 10.3 years and 58.0% of the population were female. Approximately half of the patients (52.5%) had a mean duration of angina of 1–5 years, while 36.8% had a mean duration of > 5 years. Cardiovascular risk factors included hypertension (*n* = 858/1009 evaluable patients; 85.0%), dyslipidemia (*n* = 858; 85.0%), and type 2 diabetes mellitus (*n* = 466; 46.2%). Approximately half of the population (*n* = 503/1002 evaluable patients; 50.2%) had undergone previous PCI and almost one quarter (*n* = 227; 22.7%) had previously undergone coronary artery bypass graft (CABG) surgery (Table 1). Almost half (*n* = 433; 43.2%) had experienced a myocardial infarction. At V1, 48.2% of patients (*n* = 437) had Canadian Cardiovascular Society functional class II and 14.5% (*n* = 131) had Canadian Cardiovascular Society class III or IV (i.e., limiting angina).

Prior to the addition of trimetazidine MR 80 mg OD, patients were treated with antianginal medications either as monotherapy or in combination, which mainly included beta-blockers (82.2%), trimetazidine 35 mg twice daily (36.7%), CCBs (23.0%), long-acting nitrates (22.2%) and ivabradine (5.1%; Table 1). Patients also received secondary prevention therapies, such as antiplatelet agents (90.3%) and statins (95.1%). Throughout the study, 896 of 956 patients (93.7%) who completed all visits maintained their baseline antianginal therapy (i.e., < 7% had a modification of either the dose of an ongoing antianginal treatment or the addition of a new antianginal drug).

Angina Attacks and Short-Acting Nitrate Use

Significant improvements from V1 were observed at V2 and V3 in the mean number of weekly angina attacks and short-acting nitrates used (primary outcomes; Fig. 2). Following the addition of trimetazidine MR 80 mg OD, the mean ± SD number of angina attacks per week decreased from 3.1 ± 2.8 at V1 to 1.0 ± 2.1 at V2 and 0.7 ± 1.7 at V3 ($p < 0.001$ vs. V1 for both). The mean ± SD number of short-acting nitrates consumed per week also decreased from 2.6 ± 3.5 at V1 to 0.7 ± 2.1 at V2 and 0.6 ± 1.9 at V3 ($p < 0.001$ vs. V1 for both).

Improvements in Canadian Cardiovascular Society Class and Daily Physical Activity Impairment

Canadian Cardiovascular Society functional class improved over time, with the proportion of patients with limiting angina (Canadian Cardiovascular Society class III or IV) decreasing significantly, from 14.5% at V1 to 3.2% at V2 ($p < 0.001$ vs. V1) and 2.0% at V3 ($p < 0.001$ vs. V1 and V2), and the proportion of patients with non-limiting angina (Canadian Cardiovascular Society class I) increasing, from 37.3% at V1 to 75.8% at V2 and 84.6% at V3 (Fig. 3a). There were also significant increases in the proportion of patients reporting no angina from 15.4% at V1 to 60.9% at V2 and 73.6% at V3 ($p < 0.001$ vs. V1 for both) (Fig. 3b). Moreover, mean ± SD patient-reported daily physical activity impairment scores assessed on the VAS scale decreased (i.e., improved) from 5.1 ± 2.2 at V1 to 2.8 ± 2.3 at V2 and 2.1 ± 2.2 at V3 ($p < 0.001$ vs. V1 for both) (Fig. 3c).

Treatment Adherence, Satisfaction and Tolerability

During the final visit (V3), only 4.4% (40/911 patients with available data) reported missing at least one dose in the previous month. The effectiveness and tolerability of trimetazidine MR 80 mg OD were rated as 'satisfactory' or 'very satisfactory' by cardiologists for 90.7% (850/937 patients with available data) and 94.8% (842/888) of patients, respectively. A high proportion of patients reported overall satisfaction with trimetazidine MR 80 mg OD treatment, with 97.2% (906/932 patients with available data) reporting that it was 'convenient/very convenient', and 97.1% (904/931 patients with available data) stating that it was 'satisfactory/very satisfactory'. At the completion of the study, 89.8% (837/932 patients with available data) expressed their willingness to continue taking trimetazidine MR 80 mg OD.

Table 1 Baseline patient demographics and clinical characteristics

Variable	Baseline (V1) *N* = 1026
Age, mean ± SD, years (*n* = 1010)	66.9 ± 10.3
Male, *n* (%) (*n* = 1010)	424 (42.0)
Comorbidities, *n* (%) (*n* = 1009)	
Hypertension	858 (85.0)
Dyslipidemia	858 (85.0)
Type 2 diabetes mellitus	466 (46.2)
Current smoker, *n* (%) (*n* = 1009)	108 (10.7)
Physically active, *n* (%) (*n* = 1009)	94 (9.3)
Body weight, mean ± SD, kg (*n* = 992)	77.8 ± 15.5
Height, mean ± SD, cm (*n* = 993)	165 ± 9
Systolic arterial pressure, mean ± SD, mmHg (*n* = 999)	130 ± 18
Diastolic arterial pressure, mean ± SD, mmHg (*n* = 999)	78 ± 11
Resting heart rate, mean ± SD, bpm (*n* = 998)	71 ± 11
Family history of chronic coronary syndrome, *n* (%) (*n* = 1009)	660 (65.4)
Duration of angina, years, *n* (%) (*n* = 1026)	
< 1	109 (10.6)
1–5	539 (52.5)
> 5	378 (36.8)
Past cardiovascular history, *n* (%) (*n* = 1002)	
Previous myocardial infarction	433 (43.2)
Previous PCI	503 (50.2)
Previous CABG	227 (22.7)
Peripheral artery disease	140 (14.0)
Stroke/ischemic transitory attack	55 (5.5)
Atrial fibrillation	47 (4.7)
Chronic obstructive pulmonary disease	42 (4.2)
Pacemaker/defibrillator	19 (1.9)
Concomitant medications, *n* (%) (*n* = 1001)	
Beta-blocker	823 (82.2)
CCB	230 (23.0)
Long-acting nitrate	222 (22.2)

Table 1 continued

Variable	Baseline (V1) $N = 1026$
Ivabradine	51 (5.1)
Ranolazine	3 (0.3)
Antiplatelet agent	904 (90.3)
ACE inhibitor	290 (29.0)
ARB	482 (48.2)
Diuretic	354 (35.4)
Oral anticoagulant	85 (8.5)
Amiodarone	42 (4.2)
Digoxin	8 (0.8)
Antidiabetic (oral)	442 (44.2)
Antidiabetic (insulin)	88 (8.8)
Statin ($n = 903$)	859 (95.1)
Ezetimibe ($n = 903$)	68 (7.5)
Hemodynamic antianginal regimen, *n* (%) ($n = 1001$)	
Monotherapy	560 (56.0)
Beta-blocker	500 (50.0)
CCB	45 (4.5)
Long-acting nitrate	15 (1.5)
Dual combination therapy	296 (29.6)
Beta-blocker plus CCB	130 (13.0)
Beta-blocker plus long-acting nitrate	152 (15.2)
CCB plus long-acting nitrate	14 (1.4)
Triple combination therapy[a]	41 (4.1)

n = number of patients with available data

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *CABG* coronary artery bypass graft, *CCB* calcium channel blocker, *PCI* percutaneous coronary intervention, *SD* standard deviation, *V1* visit 1

[a]Triple combination therapy consisted of a beta-blocker plus a CCB and a long-acting nitrate

Safety

Safety data were collected for all included patients (Table 2). At least one AE was reported by 63 patients (6.1%); 18 (1.8%) had an AE that was attributed to trimetazidine MR 80 mg OD. In total, 29 patients (2.8%) experienced a serious AE, one of which (increased creatinine level) was considered related to trimetazidine MR 80 mg OD. The most frequently reported ADRs were dizziness (0.8%), nausea (0.6%), abdominal pain (0.4%), and vomiting (0.2%), assessed as non-serious by the study cardiologist in each case.

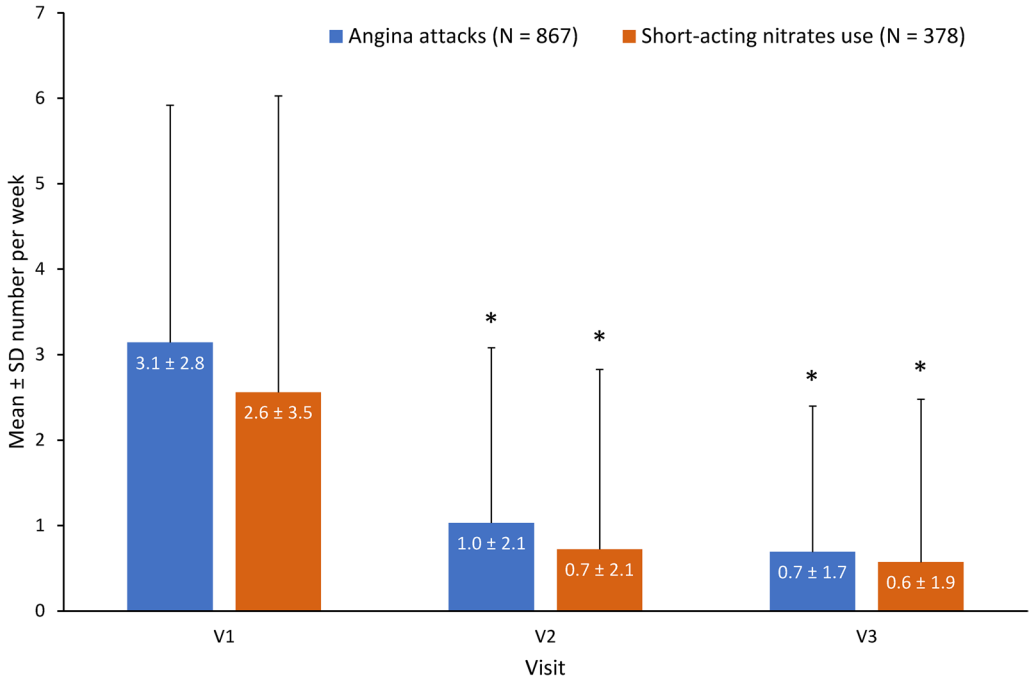


Fig. 2 Mean ± standard deviation number of angina attacks and short-acting nitrates used per week in combination with trimetazidine modified-release 80 mg once daily during the study. *Indicates statistical significance ($p < 0.001$) vs. V1. Only patients with data at all three visits were analyzed. *SD* standard deviation, *V* visit

Five deaths occurred during the study (fatal stroke, septic shock due to mediastinitis, metastatic prostate adenocarcinoma, sepsis with urinary focus, and syncope without prodromes), none of which were attributed to trimetazidine MR 80 mg OD by the study investigators.

DISCUSSION

Our research demonstrates that trimetazidine MR 80 mg OD significantly reduced the number of weekly angina attacks and the use of short-acting nitrates when added to background antianginal therapy in a large cohort of Brazilian patients with symptomatic CCS. Trimetazidine MR 80 mg OD also reduced patient-reported daily physical activity impairment and improved Canadian Cardiovascular Society functional class. Importantly, after 1 month of trimetazidine MR 80 mg OD treatment, the proportion of patients with limiting angina (Canadian Cardiovascular Society class III or IV) had decreased significantly from baseline, while the proportion of patients with non-limiting angina (Canadian Cardiovascular Society class I) was significantly increased; further improvements were observed after 3 months in both cohorts (i.e., those with and without limiting angina). This improvement in symptom control was achieved in almost all patients (93.7%) without the need to add or increase the dose of antianginal therapy, which confirms the beneficial antianginal effects of trimetazidine MR 80 mg OD when added to current background antianginal therapy.

These benefits are consistent with previous research, which demonstrated that trimetazidine (20 mg three times daily or 35 mg twice daily) consistently improved symptom control and increased exercise tolerance [10, 26]. Furthermore, our study results are consistent with those from two other real-world studies of trimetazidine MR 80 mg OD in patients with persistent angina despite antianginal therapy, including a maximally tolerated dose of bisoprolol [19, 20]. In both studies, trimetazidine MR 80 mg OD, when added to other antianginal

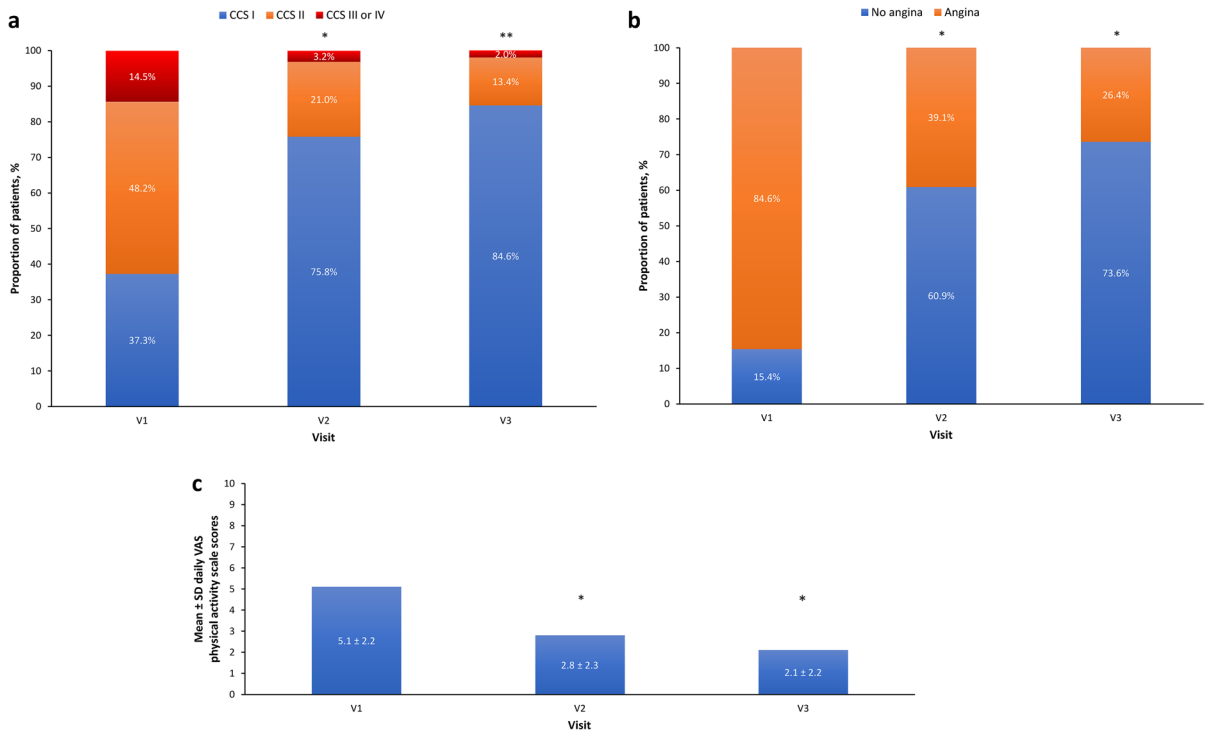


Fig. 3 Assessment of clinical outcomes during treatment with trimetazidine modified-release 80 mg once daily ($N = 906$), including assessment of **a** angina severity using the Canadian Cardiovascular Society grading scale, **b** the proportion of angina-free patients and **c** changes in patient-reported daily physical activity impairment at each study visit. *Indicates statistical significance ($p < 0.001$) vs. V1; **indicates statistical significance ($p < 0.001$) vs. V1 and V2. Only patients with data at all three visits were analyzed. *CCS* Canadian Cardiovascular Society, *SD* standard deviation, *V* visit, *VAS* visual analog scale

therapy, significantly reduced mean weekly angina attacks and short-acting nitrate use, improved quality of life, and significantly improved adherence to antianginal medications, with good tolerability [19, 20].

In a network meta-analysis of 218 randomized controlled trials and 19,028 patients with stable angina, the antianginal efficacy of trimetazidine was compared with that of other antianginal agents that have no influence on HR [27]. Trimetazidine was significantly superior to placebo for improvements in exercise tolerance and reductions in the number of angina attacks, and use of short-acting nitrates, whereas the beneficial effects of trimetazidine were similar to those of other non-HR-lowering antianginal treatments [27]. Another clinical trial has also demonstrated that trimetazidine MR 80 mg OD is safe and well tolerated compared with twice-daily trimetazidine 35 mg [18].

Clinical practice guidelines from the AHA/ACC [4] and SBC [15] both recommend a 'stepwise approach' to symptomatic management of CCS that involves the use of beta-blockers or CCBs (alone or in combination) as the first step [15]. Likewise, the 2024 ESC guidelines also recommend first-line beta-blocker and/or CCB therapy, with addition of other antianginal agents in selected patients, although these latest guidelines have shifted from the 'stepwise' approach to the 'diamond' approach, which emphasizes the importance of tailoring medical therapy for symptomatic control in patients with CCS to each individual's clinical profile and preferences [14]. First-line beta-blockers and CCBs carry a Class I recommendation [14], despite the fact that numerous observational

Table 2 Number of patients experiencing adverse events/adverse drug reactions during the study

n (%)	*N* = 1026
At least one AE	63 (6.1)
At least one ADR	18 (1.8)
SAE	29 (2.8)[a]
Most frequent ADRs[b]	
Dizziness	8 (0.8)
Nausea	6 (0.6)
Abdominal pain	4 (0.4)
Vomiting	2 (0.2)
Death	5 (0.5)[c]

ADR adverse drug reaction, *AE* adverse event, *SAE*, serious adverse event

[a]One (increased creatinine level) considered an ADR

[b]All assessed as non-serious

[c]Fatal stroke, septic shock due to mediastinitis, metastatic prostate adenocarcinoma, sepsis with urinary focus, syncope without prodromes; none considered related to treatment

and randomized controlled trials have consistently shown that this approach may not provide sufficient relief from angina in a significant proportion of patients [5, 6, 28]. According to data from 32,691 patients with stable CCS enrolled in the international CLARIFY registry (Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease), of the 7212 patients (22.1%) who reported angina at baseline, 54.8% had persistent symptoms at 1 year despite treatment with at least two antianginal strategies, including pharmacotherapy and revascularization [28]. Similarly, in our study of patients with CCS who were still symptomatic despite previous angina treatment or procedure, close to three out of four patients had a history of myocardial revascularization (PCI or CABG), indicating that angina may recur in a significant number of patients despite guideline-recommended antianginal strategies including revascularization procedures. In the CLARIFY registry, the mean ± SD HR of patients with persistent angina was reported to be 69.8 ± 10.6 bpm and mean ± SD BP was 134.4 ± 17.6/80.9 ± 10.8 mmHg, despite 83% of patients taking beta-blockers. In our study, similar findings were observed, with 82% of patients on beta-blockers, mean ± SD HR of 71 ± 11 bpm and mean ± SD BP of 130 ± 18/78 ± 11 mmHg. These findings highlight the clinical challenge of increasing beta-blocker dosage to achieve effective symptom control in patients with CCS in real-world settings.

Persistent anginal symptoms may be the result of the numerous underlying causes of angina and ischemia, and obstructive epicardial disease may or may not be the underlying pathogenetic mechanism [29]. Studies suggest that nonobstructive coronary causes of angina and ischemia, such as coronary microvascular dysfunction, vasospastic disorders, and derangement of myocardial metabolism, are more common than flow-limiting stenoses [30, 31]. This raises concerns that many important causes other than epicardial coronary artery disease (CAD) are not adequately considered or diagnosed [29]. There is a need for a more comprehensive management approach that separates the association between epicardial CAD and revascularization [30, 31]. In current clinical practice, this approach should better align diagnostic strategies that tailor treatment to the underlying mechanisms and triggers of angina and ischemia [30, 31]. When hemodynamic agents are ineffective, adding a medication with an alternative mechanism of action may provide a beneficial effect [32]. Instead of adding another hemodynamic agent or increasing the dosages of those already prescribed, using trimetazidine to shift cardiac metabolism from free fatty acid oxidation towards glucose metabolism is a complementary approach to treating patients with stable angina [9, 19, 20, 32]. Although myocardial revascularization procedures can improve the prognosis of high-risk patients (defined as those with > 90% coronary stenosis, fractional flow reserve ≤ 0.080 or instantaneous wave-free ratio ≤ 0.89 in a major vessel, or left ventricular ejection fraction ≤ 35% due to CAD or a large area of ischemia [> 10% of left ventricle]), they may only have a short-term impact on symptom control [6, 28].

In this study, trimetazidine MR 80 mg OD was highly effective in reducing the incidence of

angina attacks and patient-reported daily physical activity impairment. Moreover, trimetazidine was well tolerated, with few ADRs that were consistent with those described in the summary of product characteristics for trimetazidine [33]. Of the five reported deaths in our study cohort, only one death was potentially related to CCS – described as syncope without prodromes and likely categorized as sudden death. Data from the CLARIFY registry indicated that the 5-year rate of cardiovascular death or non-fatal myocardial infarction in patients with CCS was 8.0% overall (or 0.4% per 3 months) [16]. Therefore, the occurrence of one death due to CCS and five deaths overall (0.5%) among 1026 patients during the 3-month follow-up in our study is similar to that in the CLARIFY registry and does not raise concern.

Over 90% of patients and cardiologists alike expressed satisfaction with trimetazidine MR 80 mg OD treatment. For patients already taking multiple pills daily for comorbid conditions, such as hypertension, diabetes, or dyslipidemia, a switch from a twice-daily to a once-daily regimen is expected to significantly enhance adherence to long-term treatment while simplifying daily pill burden [34]. Our findings underline the importance of using add-on trimetazidine MR 80 mg OD as an antianginal approach to improve symptom management despite previous antianginal treatment, including patients still symptomatic despite previous revascularization.

This study has a few limitations that must be taken into consideration. Firstly, there was no parallel-controlled comparator group. Secondly, the observation period was relatively short (3 months), which prevented the assessment of further improvement in antianginal benefit, as seen in studies with longer follow-up [35] and made it impossible to assess safety and tolerance beyond 3 months. Thirdly, no data were collected on the ethnicity of the study participants. Lastly, some of the variables collected were based on cardiologist- and patient-reported questionnaires, which could have been biased by different perceptions of patients and cardiologists. Despite these limitations, it is essential to note that in clinical studies that address patients with symptomatic CCS, both patients and cardiologists should be offered the opportunity to assess any intervention (i.e., pharmacologic or revascularization) regarding perceived benefits and tolerability. One of the strengths of the study was the large number of participating clinics, which helped to provide a diverse demographic and socioeconomic patient population.

CONCLUSIONS

In our study, the addition of trimetazidine MR 80 mg OD to existing antianginal therapy in a large cohort of patients with CCS and persistent angina symptoms effectively reduced the frequency of angina attacks and short-acting nitrate use, improved the Canadian Cardiovascular Society functional class, and enabled a significant proportion of patients to become angina-free over 3 months of treatment. In addition, trimetazidine MR 80 mg OD decreased daily physical activity limitations and was well tolerated. These findings indicate that add-on treatment with trimetazidine MR 80 mg OD provides clinical benefits in patients with CCS and persistent angina when used in a real-world setting in Brazil.

ACKNOWLEDGEMENTS

We thank the patients and clinicians who participated in the V-GOOD study. A complete list of the V-GOOD Investigators is provided in the Supplementary Material.

Medical Writing/Editorial Assistance. We would like to thank Iona MacDonald of Springer Healthcare who provided editorial assistance in preparing the first draft of this manuscript, and Kate Palmer of Springer Healthcare who assisted with post-submission revisions. Medical writing assistance was supported by Servier.

Author Contributions. Luís Henrique Wolff Gowdak contributed to the study design, enrolled patients, contributed to the preparation

of the manuscript, and read and approved drafts of the manuscript. Paulo Magno Martins Dourado, Dalton Bertolim Précoma, César de Oliviera Lopes Dusilek, Francisco Maia da Silva, Juan Carlos Yugar-Toledo, Felipe Montes Pena, Domingos Antônio de Almeida Gomes, Elizabeth do Espírito Santo Cestário, Olavo Raimundo Guimarães Jr, Conrado Roberto Hoffmann Filho, Carlos Filinto de Almeida, Flávio de Souza Brito, Gerez Fernandes Martins, and Victor Rodrigues Ribeiro Ferreira enrolled patients and read and approved drafts of the manuscript. Marcella Chaves Flores and Mayara Lídia da Silva contributed to the study design and read and approved drafts of the manuscript. All authors read and approved the final version of the manuscript for submission.

Funding. This study was supported by Servier Brazil. The development of the manuscript and the journal's Rapid Service Fee were supported by Servier.

Data Availability. The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Luís Henrique Wolff Gowdak has received payments or honoraria from Servier and Novartis, support for attending meetings and/or travel from Servier, and has served on a data safety monitoring board and advisory board for Servier. Elizabeth do Espírito Santo Cestário has received payments for lectures given at events sponsored by Laboratório Servier do Brasil. Paulo Magno Martins Dourado, Dalton Bertolim Précoma, César de Oliviera Lopes Dusilek, Francisco Maia da Silva, Juan Carlos Yugar-Toledo, Felipe Montes Pena, Domingos Antônio de Almeida Gomes, Olavo Raimundo Guimarães Jr, Conrado Roberto Hoffmann Filho, Carlos Filinto de Almeida, Flávio de Souza Brito, Gerez Fernandes Martins, and Victor Rodrigues Ribeiro Ferreira declare no potential competing interests. Marcella Chaves Flores and Mayara Lídia da Silva are currently employed by Servier Brazil.

Ethical Approval. The study was performed in accordance with good clinical practice and the ethical principles derived from the revised Declaration of Helsinki. The Institutional Review Board of the National Coordinator Centre (Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil [4.884.990, approved on August 4, 2021]) approved the study protocol before the start of the study. The STROBE guidelines were used in reporting this study [25]. Participants provided written informed consent prior to their enrollment in the study.

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