



Effectiveness and Tolerability of Trimetazidine 80 Mg Once Daily in Patients with Stable Angina Uncontrolled with Bisoprolol-Based Therapy: The Modus Vivendi Observational Study

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ABSTRACT

Introduction: Modus Vivendi was conducted in routine clinical practice to evaluate the effect of adding trimetazidine 80 mg once daily (TMZ 80 OD) to treat patients with persistent symptoms despite treatment with background antianginal therapies including maximally tolerated bisoprolol.

Methods: This multicenter, prospective, observational, open-label, uncontrolled study recruited adult outpatients with a confirmed diagnosis of stable angina to whom physicians had decided to prescribe TMZ 80 OD. All patients were symptomatic despite treatment, including maximally tolerated doses of bisoprolol. Data on number of angina attacks, use of short-acting nitrates, and quality of life (QoL) were collected at baseline (V1) and at 1-month (V2) and 3-month (V2) follow-up visits. Two sub-analyses assessed efficacy in patients who remained on a stable bisoprolol dose throughout the study, and in patients in whom background antianginal therapy was known.

Results: A total of 1939 patients were recruited (57.2% women). The mean age was 65.6 ± 8.8 years; 73.8% had class II and 26.2% class III angina. At V1, the mean number of angina attacks per week was 6.2 ± 6.5 despite antianginal therapy including maximally tolerated bisoprolol dosage. Following the addition of TMZ 80 OD, this decreased to 3.4 ± 4.2 attacks per week at V2, and 1.6 ± 2.6 at V3 ($P < 0.05$ at V2 and V3), with concomitant reductions in short-acting nitrate use ($P < 0.05$). Significant improvements in QoL were observed throughout the study. Subgroup analyses showed that the addition of TMZ 80 OD to guideline-recommended antianginal therapy was associated with significant reductions in the mean number of weekly angina attacks and consumption of short-acting nitrates and improvements in QoL whether patients were treated with maximally tolerated bisoprolol and TMZ 80 OD alone, or maximally tolerated bisoprolol and TMZ 80 OD on top of other antianginal therapies. Treatment was well tolerated.

Conclusion: The study findings support the addition of TMZ 80 OD to bisoprolol with or without other antianginal therapies for patients with persistent angina.

Trial Registration: This study was retrospectively registered under the number ISRCTN29992579.

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Key Summary Points

Why carry out this study?

Despite a range of pharmacotherapy options, many patients continue to suffer from anginal symptoms. TMZ has a metabolic mechanism of action and can reduce symptoms of angina in patients resistant to hemodynamic antianginal agents.

This study assessed the efficacy and safety of a once-daily formulation (TMZ 80 OD) in patients with persistent symptoms despite treatment with guideline-recommended antianginal therapies including maximally tolerated bisoprolol.

What was learned from the study?

The addition of TMZ 80 OD to other antianginal therapies including maximally tolerated bisoprolol was associated with significant decreases in mean weekly angina attacks and consumption of short-acting nitrates, along with improvements in quality of life, independent of background therapy.

TMZ 80 OD can be safely combined with first-line antianginal therapies in patients with persistent angina.

Persistent angina symptoms have a major negative impact on health-related quality of life (QoL) including poor general health status, anxiety, depression, and inability to self-manage [3]. They also make a greater contribution to years lived with disability than either myocardial infarction or heart failure [1, 4].

In addition to the personal consequences of an angina diagnosis, there is also an associated economic burden [5, 6]. This is related to direct costs in the form of hospitalizations, surgery, and medications, as well as indirect costs in the form of angina-related work limitations or unemployment. There is therefore significant rationale for patients with stable angina to be diagnosed early and managed appropriately.

The treatment of stable angina has two major goals: first, to prevent more serious cardiovascular events such as myocardial infarction or death, and second, to improve patients' QoL by alleviating symptoms caused by ischemia [7]. Although randomized controlled trials show that antianginal drugs are equally effective in terms of symptom relief [8], guidelines continue to recommend the use of beta-blockers and calcium channel blockers (CCB) as first-line treatments in combination with effective risk factor modification and lifestyle changes [7]. Long-acting nitrates represent the first second-line addition, and newer second-line drugs such as nicorandil, ranolazine, ivabradine, and trimetazidine have class IIa recommendations when symptoms are not adequately controlled by first-line drugs and nitrates [7]. As beta-blocker positioning has remained essentially unchanged in successive guidelines, they remain one of the most widely used antianginal agents in clinical practice [9, 10]. Data from large international registries have shown that two-thirds (REACH) to three-quarters (CLARIFY) of patients with stable CCS receive beta-blockers alone or in combination [11, 12]. Among the beta-blockers, bisoprolol is the most frequently prescribed agent [11]. Nevertheless, a number of large studies have shown that angina remains a therapeutic problem despite treatment with conventional first-line hemodynamic antianginal therapies [13–15]. A significant number of patients may therefore benefit from treatment with an agent with a different mechanism of

INTRODUCTION

Angina pectoris is estimated to affect around 71 million people worldwide [1] and is often the first warning sign of an underlying chronic coronary syndrome (CCS). Data from a recent survey of CCS patients treated in primary care reported that 21.2% experienced angina at least monthly, with 12.5% reporting daily or weekly angina [2].

action from those associated with traditional antianginal therapy.

Current first-line agents improve myocardial oxygen supply or reduce demand via a range of hemodynamic actions [16]. Beta-blockers and calcium channel blockers decrease heart rate and cardiac cell contractility, resulting in a decrease in myocardial oxygen demand. Calcium channel blockers also cause coronary artery vasodilation, which can increase oxygen supply.

Trimetazidine (TMZ) is an antianginal drug devoid of hemodynamic effect, which optimizes energy metabolism in the ischemic heart by acting directly at the cellular level to inhibit free fatty acid oxidation and thereby shift cardiac cell metabolism to glucose oxidation. In this manner, the reduced oxygen supply to the heart is optimized and the integrity and function of the cardiac cells is preserved during the ischemic episode [17]. As a result of this mechanism of action, TMZ can reduce symptoms of angina in patients resistant to hemodynamic agents and has demonstrated efficacy and safety in a number of randomized controlled clinical trials as monotherapy and in combination with first-line antianginal therapies [18–21]. It is indicated as add-on therapy for the symptomatic treatment of stable angina in patients inadequately controlled or intolerant to first-line antianginal therapies. A once-daily TMZ formulation has recently become available that provides antianginal efficacy over 24 h [22, 23]. To date, there are no data on the efficacy and safety of this new formulation in combination with bisoprolol, the most widely prescribed beta-blocker for the treatment of stable angina [24]. The aim of the Modus Vivendi study was to address this evidence gap by evaluating the effect of TMZ 80 mg once daily (TMZ 80 OD) in patients with persistent symptoms despite treatment with maximally tolerated bisoprolol with or without other guideline-recommended antianginal therapies in routine clinical practice.

METHODS

Modus Vivendi was a multicenter, prospective, observational, open-label, uncontrolled study conducted between October 2017 and July 2018 in Russian clinical practice. General practitioners and cardiologists with outpatient practices included adult patients > 18 years of age with a confirmed diagnosis of stable angina (defined as class II–III angina according to the Canadian Cardiovascular Society classification) to whose treatment they had decided to add TMZ 80 OD. At the start of the study, all patients were symptomatic despite optimal treatment according to guidelines for CCS management in force at the time of the study [25]. Optimization of antianginal therapy was at the discretion of the treating physician, but included agents for secondary prevention as well as at least one agent for symptom control. The treatment regimen had to include the maximally tolerated dose of bisoprolol. Enrollment was restricted to patients receiving bisoprolol as their beta-blocker component, for three reasons. First, bisoprolol is the most frequently prescribed beta-blocker worldwide, with prescription rates particularly high in Russia, where this study was conducted [24]. Second, both bisoprolol and TMZ 80 are both taken once daily. In real clinical practice, the ability to treat with two once-daily antianginal agents may result in improved adherence compared with agents that require twice-daily administration. The third reason was to provide data on the efficacy and safety of the once-daily formulation of TMZ 80 in combination with bisoprolol, which is currently lacking. Patients could also be receiving other antianginal drugs including calcium channel blockers, long-acting nitrates, and ivabradine. Guideline-recommended secondary prevention medications, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, and antithrombotic and antiplatelet agents, were also permitted and prescribed at the physician's discretion.

Exclusion criteria were as follows: stable angina class IV or unstable angina within the past 6 months; a history of myocardial infarction or cerebrovascular accident within

the past 3 months; uncontrolled hypertension (blood pressure greater than 180/100 mmHg) despite ongoing antihypertensive therapy; beta-blockers other than bisoprolol; inability to understand the nature of the program and follow the recommendations; pregnant or breast-feeding women; and any contraindications to the use of TMZ 80 OD.

The study was performed in accordance with good clinical practice and the ethical principles derived from the revised Declaration of Helsinki. Institutional Ethics Committee approval, provided by the Volgograd Regional Cardiology Center, was sought before performing the study, and all patients provided written informed consent. The study registration number is ISRCTN29992579.

Subjects were asked to make three visits to the study site: an inclusion visit (V1) at which patients were prescribed TMZ 80 mg once daily; a 1-month follow-up visit (V2); and a 3-month follow-up visit (V3). At each visit, the following information was collected: data on number of angina attacks and number of short-acting nitrate doses taken (based on patient diary); QoL assessments using the EuroQol 5-dimension 3-level (EQ-5D-3L) questionnaire [26, 27] and a visual analogue scale (VAS); and assessment of medication adherence. Information on spontaneously reported adverse drug reactions or events was collected at the V2 and V3 visits.

The EQ-5D-3L self-administered questionnaire comprises five dimensions: mobility, self-care, usual activities (for example, work, study, housework, participation in family affairs, leisure), pain/discomfort, and anxiety/depression. Each dimension has three response levels depending on the severity of the manifestation: no problems (score of 1), some problems (score of 2), and extreme problems (score of 3). QoL was also assessed using a 100 mm VAS on which 0 was the worst level of subjective perception of personal health and 100 was perfect health. Medication adherence was assessed using a non-validated questionnaire in Russian comprising six questions where the answer of “no” to all questions indicated good adherence, “yes” to one or two questions indicated moderate adherence, and “yes” to three or more questions indicated nonadherence.

As part of the study, two sub-analyses were performed to provide a clearer picture of whether the observed effects were due to the inclusion of TMZ 80 OD in the therapeutic regimen or as a result of background antianginal therapy. To achieve this, effectiveness was evaluated in the subgroup of patients whose background bisoprolol therapy remained constant throughout the study, and in the subgroup of patients with stable bisoprolol dose and whose background antianginal therapy was known.

Statistical Analysis

Data were analyzed using Statistical Analysis System (SAS) software (SAS Institute Inc., Cary, NC, USA). Parametric tests were used for variables with a normal distribution and nonparametric tests for variables with a non-normal distribution. Continuous (quantitative) data are presented using descriptive statistics including mean, standard deviation, and 95% confidence intervals. Qualitative or categorical variables are presented as absolute number and relative frequency of occurrence of each possible value.

When analyzing between-group differences for interval variables, the Student *t*-test values were calculated for independent samples using the corresponding formulas and in three different modifications that take into account the statistical distribution of a particular variable. The significance of the between-group changes in such variables during the treatment period was evaluated by the corresponding *t*-criteria for paired measurements.

In the case of binary variables, the significance of difference in the rate of detection of the factor in the two compared groups of patients was also evaluated by Student's *t*-test, but with the Fisher's arcsine transformation.

To assess the combined effect of different binary variables on the interval variable, analysis of variance (ANOVA) was used, and the significance of the effects was evaluated by Fisher's exact test.

The relationships between rank and binary variables were evaluated using contingency tables, and the significance of such

relationships was assessed on the basis of three different modifications of the Chi-square test, Pearson test, and Fisher's exact test.

RESULTS

A total of 250 general practitioners and cardiologists recruited 1939 patients to take part in the observational study. Demographic and baseline clinical characteristics are shown in Table 1. The mean age was 65.6 ± 8.8 years. There were 829 (42.8%) men and 1110 (57.2%) women. The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) values at V1 were 142.0 ± 14.9 mmHg and 84.5 ± 8.7 mmHg, respectively, and resting HR was 75.1 ± 9.5 bpm. Class II angina had been diagnosed in 73.8% of patients, and class III in 26.2%. The mean duration of CCS was 7.8 ± 6.4 years and the mean duration of angina was 7.1 ± 6.1 years.

Hypertension was present in 93.2% of patients, 85.5% had dyslipidemia, 28.5% had type 2 diabetes, 23.3% were current smokers, and 40.5% had a family history of CCS. A history of myocardial infarction was reported in 33.8%, percutaneous coronary intervention (PCI) in 20.4%, coronary artery bypass graft (CABG) in 18.2%, both PCI and CABG in 23.4%, and a history of stroke or transient ischemic attack in 12.7%.

At V1, 45.8% of patients were receiving a CCB, 24.6% long-acting nitrates (LAN), and 44.9% short-acting nitrates; the proportions of patients receiving antiplatelet agents and statins were 86.7% and 86.4%, respectively. Other medications prescribed during the study are illustrated in Table 1. In this observational study, a violation of the inclusion criteria (e.g. myocardial infarction within past 3 months, blood pressure greater than 180/100 mmHg despite antihypertensive therapy) was reported in 43 patients, and as a result, 1896 patients (97.8% of recruited patients) were included in the efficacy analyses. The starting doses of bisoprolol in the 1896 patients who completed the study are shown in Table 2.

Angina Attacks and Short-Acting Nitrate Use

At V1, the mean number of angina attacks per week was 6.2 ± 6.5 despite maximally tolerated bisoprolol therapy and use of other antianginal drugs. Following the addition of TMZ 80 OD to the treatment regimen this had decreased to 3.4 ± 4.2 attacks per week at V2 and 1.6 ± 2.6 at V3. Reductions were statistically significant between V1 and V2 and V1 and V3 ($P < 0.05$) (Table 3). The mean consumption of short-acting nitrates per week reflected the reduction in angina attacks and decreased from 4.9 ± 5.9 at V1 to 2.6 ± 3.8 at V2 and 1.1 ± 2.2 at V3 (Table 4). The reductions were statistically significant for V2 and V3 compared with baseline ($P < 0.05$).

Quality of Life

At V1 only 2.6% of patients reported no problems on all five dimensions of the EQ-5D-3L. At V2, the proportion reporting no problems using the EQ-5D-3L had increased to 15.7%, and at V3 it had increased to 44.0%. The improvement in all five dimensions of the EQ-5D-3L was statistically significant between V1 and V3 ($P < 0.05$). When analyzed with the VAS, mean QoL scores were 48.5 at V1, 61.7 at V2, and 75.7 at V3. The improvement in QoL score measured by the VAS was statistically significant between V1 and V2, and between V2 and V3 ($P < 0.05$).

Medication Adherence

The proportion of patients with "good adherence" to antianginal therapy increased over the course of the study, from 29.9% of patients at V1, to 41.7% at V2 and 53.8% at V3. The proportions of patients with "good or moderate adherence" at V1, V2, and V3 were 75.1%, 92.6%, and 96.3%, respectively.

Table 1 Baseline patient demographics and clinical characteristics presented for the recruited patients at V1

	Total population (<i>n</i> = 1939)
Age (mean ± SD, years)	65.6 ± 8.8
Gender, <i>n</i> (%)	
Men	829 (42.8)
Women	1110 (57.2)
SBP (mean ± SD, mmHg)	142.0 ± 14.9
DBP (mean ± SD, mmHg)	84.5 ± 8.7
Heart rate (mean ± SD, bpm)	75.1 ± 9.5
Body mass index (kg/m ²)	29.7 ± 4.7
Angina Canadian Cardiovascular Society functional class, <i>n</i> (%)	
II	1431 (73.8)
III	508 (26.2)
Duration of CCS (mean ± SD, years)	7.8 (6.4)
Duration of angina (mean ± SD, years)	7.1 (6.1)
Hypertension, <i>n</i> (%)	1807 (93.2)
Dyslipidemia, <i>n</i> (%)	1658 (85.5)
Type 2 diabetes, <i>n</i> (%)	553 (28.5)
Family history of CCS, <i>n</i> (%)	785 (40.5)
Current smoker, <i>n</i> (%)	452 (23.3)
History of myocardial infarction, <i>n</i> (%)	655 (33.8)
History of PCI, <i>n</i> (%)	396 (20.4)
History of CABG, <i>n</i> (%)	353 (18.2)
History of PCI and CABG, <i>n</i> (%)	454 (23.4)
History of stroke/TIA, <i>n</i> (%)	246 (12.7)
Concomitant therapy, <i>n</i> (%)	
ACE inhibitor	1163 (60.0)
ARB	609 (31.4)
CCB	888 (45.8)
Diuretic	1061 (54.7)
Ivabradine	126 (6.5)
Short-acting nitrate	871 (44.9)
Long-acting nitrate	477 (24.6)
Antiplatelet agent	1681 (86.7)

Table 1 continued

	Total population (<i>n</i> = 1939)
Statin	1675 (86.4)

ACE inhibitor angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker, *CCS* chronic coronary syndrome, *CABG* coronary artery bypass graft, *DBP* diastolic blood pressure, *PCI* percutaneous coronary intervention, *SBP* systolic blood pressure, *TIA* transient ischemic attack

Table 2 Distribution of bisoprolol dosages at baseline in the 1896 patients who completed the study without a violation of the inclusion criteria

Bisoprolol dose (mg) at baseline (V1)	Number of patients
2.5	312
5	1080
10	339
Other doses	165
1.25	26
1.75	15
3.75	21
6.0	19
6.25	8
7.5	76
Total	1896

Table 3 Angina attacks per week, by visits, in the patients who completed the study

Parameter	Mean \pm SD	Mean change \pm SD	<i>P</i> value
Visit 1 (<i>n</i> = 1896)	6.15 \pm 6.51		
Visit 2 (<i>n</i> = 1896)	3.40 \pm 4.19	−2.76 \pm 3.75*	< 0.05
Visit 3 (<i>n</i> = 1896)	1.58 \pm 2.63	−4.57 \pm 5.23	< 0.05

*Change from visit 1 to visit 2
Change from visit 1 to visit 3

Table 4 Number of nitroglycerin doses taken per week, by visits, in the patients who completed the study

Parameter	Mean \pm SD	Mean change \pm SD	P value
Visit 1 ($n = 1896$)	4.86 \pm 5.88		
Visit 2 ($n = 1891$)	2.57 \pm 3.83	−2.31 \pm 3.25*	< 0.05
Visit 3 ($n = 1895$)	1.08 \pm 2.23	−3.78 \pm 4.76	< 0.05

*Change from visit 1 to visit 2

Change from visit 1 to visit 3

Sub-analysis in Patients Who Maintained the Same Bisoprolol Dose Throughout the Study

A sub-analysis was performed on the 1681 patients who received TMZ 80 OD and remained on the same maximally tolerated bisoprolol dose throughout the study. This included 292/312 (93.6%) who remained on 2.5 mg, 1005/1080 (93.1%) who remained on 5 mg, 323/339 (95.3%) who remained on 10 mg, and 61/165 (37.0%) who remained on “other” bisoprolol doses. At the baseline V1 visit, patients receiving the higher bisoprolol doses also had the greatest mean number of weekly angina attacks, which was as expected. Regardless of background bisoprolol dose, patients treated with TMZ 80 OD experienced statistically significant reductions in the

number of weekly angina attacks after 1 month, which were maintained at the 3-month V3 visit (Fig. 1). Mean weekly consumption of short-acting nitrates reflected the pattern of weekly angina attacks, with the highest consumption in those with the greatest number of weekly episodes. Reductions in nitrate use were also statistically significant from 1 month and were maintained at V3 (Fig. 2).

Alleviation of angina symptoms was associated with significant improvements in QoL measured by both the EQ-5D-3L and VAS. These were observed for all domains and across all bisoprolol dose groups (Figs. 3 and 4).

Mean reduction of Weekly number angina attacks in combination with Tmz 80 OD

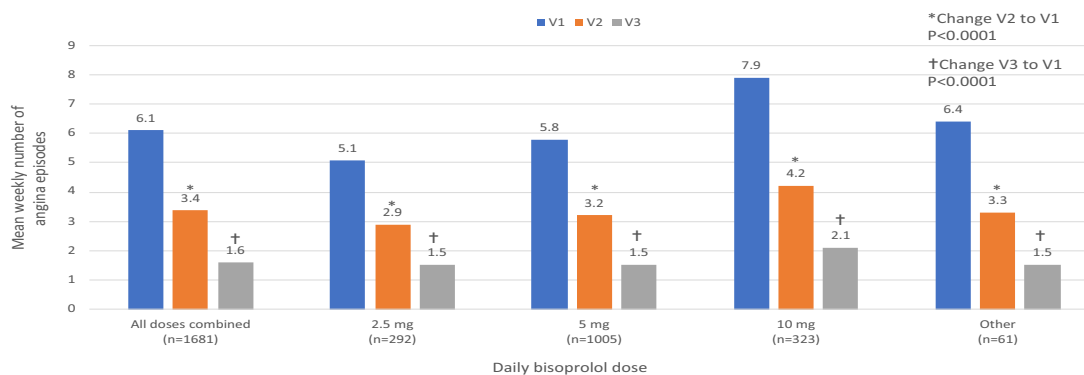


Fig. 1 Reduction in mean number of weekly angina attacks in patients who received TMZ 80 OD and maintained the same bisoprolol dose throughout the study ($n = 1681$)

Mean reduction of Weekly number SAN consumption in combination with Tmz 80 OD

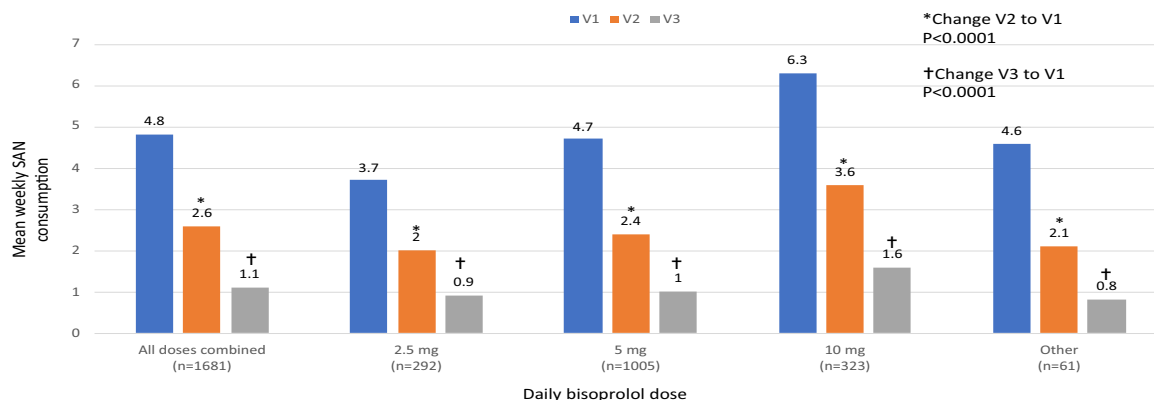


Fig. 2 Reduction in mean weekly nitrate consumption in patients who received TMZ 80 OD and maintained the same bisoprolol dose throughout the study (*n* = 1681)

EQ-5D-5L QOL (SCORE)

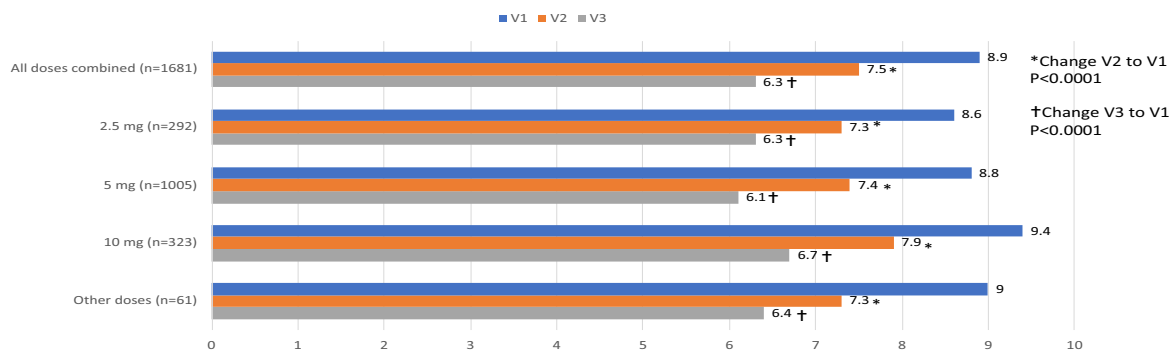


Fig. 3 EQ-5D-3L quality-of-life total score in patients who received TMZ 80 OD and maintained the same bisoprolol dose throughout the study (*n* = 1681)

Sub-analysis by Baseline Antianginal Therapy Among Patients Who Maintained the Same Bisoprolol Dose and Received TMZ 80 OD Throughout the Study

A total of 1610 patients remained on the same maximally tolerated bisoprolol dose and received TMZ OD 80 throughout the study. Of these 1610 patients, 680 were receiving bisoprolol monotherapy and TMZ 80 OD, while 930 were receiving bisoprolol plus other antianginal

therapy (529 CCB, 187 LAN, and 214 both CCB and a LAN) and TMZ 80 OD. Statistically significant reductions from V1 in weekly anginal attacks and short-acting nitrate consumption were evident at both V2 and V3 in all groups (Figs. 5 and 6). Likewise, all groups showed improvement in QoL across all five domains of the EQ-5D-3L at both follow-up visits. Patients also reported a significant improvement in their health status on the 100-point VAS (Figs. 7 and 8). For all these endpoints, similar improvements were observed whether patients were

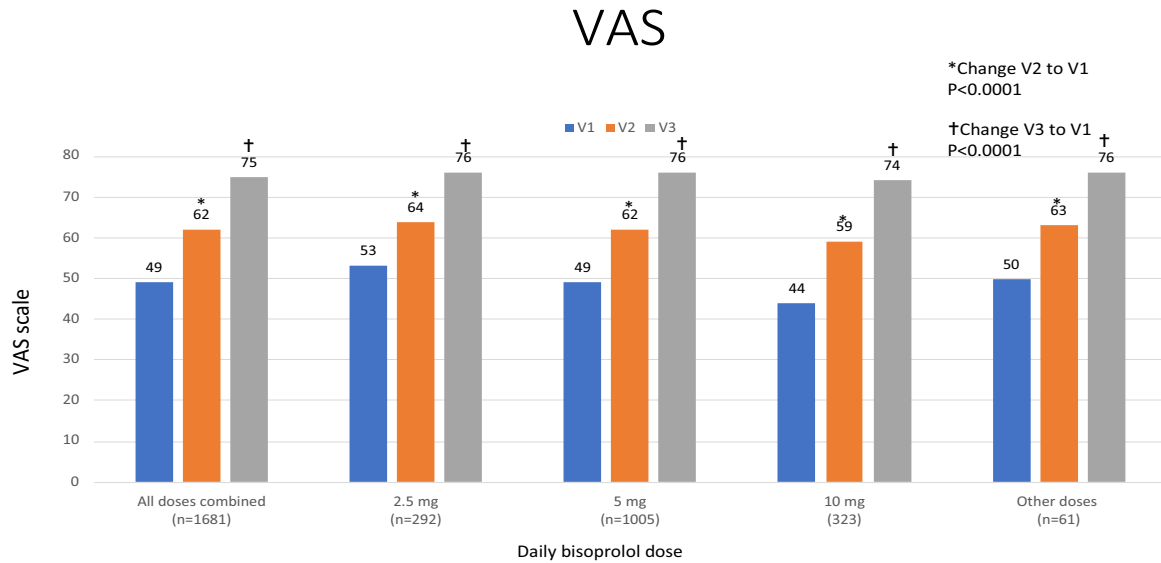


Fig. 4 VAS quality-of-life score in patients who received TMZ 80 OD and maintained the same bisoprolol dose throughout the study ($n = 1681$)

Mean reduction of Weekly number angina attacks in combination with Tmz 80 OD

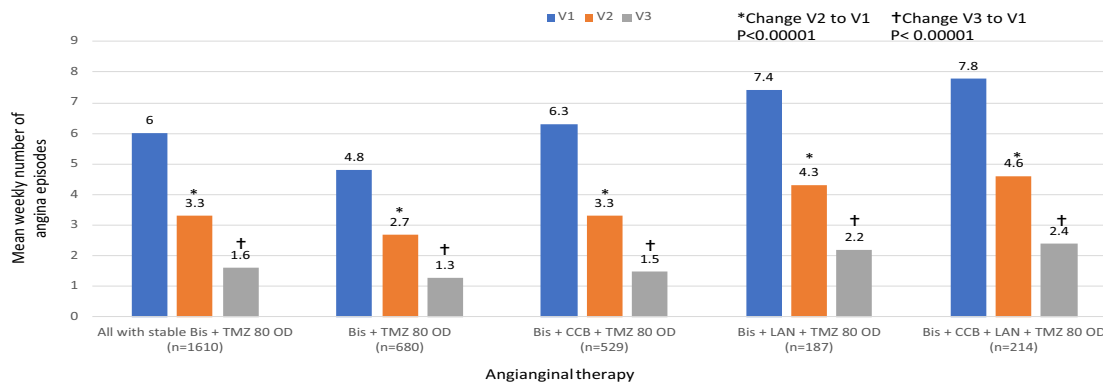


Fig. 5 Reduction in mean number of weekly angina attacks in patients receiving TMZ 80 OD throughout the study and on stable bisoprolol dose with known background antianginal therapies ($n = 1610$)

treated with maximally tolerated bisoprolol and TMZ 80 OD alone, or maximally tolerated bisoprolol and TMZ 80 OD on top of background antianginal therapy.

Modifications to Background Antianginal Therapy

Background antianginal therapy was at the discretion of the investigator and could include CCB and/or LAN in addition to maximally tolerated bisoprolol and TMZ 80 OD. Among the 930 patients whose bisoprolol dose remained the same and who were taking TMZ 80 OD

Mean reduction of Weekly number SAN consumption in combination with Tmz80 OD

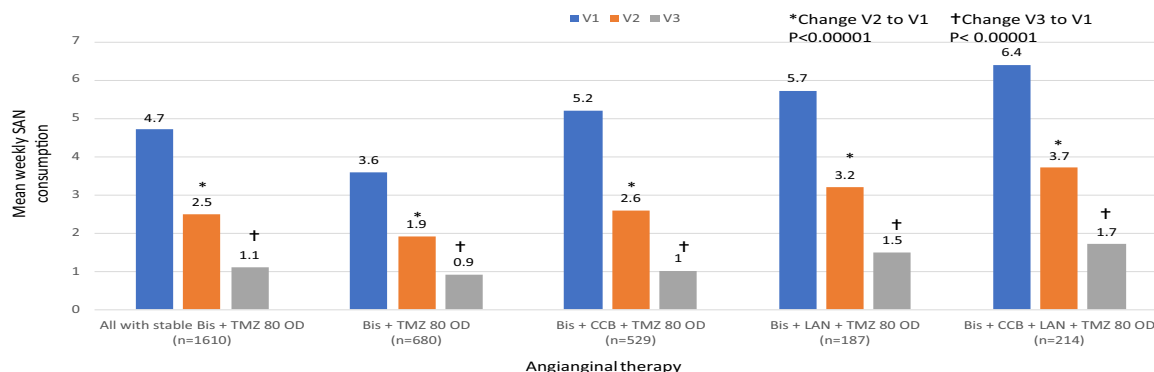


Fig. 6 Reduction in mean weekly nitrate consumption in patients receiving TMZ 80 OD throughout the study and on stable bisoprolol dose with known background antianginal therapies (n = 1610)

EQ-5D-5L QOL (SCORE)

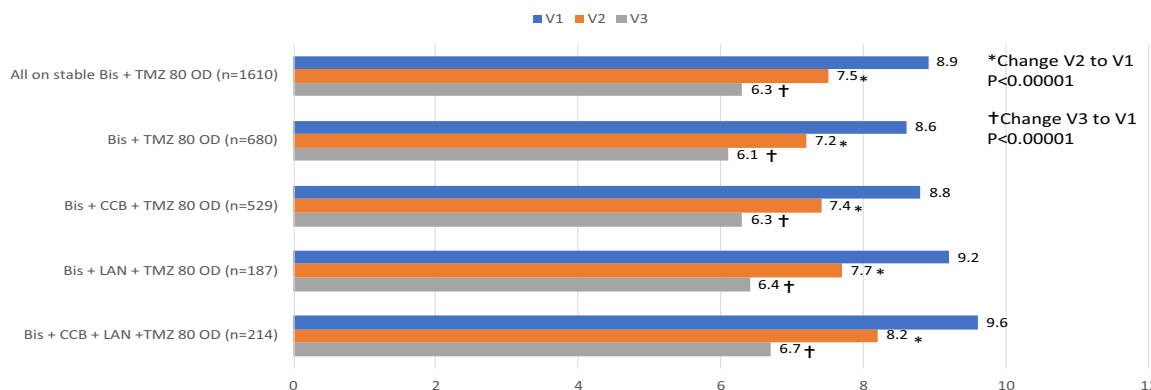


Fig. 7 EQ-5D-3L quality-of-life total score in patients receiving TMZ 80 OD throughout the study and on stable bisoprolol dose with known background antianginal therapies (n = 1610)

throughout the study, 529 were also receiving background therapy with a CCB, 187 with a LAN, and 214 with both a CCB and LAN (Table 5) The proportion of patients with no change to their background medication throughout the study was 98% in the CCB group and 85% in the LAN group. Among the patients receiving CCB and LAN background therapy, 85.5% of patients completed the study without a change in either medication, 94%

completed without a change in CCB, and 85.5% completed without a change in LAN.

In very few cases there was a replacement of the LAN or CCB therapy. There were no patients with an increase in CCB dose, two patients had an increase in LAN dose, and in some cases the CCB or LAN therapy was stopped or the dose was reduced.

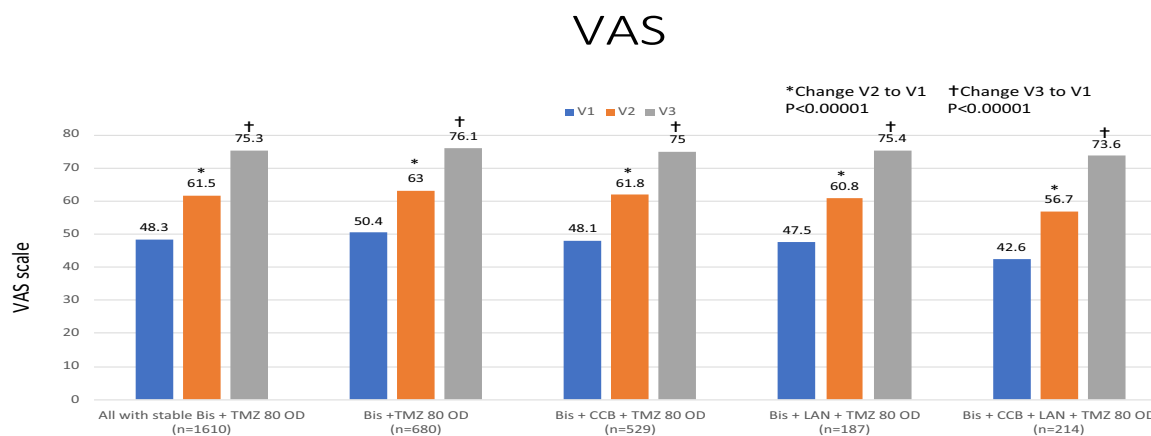


Fig. 8 VAS quality-of-life score in patients receiving TMZ 80 OD throughout the study and on stable bisoprolol dose with known background antianginal therapies ($n = 1610$)

Safety and Tolerability

Safety data were collected for all patients who received at least one dose of TMZ 80 OD. During the course of the study there were no cases of hypotension or bradycardia. Two adverse events were recorded in two patients. The first was a circulatory arrest that occurred during coronary angiography in a patient who was not receiving TMZ 80 OD. The second was cardiac pain. Although the latter occurred in a patient receiving TMZ 80 OD, the event was not considered treatment-related.

DISCUSSION

In patients with symptomatic, stable angina despite treatment with CCS guideline-recommended antianginal therapies including maximally tolerated bisoprolol, the addition of TMZ 80 OD to the therapeutic scheme reduced angina attacks and short-acting nitrate use. These findings were also observed in the subgroups of patients whose background bisoprolol therapy was unchanged throughout the study and in patients on stable bisoprolol dose receiving additional hemodynamic antianginal therapy in the form of a CCB and/or LAN. Reductions in clinical symptoms with the inclusion of TMZ 80 OD were also associated with improvements in QoL measured on two different scales, which

assessed functional parameters such as mobility and ability to perform self-care, as well as overall health status.

There is consensus that it is reasonable to use combinations of classes of antianginal drugs for the treatment of anginal symptoms when symptoms persist despite the use of a single class [7]. However, regardless of whether beta-blockers are used alone or in combination, contemporary data from large registry studies such as CLARIFY and REACH have shown that a large proportion of patients with stable angina continue to experience ischemia and angina [13, 15, 24, 28]. Data from US outpatient cardiology practices for patients with a chronic CCS diagnosis have shown that around a quarter of patients continue to report monthly anginal symptoms, and 7.6% daily or weekly symptoms, despite over half (56.3%) being treated with at least two antianginal agents [14]. More recent data from the international CLARIFY registry reveal that of over 32,000 people with stable CCS, 7212 (22.1%) reported angina. Among these, 54.8% were still symptomatic for angina at 1 year despite management with at least two antianginal strategies including pharmacotherapy and revascularization [15]. Many patients also continue to experience anginal attacks despite revascularization [29–32]. In the ORBITA trial, 50.5% remained symptomatic after PCI despite a medical optimization phase during which the majority of patients received

Table 5 Modifications to background antianginal therapy during the course of the study in the patients on a stable dose of bisoprolol in combination with TMZ 80 OD throughout the study ($n = 930$)

Background antianginal therapy ($n = 930$)	Number (%) of patients with modified dose of background medication
Bisoprolol plus CCB ($n = 529$ [100%])	
No change in CCB	518 (97.9)
CCB replaced	3 (0.6)
CCB stopped	4 (0.8)
CCB dose reduced	4 (0.8)
Bisoprolol plus LAN ($n = 187$ [100%])	
No change in LAN	159 (85.0)
LAN replaced	1 (0.5)
LAN stopped	19 (10.2)
LAN dose reduced	8 (4.3)
Bisoprolol plus CCB plus LAN ($n = 214$ [100%])	
No change in CCB or LAN	183 (85.5)
No change in CCB	202 (94.4)
No change in LAN	183 (85.5)
CCB replaced	1 (0.5)
LAN replaced	2 (0.9)
CCB stopped	6 (2.8)
LAN stopped	16 (7.5)
CCB dose reduced	5 (2.3)
LAN dose reduced	11 (5.1)
CCB dose increased	0 (0.0)
LAN dose increased	2 (0.9)

treatment with at least three antianginal agents, consisting predominantly of a beta-blocker, CCB, and LAN [32, 33].

A potential explanation for these findings is that the causes of symptomatic stable angina are multifactorial. More than one ischemic mechanism may coexist in the same patient, and these may change over a patient's life span [34, 35]. When hemodynamic agents are not effective, the addition of a medication with an

alternative mechanism of action may prove beneficial, instead of the addition of a further hemodynamic agent or increasing the dosages of those already prescribed. By shifting cardiac metabolism from free fatty acids towards glucose, TMZ is a promising approach for the treatment of patients with stable angina. By acting directly at the level of the ischemic cell, it bypasses the potential underlying vascular (macrovascular and/or microvascular) and

hemodynamic mechanisms that can cause ischemia and angina.

In the ATPCI trial, TMZ 35 mg twice daily did not demonstrate superiority compared with placebo regarding the persistence or recurrence of angina leading to coronary angiography or intensification of antianginal therapy, although the trial included patients who had undergone successful, uncomplicated revascularization for stable angina or unstable angina/non-ST-elevation myocardial infarction (NSTEMI), where angina and ischemia were not an inclusion criterion [36]. Ischemia and angina were also not evaluated at baseline, nor was ischemia evaluation compulsory during follow-up, and thus the study design did not permit the objective evaluation of the anti-ischemic and antianginal efficacy of the drug in a population practically asymptomatic at inclusion. Of note, in the RIVER-PCI trial, ranolazine did not reduce rates of the composite primary efficacy endpoint of ischemia-driven revascularization or ischemia-driven hospitalization without revascularization, in spite of the fact that patients had incomplete revascularization [37] and 85% complained of angina at baseline [38].

In the current study, patients were symptomatic despite receiving maximally tolerated bisoprolol-based therapy, which in the majority of patients was represented by the 5 mg dose. Beta-blockers are often limited by side effects at higher doses, which can decrease patient adherence [39–41]. Data from the CLARIFY study have confirmed that in clinical practice, beta-blocker dosing is typically only 50% of the dose range required for demonstration of efficacy in randomized controlled trials [24]. As a cardioselective beta-blocker, bisoprolol is associated with superior efficacy and tolerability compared with many other members of this class [42], but side effects can remain dose-limiting in a number of patients.

Unlike conventional agents, the antianginal and anti-ischemic effects of TMZ are not associated with changes in hemodynamic determinants of myocardial oxygen consumption, such as heart rate, systolic blood pressure, or myocardial blood flow [43–45]. The efficacy of TMZ has been assessed in randomized, placebo-controlled studies, both as monotherapy and in

combination with beta-blockers [19, 46, 47] and CCBs [48]. Comparator studies have shown that the efficacy of TMZ in stable angina is comparable to that of nifedipine and propranolol, with a lower incidence of side effects [43, 44], and twice as effective as LAN in patients symptomatic despite optimally tolerated beta-blocker therapy [46]. In clinical guidelines, beta-blockers or CCBs continue to be recommended as first-line agents [7], although no direct comparisons between first-choice and second-choice treatments have demonstrated the superiority of one group of drugs over the other [49]. Furthermore, no recommendations are made for the optimal combinations of drugs. Nevertheless, given the absence of effects on heart rate and blood pressure, TMZ represents an ideal agent for early combination therapy with conventional hemodynamic agents.

The current study adds to the growing body of literature supporting the use of TMZ in routine clinical practice [50–52], and in particular for the use of the once-daily formulation [23]. When TMZ 80 OD was added to the physician's initial treatment, similar antianginal efficacy was observed at both 1 and 3 months, regardless of whether the background treatment was beta-blocker monotherapy or a dual or triple therapy combination, supporting findings from previous observational studies with both the twice-daily [52] and once-daily TMZ formulations [23].

To determine whether these observations were due to the inclusion of TMZ 80 OD or as a result of changes in the patients' background antianginal therapy, a series of sub-analyses were performed. The first involved evaluation of antianginal efficacy among the subset of patients whose beta-blocker dose remained constant throughout the study. Statistically significant improvements in angina symptoms and QoL were observed regardless of beta-blocker dose. The second evaluated the efficacy of TMZ 80 OD among patients with stable beta-blocker dose receiving additional hemodynamic therapy (CCB and/or LAN). When TMZ was added to the physician's initial treatment, similar improvements were observed regardless of whether the background treatment was beta-blocker monotherapy or a dual or triple therapy

combination. During the study there were no statistically significant changes in the concomitant antianginal treatments or their doses. The benefits observed were therefore likely a result of the inclusion of TMZ 80 OD in the treatment regimen.

TMZ 80 OD was well tolerated and raised no unexpected safety concerns, including no reports of drug-induced neurotoxicity. The results of the recent ATPCI trial showed that the routine use of TMZ over several years in more than 6000 patients receiving optimal medical therapy after successful PCI was also not associated with any statistically significant safety concerns and demonstrated a safety profile comparable to that of placebo [36].

The beneficial effects of TMZ 80 OD were also obtained without adverse hemodynamic changes or an increased incidence of other side effects. In contrast, there are a number of limitations associated with the use of first-line agents in the context of the multifactorial nature of angina. Use of nonselective beta-blockers may worsen coronary vasospasm in some patients because blockade of the beta receptors, which mediate vasodilation, allows unopposed alpha receptor-mediated coronary vasoconstriction to occur [53]. Their use should therefore be avoided in patients with Prinzmetal angina. LAN have been suggested to cause endothelial dysfunction, via mechanisms such as the production of reactive oxygen species [54, 55], and worsen microvascular disease [56]. Both nitrates and CCB can also cause a phenomenon known as coronary steal, in which pharmacological vasodilation of coronary collateral arteries can shunt blood from ischemic to nonischemic zones, thereby potentially worsening ischemia [57].

Finally, in the current study, we observed an improvement in overall adherence to therapy and excellent tolerability. Treatment nonadherence, whether as a result of drug-related side effects or complexity of a dosing regimen, is known to contribute to suboptimal angina control [58–60]. It could be hypothesized that improvements in their clinical condition along with the once-daily regimen may have motivated patients to adhere to the medication,

particularly given the well-established tolerability of TMZ 80 OD.

Study Limitations

This study was subject to the inherent limitations of observational studies, which include sample bias and incomplete response data, as well as the potential inaccuracy of self-reported behavior. Confirmation of the angina diagnosis with electrocardiography (ECG), stress testing with ECG or imaging, or coronary angiography was not a prerequisite of this study. Baseline coronary anatomy was not determined, and tests to determine exercise capacity before and after the introduction of TMZ 80 OD were not performed. The questionnaire used to assess medication adherence was non-validated, and therefore the results should be interpreted with caution. As an observational study without a control arm, blinding, or randomized treatment allocation, this study does not attempt to make any causal inferences about treatment effect. Understanding the characteristics of patients presenting with angina in routine clinical practice is, however, important as primary care is generally responsible for treatment continuity in most patients with CCS, and is where prescribing decisions are made. The findings from Modus Vivendi have important implications for the treatment of a wide range of patients with stable angina in clinical practice who still suffer frequent angina attacks despite guideline-recommended treatment.

CONCLUSION

The Modus Vivendi study results support the addition of TMZ 80 OD to first-line antianginal therapy to alleviate angina symptoms and improve QoL. Similar improvements in anginal symptoms and QoL were observed when TMZ 80 OD was added to maximally tolerated bisoprolol monotherapy, and when it was part of a treatment strategy with bisoprolol in double or triple combination with other hemodynamic agents such as CCBs and LANs. Our findings suggest that a maximally tolerated beta-blocker (bisoprolol) with add-on TMZ 80 OD is as

effective as any of the other treatment combinations, and could represent an optimal first-line approach for the management of stable angina.

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Authors' contributions. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

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Compliance with ethics guidelines. The study was performed in accordance with good clinical practice and the ethical principles derived from the revised Declaration of Helsinki. Institutional Ethics Committee approval, provided by the Volgograd Regional Cardiology Center, was sought before performing the study, and all patients provided written informed consent. The study registration number is ISRCTN29992579

Data availability. The datasets generated and/or analyzed for this study are not publicly available as they include medical records of patients from a secondary source.

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