Health-Related Quality of Life of Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes—Results from the PLATO Trial

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ABSTRACT

Objectives: The purpose of this study was to compare the effects of ticagrelor versus clopidogrel on health-related quality of life in the PLATO trial.

Methods: HRQOL in the PLATO study was measured at hospital discharge, 6-month visit, and end of treatment (anticipated at 12 months) by using the EuroQol five-dimensional (EQ-5D) questionnaire. All patients who had an EQ-5D questionnaire assessment at discharge were included in the study. Patients who died prior to the end-of-treatment visit were assigned an EQ-5D questionnaire value of 0. Results: The EQ-5D questionnaire value at discharge among 7631 patients assigned to ticagrelor was 0.847 and among 7581 patients assigned to clopidogrel was 0.846 (P = 0.71). At 12 months, the mean EQ-5D questionnaire value was 0.840 for ticagrelor and 0.832 for clopidogrel (P = 0.046). Excluding patients who died resulted in mean EQ-5D questionnaire values of 0.864 among ticagrelor patients and 0.863 among clopidogrel patients (P = 0.69).

Conclusions: In patients hospitalized with acute coronary syndromes with or without ST-segment elevation, treatment with ticagrelor was associated with a lower mortality but otherwise no difference in quality of life relative to treatment with clopidogrel. The improved survival and reduction in cardiovascular events with ticagrelor are therefore obtained with no loss in quality of life.

Keywords: acute coronary syndrome, clopidogrel, quality of life, ticagrelor.

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Introduction

Dual therapy with aspirin and clopidogrel is a standard treatment in patients with acute coronary syndromes (ACS) [1]. Ticagrelor is an oral nonthienopyridine platelet P2Y12 receptor inhibitor with a reversible and direct action on the receptor that provides faster, greater, and more consistent platelet inhibition than clopidogrel [2–4]. The PLATO trial showed that ticagrelor was superior to clopidogrel for the prevention of cardiovascular death, myocardial infarction, or stroke in a broad population of patients with acute coronary syndromes [5].

The effect of ticagrelor on health-related quality of life (HRQOL) is unknown. The purpose of our study was to compare the effects of ticagrelor versus clopidogrel on HRQOL, a prespecified secondary objective of the PLATO Health Economic Substudy.

Methods

The PLATO trial was an international, prospective, randomized, double-blind, double-dummy, event-driven study of patients hospitalized with an ACS, with or without ST-segment elevation. Details of the study design, population, and outcomes have been published previously [5,6].

PLATO Trial Population

In the study 18,624 patients from 862 centers in 43 countries were enrolled from October 2006 through July 2008. Patients were randomly assigned to treatment with either ticagrelor or clopidogrel within 24 hours of onset of the most recent cardiovascular ischemic symptoms and before percutaneous coronary intervention. Ticagrelor-assigned patients received a 180-mg loading dose followed by a maintenance dose of 90 mg twice daily. Clopidogrel-treated patients who had not already received a loading dose of open-label clopidogrel, or taken clopidogrel or ticlopidine for 5 or more days before randomization, received a loading dose of open-label clopidogrel, or taken clopidogrel or ticlopidine for 5 or more days before randomization, received a
HRQOL Study

HRQOL in the PLATO study was measured by using the EuroQol five-dimensional (EQ-5D) questionnaire descriptive system [7]. The EQ-5D questionnaire descriptive system is a self-administered instrument consisting of five questions, each representing one dimension [8]. The five dimensions are mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. For each dimension responders are asked to report their status on a three-level ordinal scale: whether they experience no problems (level 1), some problems (level 2), or severe problems (level 3). The 243 different health states attainable from the EQ-5D questionnaire profile can each be assigned an EQ-5D questionnaire single index where 1 represents the HRQOL attributable to perfect health and 0 represents the HRQOL corresponding to death. Utility levels below zero can occur, indicating a health state worse than death. The single index scores of the 243 states are based on the UK time trade-off tariff, which is based on a general population study [9], in which responders were asked to value EQ-5D questionnaire states in terms of trade-off utilities. The PLATO trial enrolled patients from 43 countries; however, a majority of them were European. We therefore adopted the UK valuations of the health states for our analysis because they are the most robust and representative [10]. The EQ-Visual analogue scale, which is a part of the standard self-report EQ-5D questionnaire, was not included in the study. The EQ-5D questionnaire descriptive system has been extensively used within the cardiovascular field to assess patient utility in trials of new treatments and has demonstrated both high validity and reliability [11].

Patients who survived until discharge from index hospitalization and who were living in countries with access to official language versions of the EQ-5D questionnaire were eligible for enrollment in the PLATO HRQOL substudy (Fig. 1). The excluded countries were India, Philippines, Korea, Georgia, and Ukraine. Among 18,624 patients enrolled in the PLATO trial, 1,461 (8%) included in the model were treatment (ticagrelor vs. clopidogrel), age (divided into three classes, <49 years, 50–74 years [reference class], and ≥75 years), sex, and body mass index (divided into three classes, <25 kg/m² [normal], 25–<30 kg/m² [overweight, reference class], and ≥30 kg/m² [obese]). In addition, cardiovascular risk factors (including smoking status, hypertension, dyslipidemia, and diabetes), prior events (including prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, congestive heart failure, stroke, peripheral arterial disease, renal disease, dyspnea, chronic obstructive pulmonary disease, and asthma), and presenting diagnosis were included as covariates in the model.

Sensitivity Analyses

Six sensitivity analyses were conducted to examine the impact of varying the assumptions made in the primary analyses on treatment differences in HRQOL.

In the first sensitivity analysis, we examined treatment differences in 6-month EQ-5D questionnaire assessments in all patients included in the primary analysis population. In the second sensitivity analysis, instead of reassigning patients with health states worse than death an EQ-5D questionnaire single index value of 0, we retained the original negative values in the analysis. Patients with EQ-5D questionnaire assessments only at discharge from the index hospitalization or with early EOT assessments for unknown reasons could be considered lost to follow-up. In the third sensitivity analysis, patients with EQ-5D questionnaire assessment only at discharge from the index hospitalization or with early EOT assessments were excluded from the analysis. In the fourth sensitivity analysis, we excluded patients who died between hospital discharge and the EOT visit. In the fifth sensitivity analysis, we restricted the patient population to only those patients who had a 12-month EQ-5D questionnaire assessment; that is, patients who had an EOT EQ-5D questionnaire assessment prior to 12 months or who died prior to EOT were excluded.

Patients who died during the index hospitalization did not have an opportunity to participate in the PLATO HRQOL study. For the sixth and final sensitivity analysis, we generated a maximal data set, which included patients who died during the index hospitalization (assigned an EQ-5D questionnaire value of 0) as well as all patients with any EQ-5D questionnaire assessment. As with the primary analysis, the LVCF methodology was used for patients with the final EQ-5D questionnaire assessment prior to the 12-month time period.

All tests of statistical significance were two-tailed, and a probability value of 0.05 was considered to be statistically significant. Computations for statistical analyses were done by using the statistical software SAS, version 9.1.3.

Results

Among 18,624 patients enrolled in the PLATO trial, 1,461 (8%) were enrolled in countries in which no official language version...
of the EQ-5D questionnaire was available and 317 (~2%) did not survive to discharge from the index hospitalization (Fig. 1). Among the remaining 16,846 patients eligible for enrollment in the HRQOL study, 15,212 (90%) patients completed an EQ-5D questionnaire assessment at discharge. There were no significant differences in baseline characteristics among patients enrolled in the HRQOL study and the overall PLATO trial or across treatment groups among patients enrolled in the HRQOL study (Table 1).

The number of patients with the last EQ-5D questionnaire assessments at various time points is presented in Figure 1. The EQ-5D questionnaire value at discharge among 7631 patients assigned to ticagrelor was 0.847 and among 7581 patients assigned to clopidogrel was 0.846 (mean difference = 0.0014, \( P = 0.71 \)). In 84.0% of the ticagrelor patients and 84.2% of the clopidogrel patients, the last EQ-5D questionnaire assessment occurred either at 12 months or at 6 or 9 months as a result of the completion of the trial. In patients with complete EQ-5D questionnaire assessments at discharge and at 6 and 12 months, improvements in the single index occur mainly during the first 6 months (mean increase = 0.0142), while further changes over the last 6 months were minimal (mean increase = 0.0046).

Approximately 3% in each treatment arm had early EOT assessments for other reasons, and 11% in the ticagrelor arm and 10% in the clopidogrel arm had their last EQ-5D questionnaire assessment at discharge from the index hospitalization. Baseline characteristics of patients with early EOT or discharge EQ-5D questionnaire assessments did not differ significantly from those with complete follow-up. In 2.8% of the ticagrelor patients and 3.6% of the clopidogrel patients, the end point was assigned the value 0 because of a death. Patients who died had on average 0.15 lower EQ-5D questionnaire value at discharge compared with patients who survived until the EOT visit (\( P < 0.0001 \)).

The mean difference between 12-month EQ-5D questionnaire single index among ticagrelor and clopidogrel patients was 0.008, statistically significant with a 95% confidence interval for the difference of (0.00016, 0.016). These results were confirmed in a nonparametric bootstrap analysis: \( P = 0.047 \), 95% confidence interval for the difference (0.00014, 0.016).

Factors associated with the 12-month quality of life are presented in Table 2. Increasing age and female sex were independently associated with lower HRQOL values. In general, cardiovascular risk factors as well as prior clinical events were associated with lower quality of life.

Response to the five dimensions of the EQ-5D questionnaire at discharge and at the 12-month follow-up is illustrated in Figure 2. In all dimensions, three quarters of the patients reported no problems. There were no statistically significant differences in the separate dimensions of the EQ-5D questionnaire between the ticagrelor and clopidogrel groups.

**Sensitivity Analyses**

Results from the six sensitivity analyses are reported in Table 3. The mean difference between 6-month EQ-5D questionnaire...
The sixth and last sensitivity analysis is based on the maximal data set, which includes deaths during the index hospitalization. Compared with the result from the primary analysis, the quality-of-life difference between ticagrelor-treated patients and clopidogrel-treated patients is increased (mean difference = 0.0113, \( P = 0.010 \)), essentially because of a higher number of deaths in the clopidogrel group during the index hospitalization.

**Discussion**

In this large, contemporary cohort of patients with ACS enrolled in the PLATO trial, treatment with ticagrelor was associated with similar quality-of-life outcomes compared with treatment with clopidogrel. Patients enrolled in the HRQOL substudy of the PLATO trial (\( n = 15,212 \)) did not differ significantly in baseline characteristics from the overall PLATO trial population (\( n = 18,624 \)). The EQ-5D questionnaire single index value at 12 months between ticagrelor and clopidogrel patients was 0.0057 and was not statistically significant (\( P = 0.15 \)). A total of 153 patients (65 in the ticagrelor arm and 88 in the clopidogrel arm) reported health states worse than death. Retaining these negative EQ-5D questionnaire values in the analysis increased the difference between treatments slightly (mean difference = 0.0085, \( P = 0.041 \)), with higher EQ-5D questionnaire value in ticagrelor-treated patients. In the third sensitivity analysis, we excluded patients with EQ-5D questionnaire assessment only at discharge from the index hospitalization or those with early EOT. In this subset of patients, quality of life was numerically higher among ticagrelor-treated patients; however, the difference across treatments was not statistically significant (mean difference = 0.0072, \( P = 0.095 \)). Exclusion of deaths or restricting the analysis only to those patients with a last completed EQ-5D questionnaire assessment at the 12-month visit resulted in no treatment difference in quality of life between patients treated with ticagrelor and patients treated with clopidogrel.
was 0.840 among 7,631 ticagrelor-treated patients and 0.832 among 7,581 clopidogrel-treated patients ($P = 0.046$). This result was confirmed in a nonparametric bootstrap analysis.

Our primary analysis included all patients with at least one EQ-5D questionnaire assessment. Patients who died during the follow-up period were assigned an EQ-5D questionnaire value of 0. We conducted several sensitivity analyses, modifying some of the key assumptions of our primary analysis: In the most conservative scenario, we restricted our patient population to only those patients who were alive and had completed an EQ-5D questionnaire assessment at 12 months. In this analysis, which included less than half the original HRQOL study population, the treatment difference (ticagrelor vs. clopidogrel) in quality of life was negligible ($-0.003$, $P = 0.63$). While this result provides a useful benchmark, we believe that it may be subject to substantial selection bias. Approximately 36% of the patients in each

<table>
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<tr>
<th>Table 2 – Independent determinants of the EQ-SD questionnaire single index at 12 months (n = 15,212).*</th>
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<tr>
<td>Parameter estimate</td>
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<tr>
<td>Treatment: Ticagrelor vs. clopidogrel</td>
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<tr>
<td>Age</td>
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<tr>
<td>≥49 y vs. REF</td>
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<td>50–74 y (REF)</td>
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<td>Non-ST-elevation MI (REF)</td>
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<td>Unstable angina vs. REF</td>
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Note. $R^2 = 0.105$.
CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; dx, diagnoses; EQ-5D, EuroQol five-dimensional; LVCF, last value carried forward; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; REF, reference.

*As in the primary analysis, LVCF was used.

was 0.840 among 7,631 ticagrelor-treated patients and 0.832 among 7,581 clopidogrel-treated patients ($P = 0.046$). This result was confirmed in a nonparametric bootstrap analysis.

Our primary analysis included all patients with at least one EQ-5D questionnaire assessment. Patients who died during the follow-up period were assigned an EQ-5D questionnaire value of 0. We conducted several sensitivity analyses, modifying some of the key assumptions of our primary analysis: In the most conservative scenario, we restricted our patient population to only those patients who were alive and had completed an EQ-5D questionnaire assessment at 12 months. In this analysis, which included less than half the original HRQOL study population, the treatment difference (ticagrelor vs. clopidogrel) in quality of life was negligible ($-0.003$, $P = 0.63$). While this result provides a useful benchmark, we believe that it may be subject to substantial selection bias. Approximately 36% of the patients in each

![Fig. 2 – Percentage distribution of response to the EQ-5D questionnaire at discharge (D) and 12-month follow-up (12). C, clopidogrel; EQ-5D, EuroQol five-dimensional; T, ticagrelor.](image-url)
According to our data, however, the course of the disease is rather similar for the two treatment groups in all patients, although it was no longer statistically significant ($P=0.095$). In our primary analysis, patients who rated their health state worse than death (negative EQ-5D questionnaire) were reassigned a value of 0. The reason for censoring at the lower bound of 0 is that otherwise we have to accept that a drug that kills patients with health states valued worse than death could be considered beneficial compared with a drug that does not kill these patients. This is especially problematic because the valuation is done by the general public and not the individual patient. From an analysis point of view, the censoring is, maybe, unimportant, because there are relatively few (147) censoring cases, but from a philosophical point of view, it is important to handle this problem properly.

The major driver of differences in quality of life across treatments appears to be the valuation of deaths. The inclusion of patients who died during the index hospitalization increased the treatment difference to 0.013 in favor of ticagrelor ($P=0.01$). In contrast, excluding patients who died during the follow-up period nullified all treatment differences. Thus, there were no indications that the higher rate of spontaneous bleeding and more frequent side effects of dyspnea had any influence on the overall quality of life as measured in the study. Therefore, the gains in survival and cardiovascular events were obtained without any loss in quality of life.

Although there have been several studies that have used the EQ-5D questionnaire to assess quality of life among patients with coronary heart disease [14–18], there are only a few that have used it in the subset of patients with ACS. The MERLIN-TIMI 36 Randomized trial of ranolazine versus placebo in 6560 patients with non–ST-elevation ACS reported an EQ-5D questionnaire single index value of approximately 0.71 at baseline and 0.84 at 12 months [19]. In the PLATO study, patients were eligible for enrollment if their symptom onset was during the previous 24 hours. In acute settings it is difficult to obtain a true baseline when measuring the HRQOL. Consequently, our first EQ-5D questionnaire measure, the assessment made at discharge from the index hospitalization, cannot be considered as a true baseline because it is reported after treatment initiation of the study drug. However, the EQ-5D questionnaire values observed at 12 months are consistent with those reported in the MERLIN-TIMI 36 study.

Quality of life in patients after an episode of ACS is generally high and not substantially different from a comparable control population [20,21]. Thus, unlike some other secondary preventive treatments such as antihypertensives, the benefits in survival and reduction of cardiovascular events by long-term preventive treatment with ticagrelor as compared with clopidogrel came without any impediment to the quality of life in these patients [22].

Our study has some strength and several limitations. To our knowledge, our study is the largest reported population with EQ-5D questionnaire measurement in cardiovascular diseases including both randomized controlled trials and observational studies [11]. We have also conducted a comprehensive set of sensitivity analyses examining the impact of the assumptions made in the primary analysis. It should be pointed out, however, that the analysis presented here is a post hoc analysis, and so any reported $P$ values should be interpreted accordingly. Traditionally, the outcome of interest in HRQOL studies is the change in quality of life. Baseline quality of life prior to treatment, however, was not collected in the PLATO trial. As a result, we were able to assess absolute rather than relative difference in quality of life at 12 months. In our study, HRQOL was assessed using only the generic EQ-5D questionnaire instrument. While this instrument has the advantage of being completed with relative ease by the patients, incorporated into case report forms, and validated in many languages, it may be less sensitive than a disease-specific quality-of-life instrument [22,23]. Also, the EQ-5D questionnaire single index reflects health status derived by using an algorithm based on utility scores from a reference population. Hence, it does not provide a truly personal valuation of health status. The EQ-5D questionnaire descriptive system, however,
has been shown to be satisfactorily valid and reliable when applied to patients with ACS [11,14].

**Conclusions**

In patients hospitalized with ACS with or without ST-segment elevation, treatment with ticagrelor was associated with a lower mortality but otherwise no difference in quality of life relative to treatment with clopidogrel. The improved survival and lower risk of cardiovascular events with ticagrelor are therefore obtained with no loss in quality of life.

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**REFERENCES**


