VALUE IN HEALTH 16 (2013) 574–580

Available online at www.sciencedirect.com

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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 PLATelet inhibition and patient Outcomes (PLATO) trial. **Background:** 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. **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 from the index hospitalization (n = 15,212) 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.

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 $P2Y_{12}$ 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 PLATelet inhibition and patient Outcomes (PLATO) trial showed that ticagrelor was superior to clopidogrel for the prevention of cardiovascular death, myocardial infarction, or stroke with no significant increase in total major bleeding but associated with a significant increase in non–coronary artery bypass grafting-related spontaneous major bleeding and episodes of dyspnea in a broad population of patients with ACS [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 cardiac 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

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1098-3015/$36.00 – see front matter Copyright © 2013, International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Published by Elsevier Inc.

http://dx.doi.org/10.1016/j.jval.2013.01.013

loading dose of 300 mg, followed by a maintenance dose of 75 mg once daily. The remaining patients received the 75-mg daily maintenance dose of clopidogrel as their first dose.

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. Patients were administered the EQ-5D questionnaire at discharge from the index hospitalization, at the 6-month visit, and at the end-of-treatment (EOT) visit, which was anticipated to be at 12 months.

Statistical Analyses

As previously described, the PLATO trial was an event-driven study. The primary efficacy end point was death from vascular causes, myocardial infarction, or stroke. As part of the trial, outpatient visits were scheduled at 1, 3, 6, 9, and 12 months, with a safety follow-up visit 1 month after the EOT. The randomized treatment was scheduled to continue for 12 months, but patients left the study at their 6- or 9-month visit if the targeted number of 1780 primary end-point events had occurred by that time.

Primary Analysis

The primary end point for the HRQOL substudy was the EQ-5D questionnaire single index utility score at 12 months after enrollment. For patients who had EOT assessments at 6 or 9 months as a result of the trial reaching the requisite number of end points, the EQ-5D questionnaire value at the EOT assessment was assumed to be equivalent to that at the 12-month assessment. For patients with early EOT assessments for reasons other than completion of the trial, or with EQ-5D questionnaire assessment only at discharge from the index hospitalization, the last available EQ-5D questionnaire assessment was applied on the basis of the last value carried forward (LVCF) principle [12]. Patients who died prior to the EOT visit were assigned an end-point value of 0. And finally, patients who rated their health state worse than death (negative EQ-5D questionnaire) were reassigned a value of 0.

The mean end-point EQ-5D questionnaire single index for patients assigned to ticagrelor and clopidogrel was compared by using a Student's t test. Treatment comparisons were based on intention-to-treat. The result was confirmed by using a nonparametric bootstrap analysis with 10,000 bootstrap replicates.

A multiple linear regression model was used to study the association between treatment, demographic and clinical factors, and the end-point EQ-5D questionnaire single index. Variables included in the model were treatment (ticagrelor vs. clopidogrel), age (divided into three classes, $\leq$49 years, 50–74 years [reference class], and $\geq$75 years), sex, and body mass index (divided into three classes, <25 kg/m^2 [normal], 25–<30 kg/m^2 [overweight, reference class], and ≥ 30 kg/m^2 [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