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Clopidogrel, prasugrel, or ticagrelor use and clinical outcome in patients with acute coronary syndrome: A nationwide long-term registry analysis from 2009 to 2014

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ABSTRACT

Background: The beneficial use of dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and P2Y12 õinhibitors has been established for patients after acute coronary syndrome (ACS). However, the optimal duration of DAPT is under debate. The aim of the present study was to investigate the long-term utilization and clinical outcome of clopidogrel, prasugrel, and ticagrelor in patients with ACS from 2009 to 2014 in Austria.
Methods: We analysed data from 13 Austrian health insurance funds for the years 2009 to 2014, on 72,676 patients with a hospital discharge diagnosis of ACS. The primary end point was recurrence of ACS or death >30 days after the index event.
Results: 32,830 subjects received a prescription of a P2Y12 inhibitor within 30 days after the index ACS. 18,640 (56.8%) subjects were discharged with clopidogrel, 6683 (20.4%) with prasugrel, and 7507 (22.9%) with ticagrelor, respectively. Data from 32,174 patients with 4975 events during a median follow-up period of 24.9 months were available for survival analysis. The cumulative incidence for recurrence of ACS or death at two years was 18.7% in patients receiving clopidogrel, and 8.7% and 12.0% in those receiving prasugrel or ticagrelor, respectively.
Conclusion: Utilization of P2Y12 inhibitors in patients with ACS was consistent with guideline recommendations. Prasugrel and ticagrelor are increasingly used in ACS patients and associated with a lower number of recurrence of ACS or death compared to clopidogrel. However, clopidogrel was predominantly used in older patients with more co-morbidities.

1. Introduction

Dual antiplatelet therapy (DAPT) has been established as pharmacological treatment for patients with ACS with or without percutaneous coronary intervention (PCI) [1–4]. The co-medication of a P2Y12 receptor inhibitor such as clopidogrel, prasugrel or ticagrelor with acetylsalicylic acid (ASA) has been shown to prevent acute coronary stent thrombosis, and to reduce the risk of cardiovascular (CV) death, recurrent myocardial infarction, or stroke [5–7].

The present ESC Guidelines for the management of ACS in patients presenting with or without persistent ST-segment elevation (STEMI, NSTEMI) recommend treatment with a P2Y12 inhibitor added to ASA as soon as possible and maintenance for at least 12 months [4,8]. However, decision on DAPT duration depends on the type of intervention and co-morbidities, and is subject of ongoing debate [9]. Recent data indicate that prolonged DAPT with ticagrelor may be beneficial in patients after ACS, at the expense of increased bleeding risk [10].

Epidemiological studies from Denmark [11], Greece [12], and Australia [13] have shown a smaller number of CV events or deaths for patients treated with prasugrel or ticagrelor after ACS compared to those who received clopidogrel. This is consistent with results from earlier randomized controlled trials [14,15]. Interestingly, clopidogrel prescription is more frequent in older patients and in those who have more comorbidities [13,16]. However, the real-life comparison from epidemiological analysis are restricted to events during DAPT and do not cover events after discontinuation of intensified antiplatelet treatment.

The aim of this study was to investigate epidemiological data during and after P2Y12 inhibitor use for patients hospitalised with ACS in Austria between 2009 and 2014 and the association between the choice of therapy and recurrence of ACS or death. To this end, we utilized prescription, demographic data and information on hospital discharges with primary diagnoses coded by the International Classification of Diseases (ICD) system.

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2. Methods

This study was approved by the Ethics Committee of the Medical University of Vienna (EK-No.1006/2015) and was performed in cooperation with the Pharmacoeconomics Advisory Council of the Austrian Sickness Funds and in accordance with the Declaration of Helsinki.

2.1. Data preparation

The health insurance system in Austria provides health care for all residents who are assigned membership to one of the several health insurance funds according to their current or former employment or province of residence. Data from outpatient as well as inpatient medical services covered by the health insurance funds are stored in the respective databases, including demographic data, information on hospital discharges with primary diagnoses coded using the ICD-system, and reimbursed drug prescriptions. We analysed data of 13 Austrian health insurance funds covering >98% of the Austrian population. Observational periods of three to six years between January 2009 and December 2014 were available. Data were pseudonymised to preserve patients' privacy. Data storage and handling were in agreement with privacy laws.

Patients aged 18 years or older who were discharged with the principal diagnosis ACS (STEMI, NSTEMI) by ICD-10 (Appendix 1) and who filled a prescription of clopidogrel, prasugrel or ticagrelor within 30 days after the index diagnosis were eligible for this study. We excluded patients who had already been under P2Y12 inhibitor therapy during the period of 120 days before index diagnosis. Patients for whom this criterion could not be verified due to lack of data, i.e. with an ACS diagnosis within 120 days after the beginning of the observation period, were also excluded. For simplification, we excluded a small number of patients for whom records indicated simultaneous prescription of several P2Y12 inhibitors during the observational period.

For the analysis of the association between drug therapy and outcome (recurrence of ACS or death), any two subsequent hospitalizations for ACS within 30 days were interpreted as a single ACS episode.

2.2. Statistical methods

Metric variables are described by medians and interquartile ranges (IQR), and categorical variables by absolute and relative frequencies. The duration of P2Y12 inhibitor intake was defined as the time between the first and last recorded prescription increased by 1.07 times the average daily doses per volume for the respective patient. The factor 1.07 corresponds to the average number of volumes per prescription and was estimated using data of patients with only one prescription. Based on this definition, drug survival was estimated using the product-limit method, censoring for death and end of data availability. The distribution of time to re-admission for ACS or death was estimated using the product-limit method, censoring for end of data availability. As starting point for survival analyses, we used 30 days after the first prescription of P2Y12 inhibitors after discharge from index ACS, whichever occurred later. Thus, patients who had died or for whom data availability ended within 30 days after discharge from hospital after the index ACS or after the first prescription of P2Y12 inhibitors were excluded from this analysis since they were never at risk. Similarly, patients who had been re-admitted for ACS within 30 days after the first prescription of P2Y12 inhibitors were excluded. Univariable and multivariable Cox regressions were used to estimate crude and adjusted hazard ratios with 95% confidence intervals, respectively. In addition to the treatment group, multivariable Cox regression included the following adjustment variables: sex, the interaction of age and sex, calendar year of index admission and four binary covariables indicating prescription of anti-diabetic medicines (ATC codes A10A or A10B), anti-obstructive drugs for chronic obstructive lung disease (R03), ACE inhibitors, ARBs, or β-blockers as CV-medication (C09 or C07), and HMG CoA reductase inhibitors as lipid lowering medication (C10AA) within 120 days prior to the index admission for ACS. We also adjusted for age at the therapy start, accounting for non-linear associations by natural cubic spline basis with five degrees of freedom. Hazard ratios for age were then derived from the models by inserting the quartile medians (Q1: 49.9 years, Q2: 61.3, Q3: 71.5 and Q4: 82.2), with Q1 serving as reference. The origin of the data (one of the 13 health insurance funds) was included as random factor. Median follow-up time was estimated using the reverse Kaplan-Meier method [17]. As sensitivity analysis we also considered hospitalization with ACS and death, respectively, as separate endpoints in univariate and multivariable Cox regression. In the analysis of hospitalization with ACS, death was treated as censoring event. Two-sided p-values <0.05 or 95% confidence intervals excluding parity were considered as indicating statistical significance. Plots were prepared with the R programming language. All other analyses were performed with the Statistical Analysis System, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

72,676 patients with a hospital discharge diagnosis of ACS and without preceding P2Y12 inhibitor therapy were identified in the database (Table 1). Among these, 32,830 subjects received a prescription with a P2Y12 inhibitor within 30 days after the index event. 18,640 (56.8%) subjects were discharged with clopidogrel, 6683 (20.4%) with prasugrel, and 7507 (22.9%) with ticagrelor, respectively. Patient characteristics and drug utilization before the ACS index event according to treatment groups are summarised in Table 2. Subjects receiving clopidogrel were older than those with prasugrel or ticagrelor. >80% of elderly subjects aged >80 years received clopidogrel as P2Y12 inhibitors (Table 3). There was a continuous decline in the prescription of clopidogrel between 2010 and 2014 from 90% to 45%, paralleled by an increased prescription of prasugrel and ticagrelor (Table 3).

Table 1
Patient data for treatment and survival analysis.

Patients ≥18 years with ACS:	$n = 86.104$
Patient with lack of health care insurance data within 120 days before ACS:	$n = 7118$
Patients with P2Y12 inhibitor within 120 days prior to ACS:	$n = 6310$
Patients without P2Y12 inhibitor within 30 days after ACS:	$n = 39.816$
Patients with prescription of different P2Y12 inhibitors during the observation period:	$n = 30$
Patients included in the analysis:	$n = 32.830$
Patients who died within 30 days after index event:	$n = 304$
Patients with readmission for ACS within 30 days after index event:	$n = 42$
Patients with end of data within 30 days after index event:	$n = 310$
Patients with ACS and P2Y12 inhibitor eligible for survival analysis >30 days after index event:	$n = 32.174$

3.1. Drug survival of P2Y12 inhibitor therapy

Drug survival is shown in Fig. 2. From baseline to six months after start of therapy, discontinuation rates were 20.4% for of patients using clopidogrel, 7.9% for prasugrel, and 17.1% for ticagrelor. From baseline to 12 months, the discontinuation rates were 45.3%, 45.7%, and 57.0%, respectively. However, at approximately 12 months, the drug survival crossed, such that a higher percentage of patients continued to use clopidogrel for at least 18 months (28.8%) compared to prasugrel (15.5%) or ticagrelor (7.9%). (See Fig. 1.)

Drug survival was also associated with age, and a similar crossing of drug survival curves was observed (Fig. 3).

3.2. P2Y12 inhibitor therapy and clinical outcome

Fig. 4 illustrates event-free survival by type of treatment. For this survival analysis, data from 32,174 patients with 4975 events were available. The median follow-up period was 24.9 months (IQR 13.1; 37.2). 2604 patients had a recurrence of ACS, among them 72 patients died during the hospitalization. 2371 patients died without recurrent ACS diagnosis. The cumulative incidence for ACS or death at two years was 18.7% in patients receiving clopidogrel, and 8.7% and 12.0% in those receiving prasugrel or ticagrelor, respectively.

Adjusting for age, sex, their interaction, calendar year and pre-existing medication as proxy for comorbidity, the effect of the medication was similar but less pronounced, with a hazard ratio of 0.7 (95% [CI: 0.7; 0.8]) for prasugrel vs. clopidogrel and of 0.8 (95% [CI: 0.8; 0.9]) for ticagrelor vs. clopidogrel (Table 4).

In a separate statistical analysis for each component of the end point, the adjusted hazard ratio for ACS was similar for ticagrelor vs

Table 2
Patients characteristics and disease-specific medication before index ACS admission.

	Clopidogrel ($n = 18.640$)	Prasugrel ($n = 6683$)	Ticagrelor ($n = 7507$)
Age - median years (IQR)	71 (61; 80)	57 (50; 65)	65 (55; 74)
Female sex - n (%)	7172 (38.5)	1331 (19.9)	2350 (31.3)
Cardiovascular medication - n (%)	10,638 (57.1)	2212 (33.1)	3360 (44.8)
HMG CoA reductase inhibitors - n (%)	5347 (28.7)	1022 (15.3)	1586 (21.1)
Drugs for obstructive airway diseases - n (%)	2370 (12.7)	521 (7.8)	726 (9.7)
Anti-diabetic medicines - n (%)	3322 (17.8)	800 (12.0)	1081 (14.4)

IQR, interquartile ranges; n, number of patients.

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