Original Research

Potent P2Y12 inhibitors versus clopidogrel to predict adherence to antiplatelet therapy after an acute coronary syndrome: insights from IDEAL-LDL

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Abstract

Background: Superiority of potent P2Y12 inhibitors over clopidogrel after an acute coronary syndrome (ACS) has been well established, however potent P2Y12 inhibition is responsible for more adverse events, which may influence patient adherence to treatment. Aim of the present study is to investigate the adherence to the prescribed P2Y12 inhibitor (P2Y12i) in patients on dual antiplatelet therapy (DAPT) after an ACS. **Methods**: In an IDEAL-LDL trial substudy, we included 344 patients after ACS discharged on DAPT. The primary outcome was the difference between potent P2Y12i and clopidogrel in terms of adherence, as well as other predictors of adherence to the antiplatelet regimen. Secondary outcomes included the prevalence of DAPT continuation and its predictors and the antiplatelet regimen selection after DAPT. **Results**: Adherence to the potent P2Y12i and to clopidogrel was observed in 140/178 (78.7%) and 111/166 (66.9%) patients ($p = 0.016$), respectively. In the multivariate model, after adjustment for P2Y12i switching during the first year of therapy, there was no difference observed in adherence between potent P2Y12i and clopidogrel (odds ratio [OR] = 0.98, 95% confidence interval [CI] = 0.55–1.74). Significant predictors included history of cardiovascular disease (CVD) (OR = 0.51, 95% CI = 0.31–0.86) and percutaneous coronary intervention (PCI) index event treatment (OR = 2.58, 95% CI = 1.38–4.82). Of patients, 72% continued DAPT >12 months and female gender was a negative predictor of DAPT prolongation (adjusted OR = 0.43, 95% CI = 0.21–0.90). DAPT was continued until the end of follow-up in 42.7%, while 54.6% resumed with single antiplatelet regimen. **Conclusions**: Adherence to DAPT was not affected by the P2Y12i potency, whereas history of CVD and PCI treatment were associated with reduced and increased adherence, respectively.
Clinical Trial Registration: NCT02927808, https://clinicaltrials.gov/ct2/show/NCT02927808.

Keywords: acute coronary syndromes; P2Y12 inhibitors; clopidogrel; ticagrelor; prasugrel; adherence

1. Introduction

According to the current guidelines on dual antiplatelet therapy (DAPT), treatment with a P2Y12 inhibitor in combination with aspirin for a minimum of 12 months is generally recommended for patients after an acute coronary syndrome (ACS), except those at high or very high bleeding risk [1]. Superiority of potent P2Y12 inhibitors (ticagrelor and prasugrel) over clopidogrel in preventing ischaemic cardiovascular events, including cardiovascular death, non-fatal myocardial infarction (MI) and stroke, has been well established in PLATO and TRITON-TIMI 38 trials [2,3]. However, despite an ischaemic risk reduction, potent P2Y12 inhibition is responsible for more bleeding events, as well as other adverse events. Specifically, ticagrelor use is often accompanied by an increase in non-procedure-related bleeding, dyspnoea and Holter-detected ventricular pauses, whereas prasugrel use is associated with non-CABG-related life threatening bleeding. As a result,

premature DAPT discontinuation as well as switching from potent P2Y12 inhibitors to clopidogrel, either during the index hospitalization or after the event, are relatively common in clinical practice.

Discontinuation of P2Y12 inhibitor is often defined in studies as the temporary or definite cessation of an antiplatelet agent within the first year of DAPT. Main reasons for discontinuation include, among others, major bleedings, need for major surgery, need for oral anticoagulant, drug intolerance and older age [4–7]. Only a few studies have attempted to clarify whether interruption of adherence to the 12-month DAPT is related to the potency of P2Y12 inhibitors. Most of them suggest that discontinuation occurs more often in patients receiving ticagrelor or prasugrel than clopidogrel treatment [4–6,8]. On the other hand, de-escalation of the P2Y12 inhibition is defined as a decrease in platelet inhibition and includes switching from potent P2Y12 inhibitor to clopidogrel [9]. Although the literature

regarding the appropriateness and safety of this practice is limited, studies reveal that switching to clopidogrel occurs mainly due to adverse effects, bleeding episodes, need for concomitant anticoagulation therapy and physician's discretion without any specific reason [4,10].

Aim of the present study is to investigate the adherence to the prescribed P2Y12 inhibitor in patients on DAPT within the first year after an ACS taking into account the switch between P2Y12 inhibitors. In addition, DAPT continuation beyond one year and single antiplatelet therapy (SAPT) selection after DAPT was studied.

2. Methods

This is a substudy of the IDEAL-LDL trial (Motivational Interviewing to support low-density lipoprotein cholesterol (LDL-C) therapeutic goals and lipid-lowering therapy compliance in patients with acute coronary syndrome, ClinicalTrials.gov Identifier: NCT02927808), which included 360 ACS patients discharged from the Cardiology department of AHEPA University Hospital in Thessaloniki, Greece, from June 2016 until April 2019 [11]. Briefly, IDEAL-LDL trial was an investigator-initiated, open-label, randomized controlled trial designed to evaluate whether adherence to lipid lowering therapy and LDL-C goal attainment among post-ACS patients is reinforced by an educational-motivational intervention. Informed consent was obtained from all patients at baseline. This study was conducted according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board.

2.1 Inclusion and exclusion criteria

Inclusion criteria of this post-hoc analysis demanded patients discharged on DAPT, which was defined as a combination of either ticagrelor, prasugrel or clopidogrel with concomitant aspirin therapy or, alternatively, clopidogrel combined with an oral anticoagulant, for patients who had an indication for oral anticoagulation [1]. DAPT form at discharge and specifically the use of potent P2Y12 inhibitors or clopidogrel was decided by the attending physician and not by IDEAL-LDL investigators. Exclusion criteria included patients receiving SAPT at discharge or patients with no social security number.

2.2 Data collection definitions

All data were collected by trained, independent medical researchers, via standardized inpatient interviews at the bedside and reviewing discharge letters. The following variables were collected from the IDEAL-LDL electronic database: baseline demographics, complete medical history (including family history of cardiovascular disease), clinical characteristics (age, gender, body mass index, cardiovascular comorbidities and risk factors and antiplatelet use before the index event), as well as ACS-related details (assigned in-hospital treatment, laboratory indices) and medication at discharge.

We used the Proportion of Days covered (PDC) as a drug adherence measure which is recommended by the International Society of Pharmacoeconomics and Outcomes Research. PDC is defined as the ratio of the number of days the patient has the drug on hand divided by the number of days the patient should actually have had the medication [12] and a patient was considered as adherent to the P2Y12 inhibitor, when the PDC was equal or over 80% throughout the first 12 months of DAPT. Drug adherence was assessed by reviewing the prescription filling via the national health insurance electronic prescription system based on the national security number of each patient. Accordingly, the days covered with therapy were counted as boxes multiplied with blisters per box and then divided by 365. For patients who died during the first year of therapy, the denominator was days alive.

We considered DAPT prolongation as the continuation of the DAPT beyond 12 months [13]. We also assessed the bleeding risk of patients, by calculating the PRECISE-DAPT score, which is a simple five-item risk score (including haemoglobin, age, white blood cell count, creatinine clearance and prior bleeding) and provides a standardized tool for the prediction of out-of-hospital bleeding during DAPT [14]. P2Y12 inhibitor intraclass switching was defined as any change from one antiplatelet agent to another during the follow-up after discharge. Switching from potent P2Y12 inhibitors to clopidogrel was regarded as downgrading and switching from clopidogrel to potent P2Y12 inhibitors as upgrading [9]. Dates of P2Y12 inhibitor discontinuation or switching, months of DAPT duration and the time point of transition to SAPT were recorded.

In addition, we recorded long-term data on major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke and hospitalization because of unstable angina. Myocardial infarction was defined in accordance with the Third Universal Definition of Myocardial Infarction [15]. Ischemic stroke was defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction with symptoms lasting $\geq$24 hours or leading to death [16]. Unstable angina was defined as the presence of acute chest pain associated with ST depression, or new onset of negative T waves, and no elevation of troponin [17]. Bleeding was classified according to the Thrombolysis In Myocardial Infarction (TIMI) classification into four categories [18]. Follow-up regarding clinical events was performed as defined per the IDEAL-LDL trial's protocol, one year after each subject's inclusion in the study and data was collected by in-person and/or telephone interviews. The extended follow-up data regarding clinical events were collected in April–May 2020 by telephone interviews and data concerning mortality were also obtained from the national health insurance electronic prescription system.

2.3 Study outcomes

The primary outcome of this study was to investigate whether there is a difference between the potent P2Y12 inhibitors and clopidogrel in terms of adherence to treatment as measured by the PDC, as well as predictors of adherence. Secondary outcomes included the prevalence of intraclass P2Y12 inhibitor switching, the prevalence of DAPT continuation and its predictors and SAPT selection after DAPT. Exploratory endpoints included the effect of DAPT selection (based on either potent P2Y12 inhibitors or clopidogrel) on clinical outcomes.

2.4 Statistical analysis

The results for the normal distribution continuous data are presented as mean and standard deviation (mean ± SD), while the results for the non-normal distribution data are presented with median and interquartile range [median (IQR)]. The Kolmogorov-Smirnov test was used to assess for normality. Continuous variables were compared using the Student's t test for parametric or Mann–Whitney U test for non-parametric data. The Chi-square test was used to analyze differences in qualitative variables. McNemar's test was used to compare the differences between the adherence to the first and second P2Y12 inhibitor in patients who switched during DAPT. After univariate logistic regression, variables presenting p-values < 0.1 were included in a multivariable logistic regression model and adjusted odds ratios (aOR) were computed for the adherence to the P2Y12 inhibitor and continuation of DAPT. The model was tested for influential values (according to the Cook's distance and the absolute standardized residuals and using 3 as the reference value) and the multicollinearity assumption (by computing variance inflation factors and a value >5 indicated a problematic amount of multicollinearity). The Kaplan-Meier method was used to conduct a survival study between the two groups of DAPT treatment (ticagrelor/prasugrel or clopidogrel) for MACE, all-cause mortality and bleeding, and the log-rank test was accordingly used. Cox-proportional hazard models were used to calculate hazard ratios (HR). To account for confounders, baseline variables with $p < 0.1$ in the univariate Cox regression analysis for each outcome were added to the multivariate Cox regression model. The proportional hazards assumption was tested by comparing log(-log) curves graphically and using a goodness-of-fit test based on scaled Schoenfeld residuals. The linearity of the Cox regression model's continuous variables was checked by visualizing martingale residuals. A two-sided p-value < 0.05 was used to describe statistical significance. The R Software (R Project for Statistical Computing, version 3.6.3.) was used for all analyses.

3. Results

From a total of 360 patients with ACS who were included in the main trial, 16 patients were excluded from the analysis. Exclusion criteria included patients receiving SAPT at discharge (n = 9) or patients with no social security number (n = 7). The remaining subjects (n = 344) were grouped into two categories according to the potency of P2Y12 inhibitor treatment; 178 patients were discharged on potent P2Y12 inhibitor (172 on ticagrelor and 6 on prasugrel) and 166 patients on clopidogrel (Fig. 1). Table 1 shows the baseline characteristics of the two groups. Ticagrelor or prasugrel-treated patients were more likely to be younger men, smokers and to have a family history of coronary artery disease (CAD), whereas hypertension, dyslipidaemia and history of cardiovascular disease (CVD) were more prevalent among clopidogrel-treated patients. STEMI and PCI treatment were more common in patients receiving potent P2Y12 inhibitors. Patients who were already on antiplatelet treatment before the event were more likely to receive clopidogrel at discharge.
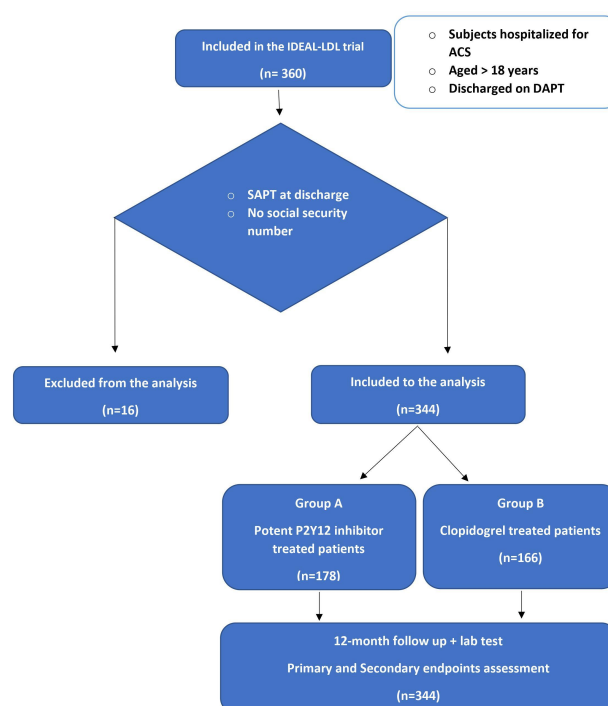

Fig. 1. Flowchart of the studied population.

3.1 Adherence to P2Y12 inhibitor treatment

Overall adherence to P2Y12 inhibitor therapy was present in 251 out of 344 patients (73%). Adherence in the potent P2Y12 inhibitor and in the clopidogrel group was observed in 140 out of 178 (78.7%) and 111 out of 166 (66.9%) patients ($p = 0.016$), respectively. In the univariate logistic regression model, clopidogrel therapy was associated with lower probability of adherence as measured by PDC (OR = 0.58, 95% CI = 0.36–0.93). However, after multivariable

Table 1. Baseline characteristics of the included population.

Characteristic	Overall, N = 344	DAPT based on potent P2Y12 inhibitor, N = 178	DAPT based on clopidogrel, N = 166	p-value[1]
Age, Median (IQR)	60 (53, 70)	58 (51, 67)	62 (56, 76)	<0.001
Gender, n (%)	65 (18.9%)	23 (12.9%)	42 (25.3%)	0.003
BMI, Median (IQR)	27.5 (25.2, 30.9)	27.2 (25.2, 29.9)	27.9 (25.2, 31.1)	0.3
Smoking, n (%)	181 (52.6%)	107 (60.1%)	74 (44.6%)	0.004
Hypertension, n (%)	189 (54.9%)	87 (48.9%)	102 (61.4%)	0.019
Diabetes, n (%)	95 (27.6%)	43 (24.2%)	52 (31.3%)	0.14
Family history of CAD, n (%)	152 (44.2%)	91 (51.1%)	61 (36.7%)	0.007
Dyslipidaemia, n (%)	144 (41.9%)	64 (36.0%)	80 (48.2%)	0.022
Prior CVD, n (%)	118 (34.3%)	46 (25.8%)	72 (43.4%)	<0.001
Prior PAD, n (%)	32 (9.3%)	13 (7.3%)	19 (11.4%)	0.2
Prior stroke, n (%)	23 (6.7%)	9 (5.1%)	14 (8.4%)	0.2
Prior CAD, n (%)	91 (26.5%)	34 (19.1%)	57 (34.3%)	0.001
Prior MI, n (%)	74 (21.5%)	27 (15.2%)	47 (28.3%)	0.003
Prior use of antiplatelets, n (%)	78 (22.7%)	31 (17.4%)	47 (28.3%)	0.016
PRECISE score, Median (IQR)	15 (8, 23)	13 (7, 21)	18 (10, 24)	<0.001
STEMI, n (%)	193 (56.1%)	119 (66.9%)	74 (44.6%)	<0.001
PCI treatment, n (%)	283 (83.0%)	164 (92.7%)	119 (72.6%)	<0.001
Total cholesterol, Median (IQR)	172 (146, 203)	174 (152, 206)	170 (139, 196)	0.043
Triglycerides, Median (IQR)	130 (96, 178)	119 (94, 174)	140 (99, 187)	0.082
HDL-C, Median (IQR)	38 (32, 46)	39 (33, 45)	37 (32, 47)	0.6
LDL-C, Median (IQR)	102 (80, 129)	107 (87, 134)	98 (73, 122)	0.009
Troponin (maximum value), Median (IQR)	1274 (288, 3742)	1915 (602, 4526)	786 (157, 3123)	<0.001
GFR, Median (IQR)	84 (66, 96)	87 (72, 97)	80 (61, 94)	0.01
CKD stage, n (%)				0.025
1	136 (39.5%)	78 (43.8%)	58 (34.9%)	
2	150 (43.6%)	81 (45.5%)	69 (41.6%)	
3	46 (13.4%)	16 (9.0%)	30 (18.1%)	
4	5 (1.5%)	1 (0.6%)	4 (2.4%)	
5	7 (2.0%)	2 (1.1%)	5 (3.0%)	
BNP, Median (IQR)	908 (342, 2320)	925 (391, 2215)	834 (280, 2937)	0.8
Unknown	94	47	47	
Anticoagulation at discharge, n (%)	35 (10.2%)	13 (7.3%)	22 (13.3%)	0.07

[1] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test. DAPT, dual antiplatelet therapy; BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; PAD, peripheral artery disease; MI, myocardial infraction; STEMI, ST elevated myocardial infarction; PCI, percutaneous coronary intervention; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; CKD, chronic kidney disease; BNP, brain natriuretic peptide.

adjustment for potential confounders, including P2Y12 inhibitor switching during the first year of therapy, concomitant anticoagulation therapy, history of CVD and PCI treatment of the index event, there was no difference observed in adherence between potent P2Y12 inhibitor and clopidogrel therapy (OR = 0.98, 95% CI = 0.55–1.74) (Table 2). A sensitivity analysis excluding patients that switched their P2Y12 inhibitor during therapy (i.e., patients that received a stable P2Y12 inhibitor therapy) also did not reveal any differences in adherence between potent P2Y12 inhibitor and clopidogrel treated patients. A sensitivity analysis excluding patients receiving prasugrel was performed (due to

the limited number of prasugrel patients, n = 6) and also did not reveal any differences. In the multivariate model, history of CVD was a negative predictor of adherence, whereas patients treated with PCI were 2.5-fold more likely to be adherent.

3.2 Switching of the P2Y12 inhibitor and DAPT prolongation

Switching between P2Y12 inhibitors occurred in 97 patients (96.9% downgrading, 3.2% upgrading), of which 62 switched within the first year of treatment (96.8% downgrading, 3.2% upgrading). In patients who switched during

Table 2. Multivariate logistic regression of adherence to the P2Y12 inhibitor therapy.

Predictor variables	Crude OR (95% CI)	Adjusted OR (95% CI)	*p*-value (Wald's test)
Potent P2Y12 inhibitor vs clopidogrel	0.58 (0.36–0.93)	0.98 (0.55–1.74)	0.943
Switching at 1st year (Yes vs No)	2.19 (1.06–4.52)	1.8 (0.8–4.09)	0.157
Concomitant anticoagulation therapy (Yes vs No)	0.47 (0.23–0.97)	0.48 (0.23–1.03)	0.061
Prior history of CVD (Yes vs No)	0.42 (0.26–0.69)	0.51 (0.31–0.86)	0.011
PCI treatment of the index event (Yes vs No)	3.01 (1.68–5.39)	2.58 (1.38–4.82)	0.003

CVD, cardiovascular disease; PCI, percutaneous coronary intervention.

Table 3. Multivariate logistic regression of dual antiplatelet therapy prolongation.

Predictor variables	Crude OR (95% CI)	Adjusted OR (95% CI)	*p*-value (Wald's test)
Gender (Female vs Male)	0.55 (0.31–1)	0.43 (0.21–0.9)	0.024
Switching at 1st year (Yes vs No)	1.78 (0.9–3.52)	1.66 (0.82–3.34)	0.159
BMI (continuous variable)	0.95 (0.9–1)	0.96 (0.91–1.02)	0.215
GFR (continuous variable)	1.01 (1–1.02)	1.01 (1–1.03)	0.054
PCI treatment of the index event (Yes vs No)	1.79 (0.96–3.32)	1.5 (0.78–2.89)	0.224
Precise score (continuous variable)	1 (0.98–1.03)	1.03 (0.99–1.06)	0.107
MACE at 1st year (Yes vs No)	0.77 (0.23–2.61)	0.71 (0.19–2.6)	0.605

BMI, body mass index; GFR, glomerular filtration rate; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

the first year there was no difference between the adherence to the first and to the second P2Y12 inhibitor. The median duration of DAPT was 19 months (IQR 12–30 months) in the potent P2Y12 inhibitor group and 17 months (IQR 8–29 months) in the clopidogrel group. After the exclusion of patients who died during the first 12 months of follow-up (n = 16 patients), DAPT continuation over 12 months was detected in 72% of patients, and particularly in 74.9% and 68.6% of patients receiving potent P2Y12 inhibitor or clopidogrel, respectively (*p* = 0.2). Predictors of DAPT continuation were examined in a multivariate logistic regression model and after adjustment for switching at first year, gender, BMI, GFR, PCI treatment, PRECISE score and MACE during the first year of DAPT, only females presented 57% less chance to prolong the DAPT (Table 3).

Antithrombotic strategy at the end of follow-up was also investigated (Fig. 2); 79 (44.4%) of potent P2Y12 inhibitor-treated patients continued antiplatelet therapy with aspirin, 17 (9.6%) with clopidogrel, 1 (0.6%) with ticagrelor, no one switched to anticoagulation therapy. Lastly, 76 (42.7%) patients continued DAPT until the end of follow-up, 42 (23.6%) of whom received a single-pill combination (clopidogrel and aspirin). In the clopidogrel-treated group, 51 (30.9%) of patients received SAPT with aspirin, 26 (15.8%) with clopidogrel, 1 (0.6%) with ticagrelor, 7 (4.2%) received anticoagulants. Lastly, 63 (38.2%) patients continued indefinite DAPT, 26 (15.7%) of whom received a single-pill combination (clopidogrel and aspirin).

3.3 Clinical outcomes

The median duration of the long-term follow up of the patients was 40 (31–45) months. In the univariate Cox regression analysis, occurrence of bleeding events did not differ between the two groups (HR = 1.90, 95% CI = 0.86–4.19), whereas the risk of MACE (HR = 2.23, 95% CI = 1.16–4.29) and the risk of all-cause mortality (HR = 3.75, 95% CI = 1.60–8.79) were increased in the clopidogrel-treated group (Fig. 3). However, in the multivariate Cox regression model these differences were no longer significant.

4. Discussion

The main finding of this observational study including patients after ACS is that there are no differences between potent P2Y12 inhibitors and clopidogrel in terms of adherence, after adjusting for switching between P2Y12 inhibitors during the first year. History of CVD was a predictor of reduced adherence to the P2Y12 inhibitor, whereas PCI treatment increased the probability of a patient being adherent. More than 7 out of 10 patients continued DAPT beyond 12 months with almost 4 out of 10 continuing it indefinitely. Female gender was an independent negative predictor of DAPT prolongation.

The initial choice of the P2Y12 inhibitor as well as switch, stop or continuation of the DAPT was based on the physician's decision and clinical indications. We observed that potent P2Y12 inhibitors were prescribed to younger patients with less comorbidities and more severe disease, as indicated by the higher STEMI and PCI rates and higher maximum troponin values, whereas patients with comor-
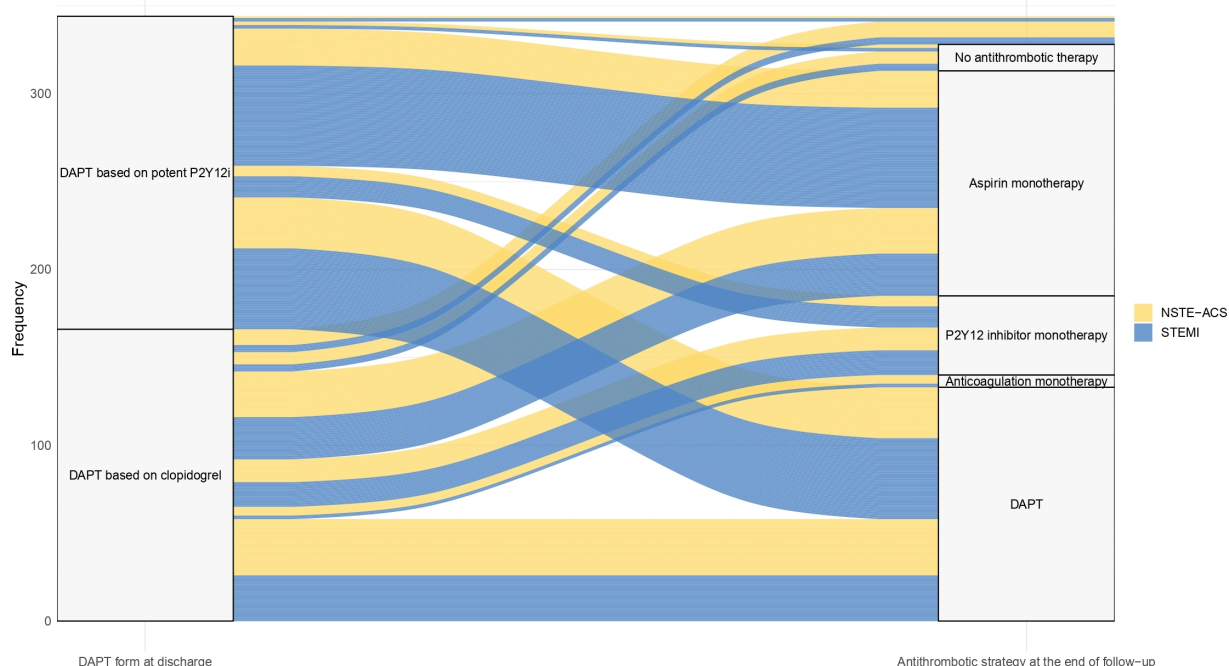
Fig. 2. Antithrombotic strategies after discharge and at the end of follow-up in patients with acute coronary syndrome. The alluvial plot depicts the number of patients to each antithrombotic strategy at discharge (DAPT based on a potent P2Y12 inhibitor or on clopidogrel) and their transition to various antithrombotic strategies at the end of follow-up. The patient sample is stratified by the type of the index acute coronary syndrome. DAPT, dual antiplatelet treatment; NSTE-ACS, non-ST elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction.
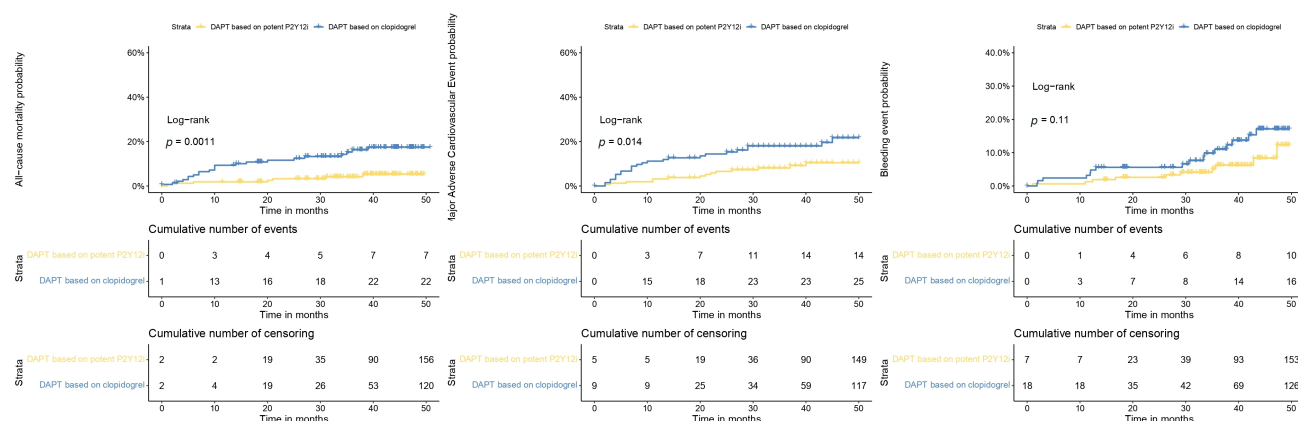

Fig. 3. Kaplan-Meier curves of major adverse cardiovascular events, all-cause mortality and bleeding events based on the form of dual antiplatelet therapy (based on either ticagrelor or clopidogrel). The curves depict the probability of each respecting event at a respective time interval. The two risk tables below each Kaplan-Meier show the absolute number of cumulative events and cumulative number of censored observation at 10-month intervals. DAPT, dual antiplatelet therapy; MACE, major adverse cardiovascular events.

bidities, such as hypertension, dyslipidaemia and history of CVD and those with have a history of antiplatelet treatment usually received clopidogrel. The cost of the pharmaceutical preparations is also considered a significant factor for the final decision, due to the need for long-term medication. Clinicians seemed to prefer treating patients with a pure CAD background with an aggressive anti-ischaemic

strategy involving ticagrelor or prasugrel, whereas patients affected by multiple diseases were treated with clopidogrel. Resistance to clopidogrel could be a reason that influences the physician's choice for prescribing a P2Y12 inhibitor, however testing for it is not widely implemented in clinical practice. Hence, clopidogrel treated patients were more likely to have MACE events and a higher probability of all-

cause mortality, however these differences were no longer significant after adjustment for other important prognostic covariates, such as cardiovascular comorbidities and choice of invasive management of the index event.

Although dual antiplatelet therapy is one of the most extensively researched treatment methods, adherence to DAPT and its predictors is a topic that has not been yet thoroughly examined. Premature discontinuation of DAPT treatment during the first 12 months after the ACS event is not uncommon and has been so far linked to several factors. Current studies suggest that ticagrelor and prasugrel-treated patients are more prone to premature discontinuation than clopidogrel-treated patients [4–6,8,19,20]. In contrast, in the univariate analysis, patients treated with potent P2Y12 inhibitors as a form of DAPT were found to be more adherent than the patients treated with clopidogrel in our study. This could be explained by the fact that patients receiving clopidogrel are usually treated either with polypharmacy or with long-time antiplatelet therapy, which is a significant reason for decreased adherence to the P2Y12 inhibitor. Previous studies have attempted to examine predictors of low adherence to clopidogrel treatment concluding to various factors [21,22]. However, after multivariate adjustment, this difference was not significant anymore. In agreement with our results, previous studies indicate PCI treatment as a predictor of DAPT adherence [6]. In our study, concomitant anticoagulant therapy was not an independent predictor of adherence (upper 95% CI boundary was 1.03), however the effect measure was heavily on the side of reduced adherence, in line with the findings in the ATLANTIS-SWITCH study [4]. Nonetheless, concomitant anticoagulation has been also suggested to be a predictor of DAPT adherence [6]. In contrast with other studies, history of CVD was also linked to premature DAPT discontinuation [7].

Switching between P2Y12 inhibitors is a common practice in DAPT even though specific guidelines have not been yet established. Switching was frequent, since roughly 1 out of 5 switched during the first year of follow-up and approximately reached 30% at the end of follow-up. Our results, in accordance with existing literature, show that switching from potent P2Y12 inhibitors to clopidogrel within the first year of follow-up is more common than vice-versa [8,10]. Other specific predictors for switching were not found. De-escalation has become more common after the publication of TOPIC trial, which associated this strategy with a decrease in bleeding risk without an increase in ischemic events. In the TOPIC trial, it has been shown that switching from ticagrelor to clopidogrel one month after ACS and reducing the number of tablets in DAPT lead to better adherence to therapy [23].

Current published data report positive yet inconclusive evidence regarding the prognostic effects of switching to clopidogrel [24,25]. Some studies enhance the argument of reduction in bleeding events with or without improved clinical efficacy [26,27], while others indicate that there is non-significant difference in terms of major bleeding, cardiovascular events and all-cause death [28]. In this cohort we observed that the occurrence of clinical outcomes such as bleeding events, all-cause mortality and MACE did not differ in terms of DAPT selection, although our study was not powered to show differences in clinical outcomes.

Of note, 7 to 10 patients continued with DAPT after the first 12 months and in fact, the median duration of DAPT was 50% longer than that suggested from the current guidelines. In addition, 4 to 10 patients continued with DAPT until the end of the observational period. We observed that only few patients stopped the antithrombotic treatment completely, but none of them before the first 12 months after discharge. A difference was detected between female and male patients, since the latter continued indefinitely with DAPT more often. This finding indicates a more aggressive treatment strategy for men and showcases the well-known gender inequalities in treating CVD [29].

5. Limitations

Our study has several limitations inherent to its observational design. Although our data provide a reflection of routine clinical practice, conclusions are limited by the small sample size of the study. There is also a selection bias as not every consecutive patient suffering from an ACS in our hospital was included in the study. In addition, rates of adherence to aspirin were difficult to obtain though the national prescription system since it is frequently administered as an over-the-counter medication, and, hence, record of adherence to DAPT overall was not feasible. Moreover, discontinuation rates due to adverse events, physician's choice, as well as the specific adverse events were not recorded. Therefore, we did not record whether switching was due to patient experiencing adverse events, existing comorbidities, the physician's choice or socioeconomic reasons. Rates of prasugrel use were low in the study and results may be more generalizable for ticagrelor-treated patients. However, it was considered more appropriate to include all patients receiving a potent P2Y12 inhibitor in the one group as the aim of the study was to compare the adherence of DAPT in terms of the potency of inhibitors and also the sensitivity analysis excluding the prasugrel treated patients did not reveal any difference. Finally, it is worth mentioning that standard DAPT duration of 12 months may not be the optimal duration of DAPT for all ACS patients and especially those who lie on the spectrum ends of bleeding and thrombotic risk, but however currently receives the strongest recommendation I by the ESC Guidelines. Despite these limitations, we believe that the conclusions of the study are of great interest. This study, being single-centre, has the advantage of the homogeneity in patient care and also, data were collected in the context of the randomized, prospective IDEAL-LDL clinical trial.

6. Conclusions

The present study did not find any difference regarding the adherence to DAPT in terms of the potency of the prescribed P2Y12 inhibitor, after adjusting for potential confounders. History of CVD and invasive approach of the index event were negative and positive independent predictors of adherence to the P2Y12 inhibitor, respectively. Switching between P2Y12 inhibitors was common and de-escalation was the most frequent switching strategy. Prolonged DAPT was observed in the majority of patients and only the female gender was associated with reduced chance to prolong the DAPT. Overall, the results of our study do not deviate from the current literature, however they enhance the belief that further research is needed in order to reach definite conclusions regarding the predictors of DAPT adherence and premature DAPT discontinuation.

Author contributions

OKour, OKons, ITF, SZ, HK and GG contributed to the conception or design of the work. OKour, OKons, ITF, SZ, GP, SG, AVT, CT, EV, AB, KS, TP, AD contributed to the acquisition, analysis, or interpretation of data for the work. OKour, OKons, ITF and SZ drafted the manuscript. HK and GG critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Ethics approval and consent to participate

Approval obtained from the Institutional Review Board of the AHEPA University Hospital Thessaloniki (approval number: 22904/25.5.2016). Informed consent was obtained from all subjects involved in the IDEAL-LDL trial (NCT02927808).

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Conflict of interest

The authors declare no conflict of interest. George Giannakoulas is serving as one of the Editorial Board members of this journal. We declare that George Giannakoulas had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Salvatore De Rosa.

Data availability statement

All data are available upon request.

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