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Impact of prolonged dual antiplatelet therapy after acute myocardial infarction on 5-year mortality in the FAST-MI 2005 registry

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ABSTRACT

Background: We document dual antiplatelet therapy (DAPT) use from discharge to 4 years after acute myocardial infarction (AMI), and investigate whether prolonged DAPT (beyond 1 year) is related to 5-year mortality.
Methods: The French Registry of Acute ST-elevation or non-ST-elevation Myocardial Infarction (FAST-MI 2005) included 3670 patients with AMI in 223 French centres. We identified predictors of DAPT (aspirin + clopidogrel) beyond 1 and 2 years, and relation with all-cause 5-year mortality.
Results: Among 3319 (96%) patients with discharge data, 2432 (73%) had DAPT, 582 (17%) single antiplatelet therapy (SAPT), and 305 (9%) no antiplatelet treatment. DAPT decreased from 75% at 1 year to 29% at 4 years, with a corresponding increase in SAPT ($p < 0.05$ for trend). Patients with DAPT were more often male, treated with a drug-eluting stent (DES), and without oral anticoagulants. Independent predictors at 1 year of prolonged DAPT were age < 75 years, in-hospital bleeding, history of MI, use of DES, discharge use of beta-blockers or statins and no chronic anticoagulation. Predictors at 2 years were age < 75 years, male gender, previous MI, diabetes, DES implantation, no chronic oral anticoagulation. By multivariate analysis, there was no difference in 5-year mortality between those on SAPT vs DAPT at 1 year. DAPT at 2 years was also not significantly related to 5-year mortality (Hazard Ratio 1.3, 95% CI [0.9; 1.8], $p = 0.21$).
Conclusion: Prolonged DAPT in selected AMI patients, observed in 47% at 1 year and 21% at 2 years, had no impact on 5-year mortality. These findings do not support the use of DAPT beyond 1 year after an initial ACS.

1. Introduction

Based on the results of randomized trials [1,2], current guidelines recommend dual antiplatelet therapy (DAPT) for one year after acute coronary syndrome (ACS), in the absence of a high bleeding risk [3–5], regardless of the type of revascularization used. Nevertheless, the optimal duration of DAPT after ACS is not clearly defined. Registry studies have shown that, in patients with ACS and stent implantation, premature discontinuation of DAPT was associated with a high risk of recurrence of ischemic events [6]. Recent randomized studies have shown that 6 months of DAPT was sufficient after implantation of a "new generation" drug eluting stent [7–10]. Conversely, the randomized DAPT trial very recently reported that prolonged DAPT, beyond 12 and up to 30 months, was associated not only with less stent thrombosis and myocardial infarction, but also with more bleeding [11]. Lastly, in a meta-analysis that included 139,000 patients and compared various DAPT durations (ranging from 3 to 30 months), a trend towards higher mortality was associated with prolonged DAPT [12]. Thus, the clinical benefit of prolonging DAPT beyond one year remains controversial. Using data from the French Registry of Acute ST-elevation or non-

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ST-elevation Myocardial Infarction (FAST-MI) 2005 registry [13], we aimed to document the use of DAPT from hospital discharge up to 4 years after acute myocardial infarction (MI), and to investigate whether prolongation of DAPT beyond 1 year is related to mortality.

2. Methods

2.1. Patient selection

The population and methods of the FAST-MI 2005 registry have previously been described elsewhere [13] (NCT01237418). Briefly, the objective of the registry was to evaluate MI management in "real life" practice, and to measure the impact of this management on acute and long term outcomes in patients admitted to coronary care units for MI over a one month period in France, irrespective of the type of institution to which the patients were admitted (university teaching hospitals, public non-academic hospitals or private clinics). Among the 374 centres in France that treated patients with ACS, 223 (60%) participated in the registry. One physician responsible for the study was recruited at each centre and collected data for every patient meeting the inclusion criteria during the inclusion period. Patient care at each centre was performed according to usual practice. The study population for this analysis comprised the SAPT group, namely patients who continued with a single antiplatelet agent after having completed one year of DAPT (from discharge to one year); and secondly, the DAPT group, comprising patients discharged with DAPT and still taking DAPT more than one year after discharge. We excluded patients who underwent surgical coronary revascularization during the index hospital stay.

2.2. Data collection

For each patient, we recorded: cardiovascular and non-cardiovascular previous history, risk factors (smoking status, hypertension or treated hypertension, dyslipidemia or treated dyslipidemia, family history, diabetes mellitus), and clinical course during hospital stay, including symptoms, Killip class, therapeutic management during the first 48 h of hospital stay (including PCI, thrombolysis), and management at discharge. All treatments, including antiplatelet agents, were collected prospectively at different timepoints, namely before admission, in the pre-hospital setting, during the first 48 h, and at discharge.

2.3. Follow-up

Follow-up was centralized at the French Society of Cardiology and completed by dedicated research technicians. Vital status was assessed by consulting data on deaths at the registrar's offices of the patient's birthplace, by writing to the general practitioner and/or cardiologist, or by direct contact with the patients themselves. Prescriptions during follow-up were recorded between 6 and 18 months ("1 year"), 18 and 30 months ("2 years"), 30 and 42 months ("3 years") and 42 and 54 months ("4 years"). Single antiplatelet therapy (SAPT) was defined as the prescription of only one of clopidogrel or aspirin. Since, at the time of inclusion, only clopidogrel was available for P2Y12 platelet receptor inhibition, DAPT was defined as the prescription of aspirin (75 to 160 mg per day) plus clopidogrel (75 mg/day). Two time-points were used to define "prolonged DAPT": at one year (namely between 6 and 18 months) and at two years (between 18 and 30 months). The outcome variable was all cause mortality at five years. A composite clinical endpoint was defined as occurrence of death, or re-hospitalization for acute myocardial infarction, or stroke. Repeat coronary revascularization was also recorded. The rate of patients lost to follow-up was 0.3% at one year, 2% at 3 years and 5% at 5 years. The follow-up was limited to 3 years for the combined clinical endpoint.

3. Statistical analysis

Categorical variables are presented as number (percentage); continuous, non-normally distributed variables as median [interquartile range (IQR)], and continuous, symmetrically distributed variables as mean ± standard deviation (SD). Patient characteristics and management were compared using Pearson's Chi squared test and Wilcoxon's rank sum test, as appropriate.

Logistic regression analysis was used to assess independent predictors of DAPT at one and two years. Variables entered into the multivariate models were: type of infarction (STEMI or NSTEMI), age, gender, cardiovascular risk factors, previous infarction, stroke or heart failure, history of cancer or chronic pulmonary disease, estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula, clinical conditions at admission (heart rate, systolic blood pressure, Killip class), pre-hospital, acute and discharge treatments, and treatment at one year (beta-blockers, ACE inhibitors, statins and oral anticoagulants), use of coronary angiography, percutaneous revascularization using a drug eluting stent (DES) or bare metal stent (BMS) and major bleeding during hospitalization.

Cox's proportional hazards model was used to compare groups according to prolonged DAPT use, adjusted for the same variables as above, for mortality at 5 years. Analyses were repeated after exclusion of patients who had a non-fatal event (re-hospitalization for MI, stroke or repeat revascularization). Interactions were tested using the Breslow–Day test for subgroups known to be at higher risk for thrombotic events, namely patients aged >75 years, patients with diabetes, implantation of a DES (versus BMS), patients with STEMI (versus NSTEMI).

As a complementary analysis, we performed a matched-pairs comparison to assess the impact of prolonged DAPT on outcomes after one year and after 2 years. Matching was performed on a propensity score (propensity to be treated with prolonged DAPT), calculated by multivariate logistic regression. Matched pairs were compared by conditional logistic regression. Survival curves were generated using the Kaplan–Meier method and compared with the Log Rank test.

For all tests, $p < 0.05$ was considered significant. All analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

4. Funding

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5. Results

5.1. Study population and prescription of DAPT over 4 years

Among the 3670 patients included in the FAST-MI 2005 registry, 207 (6%) died during hospitalization and 144 (4%) underwent surgical revascularization during hospitalization and were excluded. A total of 3319 (96%) were discharged alive with available data about discharge treatment; 2432 (73%) had DAPT, 582 (17%) had SAPT, and 305 (9%) had no antiplatelet treatment. Treatment prescriptions were available for 90% at one year, 77% at 2 years, 62% at 3 years and 60% at 4 years (Fig. 1). There was no difference in baseline characteristics, conditions at admission or acute management, between patients in whom follow-up prescriptions were available versus those with no available follow-up prescription. The proportion of patients receiving DAPT decreased from 75% at 1 year to 29% at 4 years, with a corresponding