Long term dual antiplatelet therapy after myocardial infarction: retrospective analysis in an outpatient population

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Abstract

Long term treatment with ticagrelor 60 mg and low-dose aspirin are indicated after acute coronary syndrome (ACS). We retrospectively reviewed aggregate data of 187 patients (155 males and 38 females) (mean age 63.8±9 years) in follow up after ACS with at least one high risk condition (multivessel disease, diabetes, glomerular filtration rate (GFR) <60 ml/min, history of prior myocardial infarction, age >65 years) treated with ticagrelor 60 mg twice daily (after 90 mg twice daily for 12 months). The results were compared with findings (characteristics of the patients at baseline, outcomes, bleeding) of PEGASUS-TIMI 54 trial and Eu Label. The high-risk groups were represented as fol-

lows: multivessel disease 105 patients (82%), diabetes 63 patients (33%), GFR <60 mL/min 27 patients (14%), history of prior MI 33 patients (17%), >65 year aged 85 patients (45%). Treatment was withdrawn in 7 patients: 3 cases showed atrial fibrillation and were placed on oral anticoagulant drugs, one developed intracranial bleeding, in three patients a temporary withdrawal was due to surgery (1 colon polyposis and 2 cases of bladder papilloma). Chest pain without myocardial infarction occurred in 16 patients (revascularization was required in 9 patients). Dyspnea was present in 15 patients, but was not a cause for discontinuation of therapy. Long term treatment with ticagrelor 60 mg twice daily plus aspirin 100 mg/day showed a favorable benefit/risk profile after ACS. In this study all patients had been given ticagrelor 90 mg twice daily for 12 months and the 60 mg twice daily dosage was started immediately thereafter, unlike PEGASUS-TIMI 54 trial in which it was prescribed within a period ranging from 1 day to 1 year after discontinuation of the 90 mg dose. This makes our results more consistent with current clinical practice. However, a careful outpatient follow-up and constant counseling are mandatory to check out compliance to therapy and adverse side effects.

Introduction

Ticagrelor, orally administered $P2Y_{12}$ inhibitor is indicated in a long-term regimen at dose of 60 mg twice daily in co-administration with low-dose aspirin 75–150 mg/day for the secondary prevention of atherothrombotic events in high-risk patients with a history of myocardial infarction (MI) occurred at least 1 year. Evidence is based on the results of the PEGASUS-TIMI 54 trial [1] that compared ticagrelor with placebo (in association with aspirin) in stable patients after MI occurred 1–3 years prior to enrolment with high risk of atherothrombotic events. Subsequently treatment with ticagrelor 60 mg twice daily, as recommended in the European (Eu) Label [2], initiated up to 2 years from the myocardial infarction, or within 1 year after stopping previous treatment with 90 mg twice daily, confirmed a relative risk reduction in cardiovascular (CV) death, myocardial infarction (MI), or stroke. Long term dual antiplatelet therapy (DAPT) was well tolerated, but the risk of thrombolysis in myocardial infarction (TIMI) major bleeding (primary safety endpoint) was significantly increased in ticagrelor 60 mg twice daily *versus* placebo recipients; however, the risk appeared to decline after the first year of therapy [3]. The increased use of ticagrelor was not associated with intracranial hemorrhage (ICH), whereas age and prior cardiovascular morbidities were related to the risk of ICH and a significant interaction was found [4].

Aim of study

To compare the results of PEGASUS-TIMI 54 trial and Eu Label studies with those of our clinical experience in a secondary prevention outpatient clinic.

Methods

We retrospectively reviewed data of 187 consecutive patients without exclusion criteria, scheduled from September 2017 to July 2020 (149 males and 38 females) (mean age 63.8±9 years with at least one high risk condition (multivessel disease, diabetes, glomerular filtration <60 ml/min, history of prior MI, age >65 years) attending our outpatient clinic after ACS. All patients had been one year on DAPT with ticagrelor 90 mg twice daily and aspirin 100 mg/day. Thereafter, the patients had been shifted to a long term DAPT with ticagrelor 60 mg twice daily and aspirin 100 mg/day according to clinical indications (presence of at least one of the following high-risk conditions: multiple vessel disease, diabetes, GFR <60 ml/min, previous myocardial infarction, age >65 years). According to hospital protocol, after discharge from hospital patients were seen at day 30 and after 3 months, then at six-month intervals. The intensity of bleeding was assessed according to the TIMI score [5]. Any overt bleeding event that did not meet the criteria of major and minor was defined "minimal" [5]. The results were compared with results of PEGASUS-TIMI 54 trial and Eu Label.

Statistical analysis

For the comparison between independent samples, the prevalence zeta test was used for the values expressed as a percentage and the Student's *t*-test for the values expressed as means. A p≤0.05 value was considered statistically significant.

Results

The median duration of follow-up after the start of treatment with the 60 mg dosage was 17.3±9.4 months. The characteristics of patients are shown in Table 1. The high-risk conditions were represented as follows: 155 patients with multiple vessel disease (82%), 63 patients with diabetes (33%), 27 patients with chronic renal failure (glomerular filtration rate (GFR) <60 ml/min) (14%), 33 patients with previous myocardial infarction (17%), 85 patients with age >65 years (45%). Tables 2 and 3 compare the clinical events and bleeding of the groups, respectively. Chest pain with no evidence of ECG and troponin evidence of MI occurred in 16 patients (8.5%). After angiography, however revascularization was required in nine of 16 patients. The characteristics of bleedings are shown in Tables 4 and 5. DAPT was stopped in 7 patients: onset of atrial fibrillation and prescription of oral anticoagulant (3 cases), intracranial hemorrhage which left no clinical reliquates (1 case), and in 3 cases a temporary withdrawal was necessary for surgery procedure (1 case of colon polyposis and 2 of bladder papilloma). Adverse events are report-

Table 1. Characteristics of the patients at baseline.

Characteristic	S. G. BOSCO 187 patients n (%)	PEGASUS 7045 patients n (%)	p	Eu Label 5388 patients n (%)	p
Age (yrs)	63.8±9	65.2 ± 8.4	0.049	65.1 ± 8.5	0.049
Female sex	38 (20,3)	1661 (23,9)	0,248	1267 (23.9)	0,248
Weight (kg)	82.4 ± 9,7	82.0 ± 17	0.159	81.9 ± 17.1	0.481
Hypertension	153 (81.8)	5461 (77.5)	0.159	4183 (77.65)	0.168
Hypercholesterolemia	55 (29.4)	5380 (76.4)	<0.001	4122 (76.52)	<0.001
Current smoker	27 (14.4)	1206 (17.1)	0.326	939 (17.43)	0.279
Diabetes mellitus	63 (33.6)	2308 (32.8)	0.815	1774 (32.93)	0.383
GFR<60 ml/min	27 (14.4)	1547/6955 (22.2)	0.01	1178 (22.16)	0.011
History of PCI	178 (95.1)	5879/7044 (83,5)	<0.0001	4584 (85.09)	0.0001
Multivessel coronary artery disease	155 (82.8)	4190/7042 (59.5)	<0.0001	3313 (61.5)	<0.0001
Prior myocardial infarction	33 (17.6)	1168 (16.6)	0.713	884 (16.41)	0.657
Peripheral-artery disease	17 (9.0)	368 (5.2)	<0.0001	301 (5.59)	<0.0001
Years since myocardial infarction	1	1.7 (1.2-3.2)	————	1.5 (1-2)	————
STEMI	50 (26.7)	3757/7035 (53.4)	<0.001	2872 (53.35)	<0.001
NSTEMI	138 (73.7)	2842/7035 (40.4)	<0.0001	2209 (41.04)	<0.0001
Treatment with aspirin	187 (100)	7036 (99.9)	0.665	5681 (99.87)	0.540
Treatment with statin	184 (98.3)	6495 (92.2)	0.0018	4999 (92.78)	0.0032
Treatment with beta-blocker	151 (80.7)	5796 (82.3)	0.566	4462 (82.81)	0.446
Treatment with ACE inhibitor or ARB	155 (82.8)	5631 (79.9)	0.332	4310 (79.99)	0.332

PCI, percutaneous coronary intervention; GFR, glomerular filtration rate; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; ACE, angiotensin-converting enzyme; ARBS, angiotensin-receptor blocker.

ed in Table 6. Dyspnea (described as sudden and unexpected starvation of air or unsatisfactory inspiration) was reported in 15 patients (8%), but it was judged to be non-limiting and did not cause treatment discontinuation. All patients received pump inhibitors for gastric protection.

Discussion

Multivessel patients are less represented in our study as compared with PEGASUS TIMI 54 and Eu Label. This is only partially explained by the higher percentage of males in our study. Hypercholesterolemic patients are less represented in our study probably because undeclared statin treatment at admission in intensive coronary unit (ICU).

Previous clinical practice observations had confirmed safety of the long term DAPT with ticagrelor [5]. The most frequent adverse events are essentially dyspnea and minor bleeding. No increase in intracranial bleeding was observed [6], although this risk is increased in elderly patients [4]. Our data confirm these findings and only 1 case of intracranial bleeding occurred at days 30 after switching to dose of 60 mg twice daily. No clinically significant outcome was observed.

Compared with PEGASUS-TIMI 54 trial, in our study dyspnea was less reported, probably because our patients in 1 year of 90 mg ticagrelor treatment had shown to be resistant to this side-effect. Non-serious side effects (especially minimal bleeding and non-limiting dyspnea) may cause DAPT discontinuations that are often unnecessary [7]. These discontinuations can be prevented by adequate counseling to increase adherence to medication, compliance and improve clinical efficacy [4,8,9]. In particular, dyspnea should be considered only if it is clinically limiting [10]. All adverse events judged to be "not serious" in trials may have an effect on quality of life [11] and therefore may lead to treatment discontinuation. The need to educate the patient in order to improve adherence should therefore be emphasized [12].

Study limitations

The study compare the results of PEGASUS-TIMI 54 trial and Eu Label with those of our clinical experience in a secondary prevention outpatient clinic, but the study design and the sample size widely differ between the two trials and our investigation. In this study all patients had been given ticagrelor 90 mg twice daily for 12 months and the 60 mg twice daily dosage was started immediately thereafter, unlike PEGASUS-TIMI 54 trial in which it was prescribed within a period ranging from 1 day to 1 year after discontinuation of the 90 mg dose.

In our study (according to clinical indications) all patients had been on ticagrelor 90 mg BID for 12 months and the 60 mg BID regimen was started immediately at the end of 12th month, unlike PEGASUS-TIMI 54 trial in which P2Y12 therapy prior to randomization was clopidogrel in 94% of cases, prasugrel in 5%, ticagrelor in <1%, and ticlopidine in <1% [13].

Conclusions

Long term DAPT with ticagrelor 60 mg BID with low-dose aspirin (100 mg/day) in secondary prevention after ACS, as recommended in the Eu label, appears to be characterized by a favorable risk/benefit ratio.

Although the comparisons were made with the PEGASUS-TIMI 54 trial and Eu Label, in this study all patients had been on ticagrelor 90 mg BID for 12 months and the 60 mg BID regimen was started immediately at the end of 12th month, unlike PEGASUS-TIMI 54 trial in which P2Y12 therapy prior to ticagrelor 60 mg BID was mostly clopidogrel 75 mg. This is a limitation of study but it makes our results more similar to what is observed in current clinical practice.

However, the authors underline the importance of careful outpatient follow-up and constant counselling in order to check out compliance and possible adverse effect of DAPT treatment.

Table 2. Outcomes.

	S. G. BOSCO 187 patients n (%)	PEGASUS 7045 patients n (%)	p	Eu Label 5388 patients n (%)	p
Cardiovascular death	1 (0.05)	174 (2.86)	<0.0001	119 (2.58)	<0.0001
Death from coronary heart disease	0	106 (1.72)	<0.0001	75 (1.59)	<0.0001
Myocardial infarction	7 (3.7)	285 (4.5)	0.028	230 (4.2)	0.165
Stroke – any	1 (0.05)	100 (1.61)	<0.0001	71 (1.5)	<0.0001
Death from any cause	1 (0.05)	289 (4.69)	<0.0001	206 (3.8)	<0.0001

Table 3. Bleeding.

	S. G. BOSCO n (%)	PEGASUS n (%)	p	Eu Label n (%)	p
TIMI Major	0	115 (2.30)	<0.0001	94 (1.7)	<0.0001
TIMI Minor	7 (3.7)	55 (1.18)	<0.0001	49 (0.9)	<0.0001
Intracranial hemorrhage	1 (0.53)	28 (0.61)	0.647	23 (0,42)	0.453
Fatal bleeding	0	11 (0.25)	0.608	27 (0.5)	0.0017

Table 4. Minor bleeding.

	S.G. BOSCO n (%)
Total minor bleeding	7 (3.7)
Treatment-limiting bleeding*	4 (2.1)
No treatment-limiting bleeding	3 (1.6)
Hematuria	2 (1.0)
Rectal bleeding	5 (2.6)

*Three (3) patients temporarily for non-cardiac surgery (1 case of colon polyposis and 2 cases of bladder papilloma).

Table 5. Minimal bleeding

	S.G. BOSCO n (%)
Total	31 (16.5)
Subcutaneous /dermal	19 (10.1)
Epistaxis	1 (0.53)
Hematuria	4 (2.1)
Rectal	5 (2.6)
Gingival	1 (0.53)
Conjunctival bleeding	1 (0.53)

Patients with minor bleeding (nasal, gingival, rectal, and urinary) did not require treatment interruption.

Table 6. Adverse events.

	S. G. BOSCO n (%)	PEGASUS n (%)	p
Dyspnea	15 (8.0)	987 (15.84)	< 0.0001
Limiting dyspnea	0	297 (4.55)	< 0.0001
Severe dyspnea	0	23 (0.45)	0.0029
Bradyarrhythmia	0	121 (2.32)	< 0.0001
Gout	0	101 (1.97)	< 0.001
Renal event	0	173 (3.43)	< 0.001

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