Long-term dual antiplatelet therapy and nuisance bleeding: impact on quality of life

Gennaro Ratti,[1] Cinzia Monda,[1] Federica Ratti,[2] Marco Golino,[1] Ludovica Fulgione,[3] Cosimo Fulgione,[4] Mario Mallardo,[4] Paolo Tammaro[1]

[1]Cardiology/ICU Department, S. Giovanni Bosco Hospital, Naples; [2]Pharmacy Department, Federico II University of Naples; [3]Advanced Biomedical Science Department, Federico II University of Naples; [4]Cardiac Rehabilitation, S. Gennaro Hospital, Naples, Italy

Abstract

Long term dual antiplatelet therapy (LTDAPT), with ticagrelor 60 mg and low-dose aspirin, is indicated after acute coronary syndrome (ACS) for the secondary prevention of atherothrombotic events in high-risk patients with a history of ACS of at least 1 year. LTDAPT had a good tolerability and safety profile, but the risk of TIMI major bleeding was increased. However, even non-significant bleeding may be important because it has an effect on the quality of life and therefore may lead to treatment discontinuation. We, therefore, evaluated patients' experiences with LTDAPT and the impact of nuisance bleeding on quality of life and treatment adherence. We retrospectively reviewed 225 patients in follow-up after ACS with at least one high-risk condition, treated with ticagrelor 60 mg twice daily (after 90 mg twice daily for 12 months). The outpatient follow-up program after hospitalization provides a visit on day 30 after discharge, then after 3 months, continuing with six-monthly checks. We assessed the presence and intensity of bleeding, as well as health-related quality of life (HRQoL), at each visit. The TIMI score was used to determine the severity of the bleeding. Any overt bleeding event that did not meet the major and minor criteria was labeled "minimal" and could be framed as "nuisance bleeding." The HRQoL was assessed by the EuroQol-5 and Dimension (EQ-5D) visual analog scale (VAS) score. Minimal bleedings were present in 49 patients (21%), but only in one case (by decision of the patient) there was a cause for discontinuation of therapy. However, 39 (79%) subjects had asked for opinions on stopping the therapy during the telephone consultation. Factors influencing LTDAPT knowledge included access to medication counselling, engaging with information communicated during medication counselling, and access to timely, relevant and expert information and advice after discharge from the hospital. All adverse events, judged to be "not serious" in trials, may have an effect on the quality of life and therefore may lead to treatment discontinuation. The authors underline the importance of careful outpatient follow-up and ongoing counselling, to check out compliance and possible adverse effect of LTDAPT.

Correspondence: Gennaro Ratti, Cardiology/ICU Department, S. Giovanni Bosco Hospital, Naples, Italy.
Tel. +39.081.2545268.
E-mail: genratti@virgilio.it

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Introduction

Long term treatment with ticagrelor 60 mg and low-dose aspirin is indicated after acute coronary syndrome (ACS) for the secondary prevention of atherothrombotic events in high-risk patients with a history of myocardial infarction of at least 1 year [1,2]. Long term dual antiplatelet therapy (LTDAPT) had a well tolerability and safety profile, but the risk of thrombolysis in myocardial infarction (TIMI) major bleeding was significantly increased [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]. However, even nonsignificant bleeding may be important, because it has an effect on quality of life and therefore may lead to treatment discontinuation [5]. Non-adherence to secondary prevention medication, such as dual antiplatelet therapy, was calculated around 48% of patients [6]. Nuisance bleeding (defined as easy or excessive bruising, bleeding from small cuts, petechia, and ecchymosis, epistaxis, gingival or conjunctival bleeding) was assessed during the clinical routine of follow-up and is not well reported in trials, but this one is important in the real-life [7,8]. Post-ACS $P2Y_{12}$ inhibitor non-adherence is associated with greater risk of major adverse cardiovascular events [9]. Studies evaluating patient education interventions have reported evidence of effectiveness in improving adherence rates [10]. These discontinuations can be prevented by adequate counseling to increase adherence to medication, compliance and improve clinical efficacy [11,12].

Methods

We report findings from a study exploring the experiences of patients with nuisance bleeding during LTDAPT, with ticagrelor 60 mg and low-dose aspirin, the factors influencing responses to nuisance bleeding, focusing on quality of life and help-seeking behaviors.

We retrospectively reviewed aggregate data of 225 patients (185 M e 40 F) (mean age 63.7±9 years) scheduled at S. Giovanni Bosco hospital from September 2017 to December 2021, in follow up after ACS with, at least one, high risk condition (multivessel disease, diabetes, 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 outpatient follow-up program after hospitalization provides a visit at day 30 after discharge and subsequently after 3 months, then continuing with six-monthly checks. At each visit we assessed presence and intensity of bleeding. The intensity of bleeding was assessed according to the TIMI score [13]. Any overt bleeding event that did not meet the criteria of major and minor, was defined "minimal" and could be framed as a possible "nuisance bleeding". The HRQoL was assessed by the EuroQol-5 and Dimension (EQ-5D) visual analog scale (VAS) score [14]. The EQ-5D instrument measures health status in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Every dimension is rated according to the following levels: i) no problems; ii) some problems; iii) extreme problems. The EQ-5D VAS is a quantitative measure of patients' perceived health. Patients estimated their overall health status on a 20-cm VAS with the endpoints being "best imaginable health state" (score = 100) and "worst imaginable health state" (score = 0). EQ5D and EQ5D-VAS were evaluated in all patients during follow up. The patient, that experienced nuisance bleeding, underwent a counseling program that included: i) during the visit, a detailed information on risks and advantages of LTDAPT and side effects were described (included nuisance bleeding); also the importance of compliance and the correct management of side effects (especially nuisance bleedings) were discussed; ii) a meeting with a patient's next of kin addressing the same issues; iii) at the same time, a phone number was active in prespecified days and time, to discuss potential side effects and to call before any decision about LTDAPT withdrawal; iv) phone calls every month by nurse to assess LTDAPT compliance; v) if necessary or if patient made a request, an additional visit was scheduled for a direct evaluation of the reported bleeding or disorders.

Statistical analysis

Normally distributed variables are presented as mean ± standard deviation (SD) and were compared by Student's *t*-test for unpaired data. Categorical variables are summarized in terms of number and percentages and were compared by using Chi-square test. A p-value ≤0.05 was considered statistically significant.

Results

The duration of follow up was 30.9±12.8 months. The characteristics of patients are shown in Table 1. The high-risk groups were represented as follows: multivessel disease 191 pts (84%), diabetes 72 patients (32%), GFR< 60 mL/min 30 patients (14%), history of prior MI 44 patients (19%), >65 year aged 103 patients (45%). The bleedings are shown in Table 2. Fifty-six (56) minimal bleedings defined as nuisance bleeding were reported (included nasal, gingival, conjunctival, subcutaneous/dermal, rectal and urinary). These were present in 49 patients (21%) (A group), but only in one case (by decision of patient) there was a cause for discon-

Table 1. Baseline demographics and clinical characteristics of the patients included in the study.

	225 patients, n (%)
Baseline characteristics	
Age (years)	63.7±9
Female	40 (17.7)
Weight (kg)	83.1±9.2
Hypertension	188 (83.5)
Hypercholesterolemia	68 (30.2)
Current smoker	31 (13.7)
Diabetes	72 (32)
GFR<60 ml/min	30 (13.3)
History PCI	216 (96)
Multivessel coronary disease	191 (84.8)
History of prior MI	44 (19.5)
Qualifying event	
Year from myocardial infarction	1
History of ST-elevation myocardial infarction	64 (28.4)
History of non-ST-elevation myocardial infarction	188 (83.5)
MI type unknow	0
Medications at enrollment	
Aspirin	225 (100)
Statin	218 (96.8)
B-blockers	178 (79.1)
ACE or ARBS	191 (84.8)

PCI, percutaneous coronary intervention; MI, myocardial infarction; ACE, angiotensin-converting enzyme inhibitors; ARBS, angiotensin II receptor blockers.

Table 2. Bleedings.

	225 patients, n (%)
TIMI major	0
TIMI minor	4 (1.77)
Intracranial hemorrhage	1 (0.44)
Fatal bleeding	0
Minimal	49 (21.7)

TIMI, thrombolysis in myocardial infarction.

tinuation of therapy (Tables 3 and 4). However, 39 (79%) subjects had asked opinion on stop the therapy at the telephone consultation. Discontinuations are shown in Table 4. Treatment was withdrawn in 9 patients (0.4%): 4 cases showed atrial fibrillation and were placed on oral anticoagulant drugs, one case developed intracranial bleeding. Three patients had a temporary withdrawal due to surgery (2 cases of colon polyposis and 1 case of bladder papilloma). In one patient, the discontinuation was definitive (1 case of bladder papilloma). Excluding cases with atrial fibrillation and those with bleeding, 167 patients had no bleeding and continued LTDAPT (B group). EQ5D and EQ5D-VAS values are shown in Table 5. The outcome is shown in Table 6.

Discussion

Previous clinical practice observations had confirmed safety of LTDAPT with ticagrelor. The most frequent adverse events were essentially dyspnea and minor bleeding [15-18]. All adverse events judged to be "not serious" in trials, may have an effect on quality of life [11,19] and therefore may lead to treatment discontinuation. However, in EQ-5D we have observed the significant differences for the first two levels in 5 dimensions of health status (absence or moderate problems). Only about anxiety/depression dimension, difference is significant even in the highest level (extreme problems).

Table 3. Minimal bleedings.

	49 patients, n (%)
Total minimal bleeding	56
Subcutaneous/dermal	38 (77.5)
Epistaxis	3 (6.1)
Urinary*	4 (8.1)
Rectal°	6 (12.2)
Gingival	2 (4)
Conjunctival	3 (6.1)

*After urinary tract infection; °caused by constipation.

Table 4. Discontinuation.

	225 patients, n (%)
Dyspnea	1 (0.44)
TIMI minor bleedings*	4 (1.77)
Intracranial hemorrhage	1 (0.44)
Atrial fibrillation	4 (1.77)
Minimal bleedings	1 (0.44)

TIMI, thrombolysis in myocardial infarction; *three patients had a temporary withdrawal due to surgery; in one patient, the discontinuation was definitive.

Table 5. Health-related quality of life.

EQ-5D	(Group A) 49 patients, n. (%)	(Group B) 167 patients, n. (%)	p
Pain/discomfort, no. (%)			
I have no pain/discomfort	27 (55.1)	163 (97.6)	<0.00001
I have moderate pain/discomfort	21 (42.8)	3 (1.8)	<0.00001
I am in extreme pain/discomfort	1 (2)	1(0.6)	0.35
Anxiety/depression, no. (%)			
I am not anxious or depressed	33 (67.3)	161 (96.4)	<0.00001
I am moderately anxious or depressed	13 (26.5)	5 (2.9)	<0.00001
I am extremely anxious or depressed	3 (6.2)	1(0.6)	0.012
Mobility, no. (%)			
I have no problems in walking about	45 (91.8)	165 (98.8)	0.009
I have some problems in walking about	3 (6.1)	2 (1.1)	0.04
I am confined to bed	1 (2)	0	0.06
Self-care, no. (%)			
I have no problems with self-care	39 (79.5)	164 (98.2)	<0.00001
I have some problems washing or dressing myself	9 (18.3)	3 (17.9)	<0.00001
I am unable to wash or dress myself	1 (2)	0	0.06
Usual activities (*e.g.*, work, study, housework, family or leisure activities), no. (%)			
I have no problems with performing my usual activities	44 (89.7)	166 (99.4)	0.0003
I have some problems with performing my usual activities	4 (8.1)	1 (0.5)	0.002
I am unable to perform my usual activities	1 (2)	0	0.06
EQ5D-VAS values	63±21	73±18	<0.001

Table 6. Outcomes.

	225 patients, n. (%)
Cardiovascular death	1 (0.44)
Myocardial infarction	9 (4)
Stroke – any	1 (0.44)
Death from any cause	1 (0.44)

This demonstrates that motility, self-care and usual activities are not severely altered, although the perception of the state of health can be significantly altered (as shown by the EQ-VAS). In A group of 49 patients with nuisance bleeding, 39 (79%) subjects had asked opinion on stop the therapy at the telephone consultation, but with focused counseling on actual risks and future benefits of LTDAPT, only in one case (by decision of patient) there was a cause for discontinuation. Therefore, the need to educate the patient, in order to improve adherence, should be emphasized [20,21].

We found that: i) participants adhered to treatment when they believed LTDAPT important to health outcomes; ii) those who experienced nuisance bleeding reported symptoms mild and manageable; iii) participants' and their family's understanding of LTDAPT risks and benefits, and their ability to manage symptoms, influenced medication adherence. Factors influencing LTDAPT knowledge included access to medication counselling, engaging with information communicated during medication counselling, and access to timely, relevant and expert information and advice after discharge from hospital.

Conclusions

We reported findings from a retrospective study exploring the impact of nuisance bleeding and of easier access to medication information on adherence to LTDAPT. Our findings are clinically relevant: i) incidence of nuisance bleeding in patients on LTDAPT is above 21%, but most thought symptoms to be mild and manageable; ii) impact on quality of life of nuisance bleeding is relevant and can be reduced through a counseling program directed to patients and their relatives; iii) LTDAPT withdrawal could be significantly higher without adequate follow up.

Access to information to address concerns were central to nuisance bleeding responses. The need to educate the patient in order to improve adherence should, therefore, be emphasized. The authors underline the importance of careful outpatient follow-up and constant counselling, in order to check out compliance and possible adverse effect of LTDAPT.

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