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Antiplatelet and anticoagulant therapy for non-ST-elevation acute coronary syndromes in a general hospital

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Abstract**Aim**

To audit compliance with the 2011 European Society of Cardiology (ESC) guidelines for prescribing antiplatelet and anticoagulant therapy in patients diagnosed with non-ST-elevation acute coronary syndromes (NSTEMI-ACS).

Methods

Five-month audit at Cardiac Catheterisation Suite, Mater Dei Hospital, Malta. A data collection form for inpatients diagnosed with NSTEMI-ACS was developed, psychometrically evaluated and completed for each patient by the investigator. Comparative analysis to assess whether these patients were being managed according to the guidelines was undertaken.

Results

165 patients were recruited; 73% were male, 37% were between 66 and 75 years and 44% were active smokers. The most common risk factors for cardiovascular disease in these patients were hypertension (27%), dyslipidemia and obesity (both 16%). 41% of the patients underwent a percutaneous coronary intervention, either ad hoc (34%) or elective (7%). Compliance to guidelines for prescription of aspirin and clopidogrel 300mg loading dose was 95% and 88% respectively. Compliance to guidelines for prescription of aspirin and clopidogrel 75mg daily maintenance dose was 97% and 96% respectively. Compliance to guidelines for prescription of proton pump inhibitors (PPIs) in patients receiving dual antiplatelet therapy (DAPT) was only 19%; 81% of the patients were prescribed omeprazole against guideline recommendations. Compliance to guidelines for prescription of anticoagulation therapy was 95% with respect to prescription of heparin treatment in combination with DAPT. Compliance to guidelines for prescription of enoxaparin was 81%. Compliance to guidelines for other antiplatelet and anticoagulant drugs recommended in the guidelines, including ticagrelor, prasugrel, glycoprotein IIb/IIIa receptor antagonists, fondaparinux and bivalirudin, was not measured.

Conclusions

Prescription of antiplatelet and anticoagulant therapy for NSTEMI-ACS in Malta is predominantly in accordance with ESC guidelines. Alternative antiplatelet and anticoagulant drugs and PPIs should be included in the Maltese hospital formulary to improve NSTEMI-ACS management in line with guideline recommendations.

Introduction

The 2011 European Society of Cardiology (ESC) guidelines on the management of acute coronary syndromes without persistent ST-elevation (NSTEMI-ACS)¹ define fundamental steps regarding pharmacological management in the acute phase of NSTEMI-ACS, including antiplatelet and anticoagulant treatment.

Following diagnosis of an acute coronary syndrome (ACS), the guidelines recommend loading and maintenance doses of antiplatelet drugs. Aspirin is strongly recommended, with a loading dose (LD) between 150 and 300mg, followed by a maintenance daily dose of 75 to 100mg. Aspirin is given in addition to a P2Y₁₂ receptor antagonist, such as ticagrelor, clopidogrel or prasugrel. A LD of a P2Y₁₂ receptor antagonist is recommended in addition to aspirin. Clopidogrel and ticagrelor are recommended with a LD of 300mg and 180mg respectively, followed by 12 months maintenance therapy with 75mg and 90mg respectively. Ticagrelor is recommended for all patients with a moderate to high risk of ischaemic events, including patients pre-treated with clopidogrel. Clopidogrel is recommended for all patients who cannot receive ticagrelor or prasugrel. A 600mg LD of clopidogrel is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel are not an option. Prasugrel is recommended in P2Y₁₂ receptor antagonists-naïve patients, especially diabetics, in whom anatomy is known post-angiography and who are proceeding to PCI, unless there are contraindications, such as excessive bleeding risk.

For patients on dual antiplatelet therapy (DAPT), addition of a proton pump inhibitor (PPI), preferably not omeprazole, is recommended in patients with a history of gastrointestinal hemorrhage or peptic ulcer or other risk factors including *Helicobacter pylori*, patients older than 65 years or concurrent use of anticoagulants or steroids. The glycoprotein (GP) IIb/IIIa receptor antagonists, abciximab, eptifibatide and tirofiban, are recommended as additional antiplatelet therapy in patients already receiving DAPT plus anticoagulants, taking into consideration the risk of ischaemic and bleeding complications and before PCI in high-risk patients already on DAPT. The guidelines recommend addition of anticoagulation treatment in all patients already on DAPT and to continue anticoagulation until hospital discharge. Fondaparinux 2.5mg daily by subcutaneous (SC) injection is recommended as having the highest efficacy:safety

drug profile and enoxaparin 1mg/kg SC twice daily is recommended when fondaparinux is not available. Unfractionated heparin (UFH) is recommended as third choice, if fondaparinux and enoxaparin are not available. Bivalirudin is recommended by the guidelines together with a GP IIb/IIIa receptor antagonist as an alternative to UFH and in patients scheduled for an invasive strategy with a high risk of bleeding.

Aim

To assess compliance with the ESC guidelines for antiplatelet and anticoagulant therapy in patients diagnosed with NSTEMI-ACS at the time of coronary angiography at Mater Dei Hospital (MDH) in Malta.

Standards for audit

The European Society of Cardiology (ESC) guidelines for the management of NSTEMI-ACS (2011).¹

Methods

Approval from the University of Malta Research Ethics Committee was granted. A patient data collection form (DCF) was developed and psychometrically evaluated. Information collected included patient demographic information, co-morbidities, cardiovascular (CV) risk factors, social history, laboratory investigation results and prescribed medications. 165 inpatients diagnosed with NSTEMI-ACS were recruited by convenience sampling from the Cardiac Catheterisation Suite, MDH, over a 5-month period. The DCF was completed for each patient by reviewing patient treatment files, through discussions with consultant cardiologists and nurses and by attending procedures performed. Comparative analysis was undertaken and compliance to guideline recommendations was categorised into 4 options (Table 1).

Table 1: Categorisation of compliance to guideline recommendations

Categorisation of compliance to guidelines	
1	Drug given, in accordance with guideline recommendations
2	Drug not given, in accordance with guideline recommendations
3	Drug given, against guideline recommendations
4	Drug not given, against guideline recommendations

Results

Patient demographic information

165 patients were recruited. 73% of the patients were male and 37% of the patients were between 66 and 75 years. 44% of the patients were active smokers, 32% of the patients had a body mass index (BMI) in the pre-obesity class and 30% of the patients had a BMI in obesity class I. The most common risk factors for CV disease were hypertension (27%), dyslipidaemia and obesity (both 16%). Following coronary angiography, 41% of the patients underwent a PCI, either ad hoc (34%) or elective (7%).

Compliance to guidelines for antiplatelet treatment

Compliance to guidelines for prescription of aspirin 300mg LD at hospital admission was 95% (Table 2). Patients who were not given a LD of aspirin in accordance with guideline recommendations were already on aspirin therapy and did not require a LD. Aspirin LD was not given, against guideline recommendations, in 5% of the patients. Reasons for not giving aspirin LD were: risk of bleeding, current meningitis and hypersensitivity to aspirin. Compliance to guidelines for prescription of aspirin 75mg daily maintenance dose (DD) was 97%. Aspirin daily maintenance dose was given against guidelines recommendations in 3% of the patients. These patients had gastro-oesophageal reflux disease (GORD), haematuria or hypersensitivity to aspirin, therefore should not have been prescribed aspirin.

Table 2: Compliance to guidelines for aspirin treatment

Guideline recommendation	Categorisation of compliance to guidelines	Compliance (%)
Aspirin 300mg loading dose (LD)	<i>Drug given, in accordance with guideline recommendations</i>	46
	<i>Drug not given, in accordance with guideline recommendations</i>	49
Aspirin 75mg maintenance daily dose (DD)	<i>Drug given, in accordance with guideline recommendations</i>	97

Compliance to guidelines for prescription of clopidogrel 300mg LD at hospital admission was 88% (Table 3). Patients who were not given a LD of clopidogrel in accordance with guideline recommendations were already on clopidogrel therapy and did not require a LD. No reasons for giving or not giving clopidogrel LD against guideline recommendations were documented. In 4 patients scheduled for an invasive strategy immediately post-hospital admission, a 600mg LD of clopidogrel was required and was given according to guideline recommendations in all patients. Compliance to guidelines for prescription of clopidogrel 75mg DD was 96%. No reasons for not giving clopidogrel LD, against guideline recommendations (4% of patients) were documented. Compliance to guidelines for ticagrelor, prasugrel and GP IIa/IIIb receptor antagonists was not measured.

Table 3: Compliance to guidelines for clopidogrel treatment

Guideline recommendation	Categorisation of compliance to guidelines	Compliance (%)
Clopidogrel 300mg loading dose (LD)	<i>Drug given, in accordance with guideline recommendations</i>	74
	<i>Drug not given, in accordance with guideline recommendations</i>	14
Clopidogrel 75mg maintenance daily dose (DD)	<i>Drug given, in accordance with guideline recommendations</i>	96

Compliance to guidelines for proton pump inhibitors in patients receiving DAPT

Compliance to guidelines for prescription of PPIs for gastrointestinal protection in patients receiving DAPT was only 19%. 81% of the patients were prescribed PPIs against guideline recommendations since they were prescribed omeprazole, which is preferably not recommended in the guidelines to be given with clopidogrel. 14% of the patients were prescribed ranitidine, which is not reported to interact with clopidogrel, whilst 5% of the patients were prescribed alternative PPIs (pantoprazole and rabeprazole).

Compliance to guidelines for anticoagulant treatment

Compliance to guidelines for prescription of anticoagulation therapy was 95% with regards to prescription of heparin treatment in combination with DAPT, 96% with respect to evaluation of ischaemic and bleeding risk and 70% for continuation of anticoagulation until hospital discharge. Compliance to guidelines for prescription of enoxaparin was 81%. Documented reasons for non-compliance were: not administered according to body weight, administered only once daily, bleeding complications and UFH or warfarin prescribed instead. Compliance to guidelines for fondaparinux and bivalirudin was not measured.

Discussion

This audit assesses whether prescription of antiplatelet and anticoagulant therapy at MDH was in accordance with the ESC guidelines. This analysis also identifies reasons for management which was not in accordance with the guidelines.

Aspirin and clopidogrel are well recognised as fundamental pharmacological agents in the management of NSTEMI-ACS.¹⁻⁴ Most of the patients in this audit were managed according to guideline recommendations with respect to aspirin therapy, both with respect to LD (95%) and DD (97%). Management which was not according to guidelines was justified by contra-indications and/or comorbidities, such as bleeding, GORD and hypersensitivity.¹ With respect to prescription of clopidogrel, the majority of patients in this audit were also managed according to guideline recommendations, both with respect to LD (88%) and DD (96%).

Ten patients were suitable candidates for ticagrelor, however this drug was never prescribed since it is not yet available in Malta. These patients were prescribed clopidogrel instead. Ticagrelor is recommended in favour of clopidogrel for all patients at moderate-high risk of ischaemic events.¹ In the PLATO trial, ticagrelor markedly reduced death rates from vascular causes, myocardial infarction and death from any causes. No significant differences were found in the ticagrelor group compared to the clopidogrel group regarding major bleeding events.⁵

Seventeen patients in this audit were suitable candidates for prasugrel since they were diabetic and were scheduled for an invasive strategy. These patients were treated with clopidogrel instead since prasugrel is not available on the Maltese Government Formulary List (GFL). In the recent TRITON-TIMI 38 trial, prasugrel was found to be superior to clopidogrel in reducing death from CV causes and significantly decreasing rates of myocardial re-infarction, urgent target-vessel revascularization and stent thrombosis. According to literature, major bleeding occurs more frequently in patients on prasugrel.⁶ Studies demonstrating the long-term effects of GP IIb/IIIa receptor antagonists are lacking. No patients were prescribed GP IIb/IIIa receptor antagonists since they are not yet available in Malta.

A clinically significant interaction with concomitant use of clopidogrel and PPIs, especially omeprazole, has been reported.⁷ Alternative PPIs such as pantoprazole have been reported to interact less with clopidogrel.⁸ 81% of the patients in this audit were co-prescribed omeprazole, which is the only PPI available on the Maltese GFL. Two patients were each prescribed rabeprazole or pantoprazole, both of which are not available on the Maltese GFL and were purchased by the patients.

Anticoagulants are considered fundamental in addition to DAPT to inhibit thrombin generation and activity, to prevent thrombus formation in NSTEMI-ACS.¹ In this audit, anticoagulation treatment was added to DAPT according to guidelines in the majority of patients (95%) and most patients (81%) were administered enoxaparin according to guidelines. A systematic review of 6 randomised controlled trials comparing enoxaparin and UFH in NSTEMI-ACS shows that enoxaparin has higher efficacy compared to UFH in preventing CV death and MI.⁹

Fondaparinux was never prescribed since it is not available in Malta. It is recommended by the guidelines as a first choice anticoagulant for NSTEMI-ACS patients in the absence of renal failure.¹ In a study by Yusuf et al.¹⁰ fondaparinux showed its superiority over enoxaparin with respect to the CV outcomes of death, MI or refractory ischaemia at 9 days, and major bleeding events were also substantially decreased in those patients on fondaparinux treatment. Bivalirudin was also never prescribed since it is not yet available in Malta. This drug was tested in NSTEMI-ACS patients in the ACUITY trial, where patients on bivalirudin alone had a significantly lower rate of major bleeding.¹¹

Limitations

Guideline recommendations were stringently categorised into whether the drug was given or not, according to or against guideline recommendations. Although this categorisation was important for data analysis, it was not always easy for the investigator to decide on the correct option during data collection. Therefore, some assumptions could have led to inaccuracies. Moreover, pharmacological management decisions depend on the experience of the consultant taking care of the patient and it was not always easy for the investigator to deduce the reason for each management decision. Classifying the prescribing action as according to or against guideline recommendations may not reflect professional flexibility, therefore strict categorisation of borderline cases may also have led to inaccuracies.

Conclusions and recommendations

Prescription of antiplatelet and anticoagulant therapy for NSTEMI-ACS in Malta is predominantly in accordance with ESC guidelines. The main reason for lack of compliance to guidelines was that the drug preferred was either not available on the Maltese GFL or not even available on the Maltese market. Drugs not on the GFL need to be purchased by the patient and since they are relatively expensive, patients are reluctant to do so. Additional antiplatelet and anticoagulant drugs and PPIs should be included in the Maltese GFL to improve NSTEMI-ACS management in line with European guidelines.

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