Individualised Antiplatelet Therapy Prescribing after Percutaneous Coronary Intervention

Submitted in partial fulfilment

of the requirements of the

Degree of Master of Pharmacy

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Department of Pharmacy

2023

To my late grandfather

whose absence is deeply felt,

but whose pride would have shone brightly on this occasion

Abstract

Antithrombotic therapy prescribing after percutaneous coronary intervention (PCI) is challenging and requires consideration of bleeding and ischaemic risk. The aims were to: assess bleeding risk, optimise antithrombotic therapy prescribing, and evaluate outcomes, in a cohort of patients undergoing PCI. Patients (N=200) undergoing PCI and candidates for dual antiplatelet therapy (DAPT) were prospectively recruited by convenience sampling after ethics approval. A data collection sheet was developed, validated, and completed via patient interview and hospital records. The PRECISE-DAPT score, presently not routinely used in local practice, was applied in all patients to calculate bleeding risk (≥25 high, 18-24 moderate, <18 low). All moderate and high bleeding risk patients and low risk patients on oral anticoagulation were discussed with cardiologists for antithrombotic therapy optimisation. Patients were followed-up over one-year post-PCI for mortality, bleeding, and ischaemic outcomes (stent thrombosis, stable/unstable angina, myocardial infarction, coronary revascularisation), and comparison of outcomes between short-term (≤6-months) and long-term (12-months) DAPT duration was carried out. Descriptive statistics were performed ($p<0.05$ considered statistically significant). The 200 patients recruited (81% male, mean age 66 years, 48% primary PCI) were scored as high (41%), moderate (24.5%) or low (34.5%) bleeding risk. The bleeding risk score was discussed with cardiologists for 126 (63%) patients and was accepted for antithrombotic therapy optimisation in 53 (27%) patients, in whom short-term DAPT was prescribed. The other patients (n=147) were prescribed long-term (63%) or short-term (10%) DAPT according to cardiologist discretion. There was no statistically significant difference ($p>0.05$) between short-term and long-term DAPT duration for ischaemic outcomes and mortality. No cases of major bleeding were

documented. For minor bleeding (melaena, haematuria or gingival bleeding), a significant difference ($p<0.05$) between short-term and long-term DAPT duration was observed, with higher bleeding in the short-term cohort. When not considering patients (n=40) prescribed other drugs known to increase bleeding in the analysis, no statistically significant difference ($p>0.05$) in minor bleeding between DAPT durations was observed. Pharmacist-led bleeding risk evaluation in patients undergoing PCI was useful in supporting cardiologists in the personalisation and optimisation of antithrombotic therapy. Outcomes in the patient cohort studied were comparable between short- and long-term DAPT duration.

Acknowledgments

I would first and foremost like to express my sincere and profound appreciation to my supervisor Dr Francesca Wirth for her guidance, persistence, and commitment while carrying out this study.

I would like to extend my gratitude to Professor Lilian M. Azzopardi, Head of Department, along with all the lecturers and staff at the Department of Pharmacy of the University of Malta for their support and dedication throughout the course.

I would like to thank Professor Liberato Camilleri for his invaluable help in carrying out the statistical analysis.

I am deeply thankful to Dr Robert G. Xuereb, Chair of the Department of Cardiology, and to all the physicians, nurses, radiographers and administrative staff at the Cardiac Catheterisation Suite, Mater Dei Hospital. My gratitude extends to all the patients who participated in the study.

Above all, I wish to express my heartfelt thanks and appreciation to my family, especially my parents and brother, for their continuous patience and support, and for guiding me in the right direction. I am also sincerely grateful to my boyfriend who has been there for me in the toughest of times and never left my side. Lastly, I would like to express my gratitude to my best friends and managing pharmacist, without whom I would not have been able to complete my studies.

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List of Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
CAD	Coronary Artery Disease
CVIS	Cardiovascular Information System
DAPT	Dual Antiplatelet Therapy
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
GI	Gastrointestinal
HBR	High Bleeding Risk
LVEF	Left Ventricular Ejection Fraction (LVEF)
MI	Myocardial Infarction
NSTEMI	Non-ST-segment Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PRECISE-DAPT	Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy
STEMI	ST-segment Elevation Myocardial Infarction
TIMI	Thrombolysis in Myocardial Infarction

Chapter 1

Introduction

1.1. High Bleeding Risk in Patients Undergoing PCI: Risk Factors and Complications

When a decision to perform percutaneous coronary intervention (PCI) is taken, consideration of a patient's bleeding risk is important since bleeding may occur during and post-PCI (Kern, 2018; Susanu *et al.,* 2018; Collet & Thiele, 2020). Research reports that approximately a third of patients undergoing PCI are found to be at high risk of bleeding, which could be attributed to previous history of cerebrovascular accident or bleeding, decreased haemoglobin levels, older age, thrombocytopaenia, chronic kidney disease and current or prior history of malignancy (Urban *et al.,* 2019; Jiménez Díaz *et al.,* 2020; Nakamura & Iijima, 2021; Costa *et al.,* 2023). High bleeding risk (HBR) in patients undergoing PCI is associated with several risk factors at the time of PCI, which may be classified as minor or major (Table 1.1) (Urban *et al.,* 2019).

When bleeding occurs, the capacity of the blood to transport and deliver oxygen efficiently and sufficiently is diminished, resulting in myocardial hypoperfusion, which may potentially trigger myocardial ischaemia (D'Ascenzo *et al.,* 2020; Costa *et al.,* 2023). A complication of bleeding involves enhanced activation and aggregation of platelets, prompting further coronary adverse outcomes. Bleeding has been correlated with an enhanced risk of myocardial infarction (MI), cerebrovascular events, stent thrombosis, and death (D'Ascenzo *et al.,* 2020). Bleeding may lead to decreased therapy adherence, which is especially relevant with medications such as antiplatelet agents, and may lead to further complications (O'Donoghue & Patel, 2021; Costa *et al.,* 2023).

Table 1.1: Risk Factors for High Bleeding Risk at Time of PCI

Minor Criteria	Major Criteria
Age ≥75 years	Long-term oral anticoagulation therapy
Moderate chronic kidney disease	Severe/end-stage chronic kidney disease
Spontaneous bleeding requiring hospitalisation/transfusion in past 12-months not meeting major criteria	Spontaneous bleeding requiring hospitalisation/transfusion in past 6-months
Long-term use of NSAIDs and steroids	Moderate to severe thrombocytopaenia
Stroke at any time not meeting major criteria	Chronic bleeding diathesis
	Liver cirrhosis with portal hypertension
	Active malignancy
	Intracranial haemorrhage Brain arteriovenous malformations Moderate-to-severe stroke in past 6-months
	Non-deferrable major surgery on DAPT
	Recent major surgery/trauma a month before PCI

Adopted from: Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, et al. Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention. Circulation. 2019; 140 (3): 240-261. doi: 10.1093/eurheartj/ehz372.

With respect to race and ethnicity, East Asians tend to be correlated with a greater tendency of experiencing bleeding events, and have a decreased prevalence of ischaemic complications compared to Western patients (Kang *et al.,* 2019; Chi *et al.,* 2020; Cho *et al.,* 2020; Lee *et al.,* 2021). Black Africans are more likely to progress to acute coronary syndrome, especially at younger ages, and have a greater tendency of experiencing bleeding when compared to Caucasians (Folsom *et al.,* 2020; Garcia *et al.,* 2021).

High bleeding risk (HBR) is associated with increased episodes of bleeding, as well as a greater risk of ischaemia. This presents a challenge when selecting the optimal antithrombotic regimen for each patient, warranting personalised prescribing. Enhancing patient outcomes involves individualised therapy to balance cardiovascular benefits and bleeding risk (Costa *et al.,* 2019, Costa *et al.,* 2023). Recognising causes and risk factors associated with bleeding, careful selection of $P2Y_{12}$ inhibitors with appropriate dosing, and addition of proton pump inhibitors (PPIs) are strategies used to improve patient outcomes (Valgimigli *et al*., 2018). Various international guidelines recommend assessment of bleeding and ischaemic risks to help guide treatment choices, suggesting a more cautious approach regarding the type of therapy and its duration for patients at HBR (Valgimigli *et al*., 2018; Marquis-Gravel *et al.,* 2020; Collet *et al.,* 2021; Costa *et al.,* 2023).

1.2. Definitions of High bleeding risk and Bleeding Risk Determination

High bleeding risk is not easily defined owing to lack of standardisation among various clinical trials and research studies (Urban *et al.,* 2019). This complicates the process of organising clinical trials and establishing qualified comparative safety outcomes for antithrombotic agents (Mehran *et al.,* 2011; Nguyen & Nguyen, 2013).[1] Various bleeding scales exist, namely the 'Bleeding Academic Research Consortium (BARC)', 'Global Utilization of Streptokinase and Tpa for Occluded Arteries (GUSTO)' and 'Thrombolysis in Myocardial Infarction (TIMI)' (Bergmark *et al.,* 2019). The TIMI score considers decreased haemoglobin or haematocrit levels and intracranial haemorrhage to categorise bleeding as major, minor, or minimal (Urban *et al.,* 2019). The 'Academic Research Consortium for High Bleeding Risk (ARC-HBR)' developed a harmonised definition for HBR as a "BARC Type 3 or 5 bleeding risk of at least 4% at one year or a risk of intracranial haemorrhage of at least 1% at one year" (Urban *et al.,* 2019; Ueki *et al.,* 2020; Okabe *et al.,* 2022).

Dual antiplatelet therapy (DAPT) is not typically intended for an indefinite duration since this may result in greater bleeding risk without providing additional patient benefit (Choi *et al*., 2018; Moerlie *et al*., 2020). Bleeding risk stratification weighs the advantages and disadvantages of continued DAPT exceeding twelve-months (Long *et al.,* 2018). The European Society of Cardiology (ESC) guidelines regarding DAPT in patients with ST-

[1] PCRonline. EuroPCR 2019 Press Release: A Pragmatic Approach to Defining High Bleeding Risk for Patients Undergoing PCI [Internet]. Paris (France): PCRonline; 2019 [cited 2023 Aug 17]. Available from: https://www.pcronline.com/News/PCR-Press-Releases/EuroPCR-2019-Press-Release-A-pragmatic-approach-to-defining-high-bleeding-risk-for-patients-undergoing-in-PCI

segment elevated myocardial infarction (STEMI) highlights the DAPT and 'Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy' (PRECISE-DAPT) scores, which are aimed at assigning a score and bleeding risk category to patients so as to guide DAPT prescribing (Valgimigli *et al*., 2018; Collet *et al.,* 2021). The PRECISE-DAPT score considers five items to estimate bleeding risk namely, age, creatinine clearance, leukocyte count, haemoglobin level and history of impulsive bleeding (Costa *et al.,* 2017; Costa *et al.,* 2019). A score greater than or equal to 25 implies that the ideal DAPT duration should be three to six months shorter than patients with a score less than 25 (Choi *et al.,* 2018; Ando *et al.,* 2020; Guedeney & Collet, 2020).

The American College of Cardiology (ACC) / American Heart Association (AHA) recommends the DAPT score to estimate and evaluate the risk to benefit ratio of more than twelve-months of DAPT post-PCI (Levine *et al.,* 2016; Floyd, 2020).[2] The score assigns positive and negative values to risk factors associated with PCI. Scores greater than two predict that prolonged $P2Y_{12}$ inhibitor therapy may reduce ischaemic events, whereas scores less than two implicate that more bleeding may occur (Long *et al.,* 2018).

[2] European Society of Cardiology (ESC). Comparing Treatment Recommendations for the DAPT and PRECISE-DAPT Scores after Percutaneous Coronary Intervention [Internet]. Brussels (Belgium): ESC; 2019 [cited 2023 Aug 17]. Available from: https://esc365.escardio.org/Congress/195987-comparing-treatment-recommendations-for-the-dapt-and-precise-dapt-scores-after-percutaneous-coronary-intervention#abstract

The DAPT and PRECISE-DAPT scores do not show complete concordance in recommending treatment to patients (Collet *et al.,* 2021). High DAPT scores were correlated with larger ischaemic risk, while high PRECISE-DAPT scores were linked with higher bleeding risk (Long *et al.,* 2018). High PRECISE-DAPT scores have been correlated with greater risk of mortality (Choi *et al.,* 2018; Ando *et al.,* 2020; Guedeney & Collet, 2020).

1.3. Antiplatelet Therapy and Outcomes in Patients Undergoing PCI

Antiplatelet therapy post-PCI in patients presenting with STEMI or non-ST-segment elevation myocardial infarction (NSTEMI) is recommended to decrease the risk of significant adverse cardiac and thrombotic events (Degrauwe *et al.*, 2017; Ibanez *et al*., 2018; Collet *et al.,* 2021). Conflicting study outcomes have led to an ongoing dilemma with regards to the optimal choice and duration of DAPT prescribed in patients undergoing PCI at high bleeding risk (Wernly *et al.,* 2020; Apostolos *et al.,* 2023; Kinlay *et al*., 2023). This has led to an evolution in antithrombotic regimens, advanced stent technologies, and greater knowledge on treatment and complications (Angiolillo *et al.,* 2022). The main objective for cardiologists is to prescribe and optimise antiplatelet strategies using a personalised approach, while maintaining a balance between ischaemic and bleeding risk (Costa *et al.,* 2019; Tersalvi *et al.,* 2020; Wernly *et al.,* 2020; Kinlay *et al*., 2023).

1.3.1. Comparison of Antiplatelet Agents

The antiplatelet drugs prescribed post-PCI are mainly aspirin in addition to a $P2Y_{12}$ inhibitor, namely clopidogrel, ticagrelor or prasugrel (Amsterdam *et al*., 2014; Nikolaou, 2017; Ornelas *et al.* 2017; Costa *et al.,* 2023; Kang *et al.,* 2023b). Benefit from $P2Y_{12}$ inhibitors is highest during the early stages since chronic administration has been reported to increase risk of bleeding (Han, 2019; Kim *et al.,* 2020; Costa *et al.,* 2023). Sustaining an equilibrium between reduced bleeding and reaping ischaemic protection benefits with antiplatelet therapy is becoming increasingly important. In the past few years, there has been a notable rise in the perception that bleeding experienced with long-term antithrombotic therapy is not simply a minor inconvenience, but is correlated with a significant risk of cardiac and bleeding adverse outcomes. If this equilibrium is not maintained, the ischaemic protective benefits gained with antiplatelet therapy may be lost (Valgimigli *et al.,* 2018; Costa *et al.,* 2023; Kinlay *et al.,* 2023).

Updated European guidelines for the management of acute coronary syndrome (ACS) state that prasugrel and ticagrelor should be regarded as first line antiplatelet agents over clopidogrel in patients experiencing NSTEMI (Collet *et al.*, 2021). Prasugrel is preferred to ticagrelor since it improves endothelial function (Schnorbus *et al.,* 2020; Collet *et al.*, 2021). Prasugrel is proposed in preference to ticagrelor for diabetics and for individuals who have previously experienced sinus tachycardia with clopidogrel (Han, 2019; Eliaz *et al.,* 2022). With regards to patients undergoing PCI due to STEMI, various studies showed no considerable difference regarding primary end points between prasugrel and ticagrelor indicating similar efficacy and safety (Han, 2019; Aytekin *et al.,*

2020; Venetsanos *et al.,* 2021; Fong *et al.,* 2022). However, ticagrelor was found to be correlated with a greater risk of recurrent myocardial infarction when compared to prasugrel in a study by Aytekin et al. (2020). Ticagrelor administration may be applied despite coronary angiography results, while prasugrel prescribing requires identification and examination of the coronary anatomy (Eliaz *et al.,* 2022). Prasugrel is the only $P2Y_{12}$ inhibitor that allows for an adjusted dose (10mg reduced to 5mg) in the elderly or in patients weighing less than 60kg (Andreotti *et al.,* 2023). Compared to clopidogrel, prasugrel is more potent and has a quicker onset of action. Prasugrel and clopidogrel were compared in the 'Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38)', where patients prescribed prasugrel experienced less risk of stroke, MI, or death in comparison to clopidogrel (Jurisic *et al.,* 2021).

Clopidogrel is indicated for patients undergoing procedures including elective stenting, while prasugrel and ticagrelor are usually considered for high-risk patients, or in those who have a previous history of stent thrombosis with clopidogrel (Neumann *et al.,* 2019). Clopidogrel is generally utilised if ticagrelor and prasugrel are not currently available for administration, or are contraindicated. Clopidogrel is correlated with higher tendency of stent thrombosis, but has lower overall bleeding than prasugrel and ticagrelor (Koski & Kennedy, 2018; Zhou *et al.,* 2018; Ziada & Moliterno, 2019).

For individuals at moderate to high risk of bleeding, clopidogrel is favoured over prasugrel and ticagrelor, and DAPT duration may be reduced to one- to six-months,

depending on which antiplatelet agent is prescribed as monotherapy and the type of ACS. DAPT for one-month is warranted for clopidogrel monotherapy, while three- and six-months are recommended for NSTEMI and STEMI respectively, if aspirin is the single antiplatelet agent of choice (Ibanez *et al.,* 2018; Collet *et al.*, 2021). When comparing aspirin with clopidogrel as single chronic maintenance antithrombotic therapy in patients with previous PCI in the 'Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases (HOST-EXAM)' trial, clopidogrel monotherapy was correlated with a substantial decrease in resulting death, MI, stroke, hospital readmission or bleeding (Capodanno & Angiolillo, 2023; Kang *et al*., 2023a).

The ESC guidelines for NSTE-ACS recently recommended monotherapy with ticagrelor for three-months following PCI in specific persons found to be at a low risk of ischaemia (Collet *et al.*, 2021). The 'Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT)' trial evaluated use of ticagrelor compared to prasugrel, where prasugrel exhibited a reduced death rate, stroke or MI after one year compared to ticagrelor. Both ticagrelor and prasugrel are recommended for patients at higher risk of experiencing ischaemic consequences (Floyd, 2020). In comparison to clopidogrel, ticagrelor is regarded to be more potent, direct, and rapid acting, and exhibits anticipated pharmacodynamic responses than clopidogrel, owing to its rapid absorption (Han, 2019). According to the 'Platelet Inhibition and Patient Outcomes (PLATO)' trial, ticagrelor is more potent than clopidogrel and more compelling in decreasing cardiovascular events in patients on aspirin (Degrauwe *et al.,* 2017; Mehran *et al.,* 2019; Jurisic *et al.,* 2021). The combination of ticagrelor with aspirin was

favourable in the 'Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54)' trial (Bonaca *et al.,* 2015; Jurisic *et al.,* 2021).

1.3.2. Monotherapy versus Dual Antiplatelet Therapy

Aspirin and a $P2Y_{12}$ inhibitor are the primary antiplatelet agents used in the initial stages of DAPT, which is subsequently followed by one of the two agents as monotherapy (Moerlie *et al.,* 2020).[3] Studies were performed to establish optimum antiplatelet treatment regimens, considering bleeding and adverse cardiovascular events (Shuvy & Ko, 2014; Lee *et al.,* 2017). Limited trials comparing single antiplatelet therapy consisting of a $P2Y_{12}$ receptor inhibitor versus DAPT have been performed, resulting in lack of evidence-based research to support monotherapy after stent implantation (Lee *et al.,* 2017; Nunez-Gil *et al.,* 2018).

Initially following stent implantation, DAPT diminishes threats of stent thrombosis. Once this risk subsides, effects of DAPT become more focused on reducing the risk of recurrent ischaemic effects by preventing coronary plaque rupture (Tersalvi *et al*., 2020). DAPT provides more potent platelet inhibition and ischaemic risk prevention than monotherapy, minimising thrombotic events post-PCI. Simultaneous use of aspirin and

[3] National Institute for Health and Care Excellence (NICE). Myocardial Infarction: Cardiac Rehabilitation and Prevention of further cardiovascular disease [Internet]. London (United Kingdom): NICE; 2013 [cited 2022 Dec 28]. Available from: https://www.nice.org.uk/guidance/cg172/chapter/2-Research-recommendations

clopidogrel results in a greater chance of bleeding compared to aspirin monotherapy (Moerlie *et al.,* 2020). It is still uncertain whether $P2Y_{12}$ monotherapy could sustain efficacy in preventing ischaemia while decreasing bleeding risk compared with DAPT (Valgimigli *et al.,* 2022).

The 'Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE)' trial resulted in superiority of clopidogrel with aspirin compared to aspirin monotherapy for stroke reduction (Hahn *et al*., 2019; Luo *et al.,* 2020). Combination treatment did not cause more haemorrhagic events than aspirin alone (Wang *et al.,* 2013; Song *et al.,* 2018). The 'Short and Optimal Duration of Dual Antiplatelet Therapy-2 (STOPDAPT-2)' trial studied the outcomes of one-month DAPT after clopidogrel versus twelve-month DAPT. The length of therapy did not affect the outcome since neither short- nor long-term DAPT was superior. Short-term treatment was correlated with a decreased probability of bleeding, in contrast with longer durations. Patients at HBR who had previously experienced a recent stroke or ischaemic attack did not experience increased thrombotic risk (Watanabe *et al*., 2019; Watanabe *et al.,* 2022). A recent study by Räsänen et al. (2023) evaluated the use of single antiplatelet therapy post-PCI with a drug-coated balloon. Results showed that ischaemic cardiac and bleeding events were not common with this regimen, implying that with further studies, this could lessen bleeding risk in coronary artery disease (CAD) patients at HBR post-PCI (Räsänen *et al.,* 2023).

1.3.3. Short-Term Dual Antiplatelet Therapy

Understanding the longevity of DAPT entails balancing lowering risks of ischaemic events with escalated and extended antiplatelet therapy and decreasing risks of bleeding events with milder and shorter antiplatelet therapy (Ziada & Moliterno, 2019). The current subject of discussion is the superiority or inferiority of shortened one-month DAPT duration versus standard DAPT duration, typically six- to twelve-months in HBR patients undergoing PCI (Wernly *et al.,* 2020).[4]

In most individuals diagnosed with stable CAD, short DAPT durations, varying between one-, three- or six-months, are the most practical approaches and may be prescribed when there are no increased ischaemic risks. Short DAPT duration is correlated with decreased risk of major bleeding despite non-inferiority to long-term therapy observed in the 'DAPT-STEMI' trial (Kedhi *et al.,* 2017; Kinnaird *et al.,* 2018). Early withdrawal of $P2Y_{12}$ inhibitors after three- to six-months post-PCI may be advised in patients with HBR or in those who experience substantial bleeding (Wernly *et al.,* 2020). DAPT comprising aspirin and clopidogrel as the agents of choice should be discontinued in scenarios where patients are found to be at even higher bleeding risks (Collet *et al.,* 2021). The ACC/AHA recommend continuous aspirin combined with clopidogrel for one- to six-months depending on the type of stent implanted (Levine *et al.,* 2016; Floyd, 2020). The ESC advises six-months of therapy regardless of stent type. Patients tolerating DAPT

[4] McKeown LA. Oxynx ONE: Shorter DAPT Plus ZES Noninferior to Polymer-Free Stent in High-Bleeding-Risk Patients. TCTMD; 2019 [cited 2022 Dec 28]. Available from: https://www.tctmd.com/news/onyx-one-shorter-dapt-plus-zes-noninferior-polymer-free-stent-high-bleeding-risk-patients

without HBR may continue this treatment accordingly, whereas those with HBR should stop DAPT after three-months (Capodanno *et al.,* 2018).

Recent trials, namely 'Safety of 6-month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndromes (SMART-DATE)' (Hahn *et al.,* 2018; Choi *et al.,* 2020), 'Smart Angioplasty Research Team: Comparison Between $P2Y_{12}$ Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE)' (Hahn *et al.,* 2019), 'GLOBAL-LEADERS' (Vranckx *et al*., 2018), and 'Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT)' (Mehran *et al.,* 2019), examined the advantage of reduced DAPT duration for one- to three-months, and results showed that bleeding and ischaemic occurrences decreased (Hahn *et al.,* 2019; Luo *et al.,* 2020; Collet *et al.,* 2021; Jurisic *et al.,* 2021). The 'Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen (MASTER DAPT)' trial showed non-inferiority of DAPT in HBR patients beyond one-month compared to DAPT lasting three- to twelve-months. The threat of bleeding was increased without any clear advantage on cardiovascular outcomes (Valgimigli *et al.,* 2021). Findings from such research have resulted in recommendations to curtail DAPT to six-months in high-risk patients to decrease bleeding incidents without considerable ischaemic liability (Costa *et al.,* 2017; Valgimigli *et al.,* 2021; Costa *et al.,* 2023). Novel studies are persistently investigating the effects of shorter DAPT durations lasting one- or three-months in comparison to extended regimens (Costa *et al.,* 2023).

When compared to long-term DAPT, one- to three-months of short-term DAPT provided a better risk to balance ratio, as it decreased bleeding events while maintaining ischaemia in persons undergoing a drug eluting stent implantation (Rout *et al.,* 2022). The recently conducted 'The Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen' (MASTER-DAPT) trial exhibited that shortening DAPT to one-month was neither superior nor inferior to six-months therapy with regards to major cardiovascular or cerebrovascular adverse outcomes in patients with drug eluting stents (Valgimigli *et al.,* 2021; Costa *et al.,* 2023). Yamamoto et al. (2023) concluded that, compared to DAPT lasting twelve-months, single antiplatelet therapy with clopidogrel after one-month of DAPT in diabetic patients decreased bleeding outcomes without any rise in negative cardiovascular outcomes. The 'Ticagrelor Monotherapy After 3 Months in the Patients Treated with New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome (TICO)' trial showed that switching to ticagrelor monotherapy for three-months post-DAPT was safer than long-term therapy in STEMI patients (Kim *et al.,* 2020).

1.3.4. Long-Term Dual Antiplatelet Therapy

The prescribed period of long-term antithrombotic therapy ranges from 12- to 24-months post-PCI. The prospective benefit of prolonged DAPT for more than 12-months regarding secondary prevention of cardiovascular events continues to be discussed (Costa *et al.,* 2019; Watanabe *et al.,* 2019; Collet *et al.,* 2021; Balaji Srinivasan *et al.,* 2023).

Prolonged DAPT duration increases bleeding risk despite reducing ischaemic events in patients without HBR. The DAPT trial resulted in 30-month DAPT exhibiting a diminished risk for cardiovascular outcomes along with greater bleeding risk compared to 12-months DAPT (Collet *et al.,* 2021; Jurisic *et al.,* 2021). There is no benefit of extended periods of DAPT in HBR patients. Individuals with high ischaemic risk post-PCI who were able to tolerate DAPT without triggering bleeding and were not at HBR, were investigated. Prolongation of DAPT with clopidogrel for a duration lasting longer than one-month in individuals implanted with bare metal stents, or more than six-months in patients implanted with drug eluting stents could be rational therapy (Costa *et al.,* 2019).

The 'TWILIGHT' trial analysed the efficiency and safety of single antiplatelet therapy with ticagrelor following three-months of DAPT in comparison with standard twelve-months DAPT consisting of aspirin and ticagrelor (Degrauwe *et al.,* 2017; Mehran *et al.,* 2019). Results show that in comparison to DAPT consisting of ticagrelor and aspirin, monotherapy with ticagrelor decreased risk of bleeding without a greater risk for ischaemic events (Angiolillo *et al.,* 2020).

Initial potent $P2Y_{12}$ receptor inhibitory monotherapy, alternating from novel $P2Y_{12}$ inhibitors, decreasing $P2Y_{12}$ receptor inhibitor dose, and reducing duration of DAPT are actions taken to prevent ischaemic adverse outcomes (Capodanno *et al.,* 2018; Han*,* 2019). These strategies are highly recommended for patients over the age of 75 years, since such populations should not be prescribed DAPT for durations longer than 12-months (Andreotti *et al.,* 2023). The ESC guidelines advocate for a duration of DAPT

lasting at least twelve-months in ACS and no less than six-months in stable CAD without HBR (Watanabe *et al.,* 2019). The 'Randomised Evaluation of short-term Dual antiplatelet therapy in patients with acute coronary syndrome treated with the COMBO dual-therapy stent (REDUCE)' trial advised twelve-months DAPT in persons with ACS due to increasing rates of mortality with DAPT for three-months (De Luca *et al.,* 2019).

In the long-term post-PCI, there appears to be a progressive change in bleeding and ischaemic risks, where the greatest thrombotic potential occurs instantly after PCI, but decreases substantially when the patient is stabilising (Gallone *et al.,* 2018). Research is suggesting novel concepts and ideas with the aim of maintaining the ischaemic and bleeding balance post-PCI, such as de-escalating the $P2Y_{12}$ inhibitor (Kang *et al*., 2023b). De-escalation involves reducing the potency of DAPT by exchanging the oral $P2Y_{12}$ inhibitor and transitioning from a more potent antiplatelet agent immediately post-PCI to a less potent agent later (Angiolillo *et al.,* 2017; Neumann *et al.,* 2019). Four main trials analysed this concept, namely the 'Testing Responsiveness to Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndrome (TROPICAL-ACS)' (Sibbing *et al.,* 2017), 'CYP2C19 Genotype-Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients – Patient Outcome After Primary PCI (POPular Genetics)' (Claassens *et al.,* 2019), 'Ticagrelor Versus Clopidogrel in Stabilized Patients With Acute Myocardial Infarction (TALOS-AMI)' (Volney *et al.,* 2019) and the 'Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial – Comparison of REDUCTION of Prasugrel Dose & Polymer Technology in ACS Patients (HOST-REDUCE-POLYTECH-ACS)' (Kim *et al.,* 2020). These trials showed that de-

escalating the antiplatelet agent from twelve-months post-PCI resulted in decreased bleeding without increased ischaemic risk (Kang *et al.,* 2023b).

1.3.5. Adjunctive Therapy

DAPT may not be adequate to prevent ischaemia in all patients. Certain patients, particularly those with atrial fibrillation (AF), are additionally prescribed oral anticoagulation. The direct oral anticoagulants (DOACs), which include factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) or factor IIa/thrombin inhibitors such as dabigatran, are preferred to the vitamin K antagonist, warfarin (Kim *et al.,* 2019; Collet *et al.,* 2021; Angiolillo *et al.,* 2022). European guidelines propose triple antithrombotic therapy (TAT), comprising aspirin with a $P2Y_{12}$ inhibitor and a DOAC for seven days following PCI, after which dual antithrombotic therapy comprising of a DOAC with a $P2Y_{12}$ inhibitor should be prescribed for not more than twelve months (Andreotti *et al.,* 2023). If patients are considered to have a greater tendency to experience ischaemia, but are associated with a low risk of bleeding, TAT may alternatively be extended up to one-month (Angiolillo *et al.,* 2021; Collet *et al*., 2021; Andreotti *et al.,* 2023).

DAPT post-PCI is known to cause gastrointestinal (GI) bleeding as the main source of bleeding experienced. Antiplatelet agents are reported to exhibit adverse GI effects that could lead to ulceration (Sehested *et al.,* 2019; Saven *et al.,* 2022). PPI therapy is recommended throughout the DAPT period to improve clot stability and to reduce GI bleeding (Vaduganathan *et al.,* 2016; Sehested *et al.,* 2019; Wu *et al.,* 2019). Prescribing

PPIs with aspirin and clopidogrel led to a considerable decrease in complications throughout the gastrointestinal tract (Saven *et al.,* 2022; Xu *et al.,* 2022; Luo *et al.,* 2023). A drug-drug interaction between PPIs and clopidogrel has been reported to result in reduced plasma concentrations of clopidogrel and ultimately decreased antiplatelet effects (Tersalvi *et al.,* 2020; Saven *et al.,* 2022; Luo *et al.,* 2023). This interaction is most prominent with omeprazole and esomeprazole since they are the most potent inhibitors of the CYP2C19 enzyme, which is an important enzyme required for activation of certain $P2Y_{12}$ inhibitors, namely the prodrug clopidogrel. Rabeprazole and pantoprazole are associated with the weakest CYP2C19 inhibition, making them the safest alternative PPIs to prescribe with clopidogrel (Abrignani *et al*., 2021; Catapano *et al.,* 2022; Xu *et al.,* 2022).

Another class of drugs often prescribed in conjunction with antiplatelet therapy post-PCI are lipid lowering drugs, including statins, fibrates or ezetimibe. These drugs are co-prescribed for dyslipidaemia and to prevent and reduce risk of further atherosclerosis, re-infarction or stent thrombosis in the long-term (Grundy *et al.,* 2018; Lee & Lam, 2022).

1.4. Aims of the Study

The aims were to: 1) assess bleeding risk, 2) optimise antithrombotic therapy prescribing according to individual ischaemic and bleeding risk, and 3) evaluate outcomes in a cohort of patients undergoing PCI.

Chapter 2

Methodology

2.1. Study Design and Setting

The methodology adopted for this cohort study involved literature review and selection of a bleeding risk score to be used to evaluate bleeding risk, development and validation of a data collection sheet, ethics approval, data collection and calculation of bleeding risk, discussion with cardiologists for therapy optimisation, patient follow-up for outcomes, and data analysis (Figure 2.1). The study was carried out at the Cardiac Catheterisation Suite within the Cardiology Department at Mater Dei Hospital.

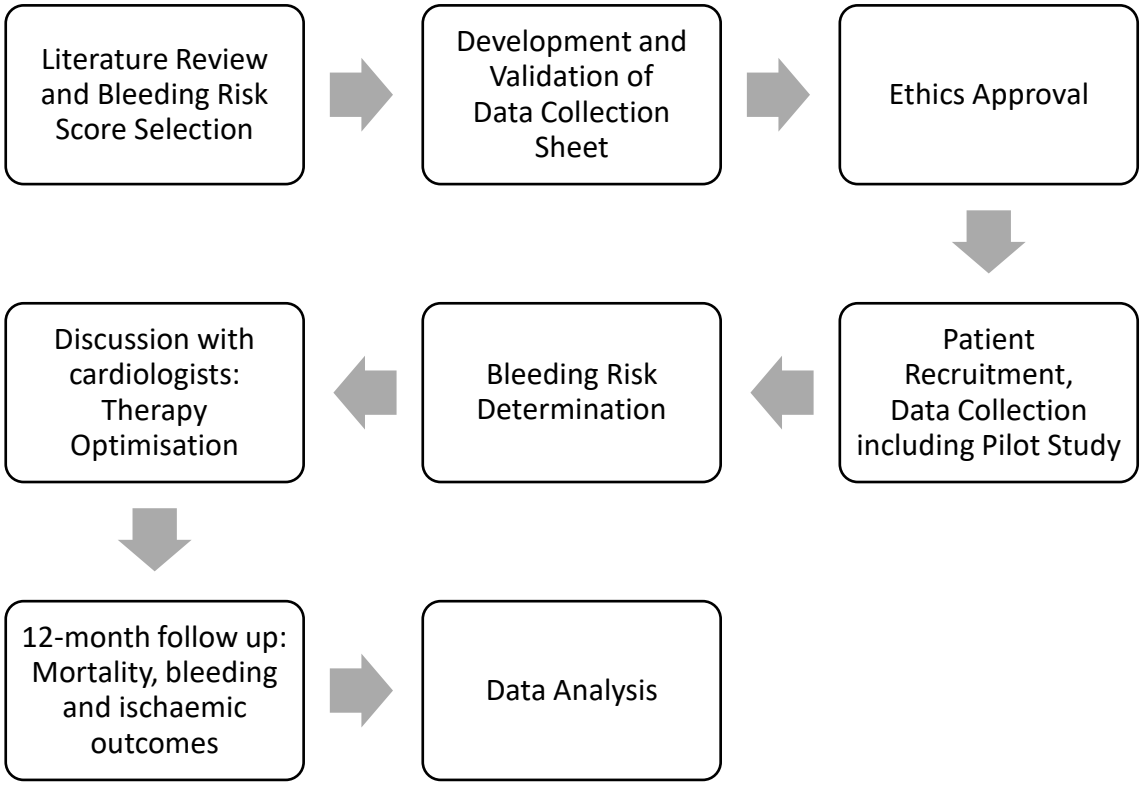

Figure 2.1: Overview of Methodology

2.2. Literature Review

A literature review was carried out to provide background information and obtain evidence-based knowledge on the research topic. Electronic databases and digital libraries such as HyDi, PubMed and Google Scholar were used. Keywords utilised were 'percutaneous coronary intervention', 'dual antiplatelet therapy', 'DAPT post-PCI', 'STEMI and NSTEMI guidelines', 'bleeding risk', 'ischaemic risk' and 'P2Y12 inhibitors'. The 2020 ESC guidelines for 'Acute Coronary Syndromes (ACS) in Patients Presenting without Persistent ST-Segment Elevation (Management of) Guidelines' and the 2017 'Guidelines on Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation' were utilised for development of the Data Collection Sheet and for the selection of the bleeding risk score to be used in this study (Capodanno *et al.,* 2018; Costa *et al.,* 2019). The guidelines issued by the American College of Cardiology/American Heart Association were also considered (Levine *et al.,* 2016).

2.3. Development and Validation of Data Collection Sheet

A Data Collection Sheet (Appendix 1) was developed based on the literature review. Face and content validation of the data collection sheet was undertaken by an expert panel composed of three cardiologists, a general practitioner and four pharmacists (from the academia, hospital, community, and pharmaceutical policy sectors). The data collection sheet was validated with respect to relevance and accuracy of content, comprehensibility, and presentation, to ensure suitability of the information to be gathered for the target population and reproducibility of data during the subsequent

data collection stages. Comments from the panel were taken into consideration and data collection sheet was updated (Table 2.1).

Table 2.1: Recommended Changes During Validation

Section	Recommended Changes
1	PCI Details: changing 'Emergency' to 'Primary' for type of PCI to improve terminology and adding 'Stable Angina' as an option for reason for PCI since latest guidelines specify different antiplatelet strategies for stable angina and ACS
3	Past Medical History; including 'GI disorders' in the list of risk factors
5	Laboratory Investigations; specifying 'male' and 'female' reference ranges for test parameters
Annex	Addition of a list of medications known to increase risk of bleeding

The Data Collection Sheet after validation was divided into eight sections (Table 2.2). The information collected included: relevant patient and PCI details, past medical history focusing on ischaemic and bleeding risk factors, medications and drug allergies, relevant laboratory investigations, bleeding risk determination, DAPT regimen prescribed and patient outcomes during follow-up. Ischaemic risk factors included smoking, hyperlipidaemia, previous MI, obesity (BMI ≥ 30kg/m^2) and a history of excessive alcohol intake or abuse. Bleeding risk factors included anaemia and drugs predisposing patients to bleeding. Factors associated with both ischaemic and bleeding risk comprised diabetes mellitus, hypertension, atrial fibrillation, prior bleeding, previous transient ischaemic attack or cerebrovascular accident, previous PCI or coronary artery bypass

graft (CABG), major surgery/trauma in the past 30 days, CAD, congestive heart failure, malignancy, chronic kidney disease and acute or chronic liver impairment.

Table 2.2: Content of Data Collection Sheet

Section	Title	Content
1	Patient Details	Age, weight, sex, type of patient admission, ethnicity
2	PCI Details	Date and type of PCI, reason for PCI, number of diseased vessels, culprit lesions
3	Past Medical History	List of disease states considered to be ischaemic and/or bleeding risk factors
4	Medications	Drug allergies, relevant drug history with regards to bleeding, current list of medications at time of PCI
5	Laboratory Investigations	Most recent relevant test parameters (haemoglobin, white blood cell count, left ventricular ejection fraction, estimated glomerular filtration rate, serum creatinine, triglycerides, HDL cholesterol, total cholesterol, LDL cholesterol, HbA1c) and calculated parameters (creatinine clearance, body mass index)
6	Bleeding Risk Determination	PRECISE-DAPT score calculation and categorisation to predict bleeding risk (low, moderate, high)
7	Antiplatelet Therapy	DAPT prescribed, planned DAPT duration, planned monotherapy post-DAPT, additional drug therapy (PPI, oral anticoagulant)
8	Outcomes	Outcomes at each follow-up timepoint (1-, 3-, 6-, 12-months post-PCI): None, minor/major bleeding, coronary revascularisation, stent thrombosis, myocardial infarction, CVA/TIA, angina, death. Haemoglobin at each follow up stage and any relevant actions taken regarding antiplatelet therapy.

2.4. Ethics Approval

Ethics approval was granted by the University of Malta Faculty of Medicine and Surgery Research Ethics Committee (FRECMDS_2021_065) (Appendix 2).

2.5. Patient Recruitment

Patients (N=200) undergoing PCI and who were candidates for DAPT, age ≥18 years, any gender, any ethnicity, were prospectively recruited by convenience sampling on days when the researcher was present at the Cardiac Catheterisation Suite. Patient recruitment took place between April 2021 and April 2022. Eligible patients were approached by an intermediary nurse at the time of PCI, and were provided with an information sheet, available in English and Maltese. Written informed consent was acquired by the intermediary from individuals who were willing to participate in the study, using a consent form available in English and Maltese. A pilot study was carried out in 10 patients to assess feasibility of the methodology. There were no changes made to the data collection sheet and the methodology following the pilot study.

2.6. Data Collection and Calculation of Bleeding Risk

The data collection sheet was completed by the researcher at the time of PCI using relevant information from the patient's hospital file, CardioVascular Information System (CVIS), iSOFT clinical manager, and via patient interview. Since patient height and weight were not available in most cases, these parameters were measured by the researcher using a weighing scale and tape measure, and body mass index was calculated.

Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault Equation (Cockcroft & Gault, 1976), where:

$$\mathrm{CrCl} = \frac{(140 - \mathrm{age}) \times (\mathrm{weight, kg}) \times (0.85 \text{ if female})}{\mathrm{creatinine}}$$

Bleeding risk was calculated using the PRECISE-DAPT score, which is currently not routinely used in local practice. The rationale for selecting this score is that compared to other scores, the PRECISE-DAPT score has the advantage of being applied at the time of stent implantation rather than requiring a waiting time of 12-months DAPT. This implies that critical decisions on DAPT choice and duration can be made at an early stage following PCI and not during follow-up appointments (Floyd, 2020; Boudreau *et al.,* 2021).

The PRECISE-DAPT score was applied and calculated for each patient using an online web-calculator.[5] Patient age, haemoglobin level, leukocyte count, creatinine clearance and history of previous episodes of bleeding were utilised to calculate the bleeding score. A patient was deemed to be at 'high risk' of bleeding if the score obtained was ≥25, 'moderate risk' if the score was between 18-24, and 'low risk' if the patient had a score <18. The '12-months risk of TIMI major or minor bleeding', and '12-months risk of TIMI major bleeding' were documented from the online PRECISE-DAPT score calculator for each patient.

[5] Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT). Webcalculator [Internet]. Italy: PRECISE-DAPT; 2017 [cited 2022 Dec 28]. Available from: http://www.precisedaptscore.com/predapt/webcalculator.html

2.7. Discussion with Cardiologists for Therapy Optimisation

All patients at moderate and high risks of bleeding and patients at low bleeding risk prescribed oral anticoagulants were discussed within the firm with each patient's cardiologist for therapy optimisation, considering also ischaemic risk. Eleven consultant cardiologists accepted to participate in the study. The cardiologists considered and accepted the bleeding risk evaluation proposed by the researcher for antithrombotic therapy optimisation on an individual patient basis. The agreed DAPT combination and duration following discussion was noted in the data collection sheet. Additional medications to be prescribed, namely PPIs and oral anticoagulants, were considered on an individual patient basis and were reviewed with the cardiologist.

2.8. Patient Follow-Up

Patient follow-up was undertaken for all patients for a one year period at 1-, 3-, 6- and 12-months after PCI using iSOFT and CVIS to monitor for mortality, major or minor bleeding, ischaemic cardiac outcomes (stent thrombosis, coronary revascularisation, myocardial infarction, stable/unstable angina) and CVA/TIA. Any actions taken in relation to the patient's antiplatelet therapy regimen were noted in addition to other significant observations. Follow-up was completed for all patients in April 2023.

2.9. Data Analysis

All relevant data acquired throughout the data collection and follow-up stages were compiled into Microsoft® Office Excel®. Descriptive statistics were carried out using

IBM® Statistical Package for the Social Sciences (SPSS®) version 27. Frequencies and percentages were adopted to present categorical variables, while continuous variables were described by mean and range.

The normality and skewness of the PRECISE-DAPT score distributions were determined using the Shapiro-Wilk test. This assumes a normal distribution for the null hypothesis and is accepted if a p-value greater than 0.05 is obtained. A p-value less than 0.05 indicates acceptance of the alternative hypothesis, which predicts the distribution to be skewed. The One-Way ANOVA test was employed to provide a comparison between the average PRECISE-DAPT scores among participants clustered by DAPT duration (short, long-term) and by outcomes (none, bleeding, angina, coronary revascularisation, stent thrombosis, death). The null hypothesis is acknowledged to be true if the p-value exceeds the 0.05 threshold, which implies that the mean PRECISE-DAPT scores vary only slightly across the groups. In the instance where the p-value is less than 0.05, the alternative hypothesis was assumed, indicating that mean PRECISE-DAPT scores differ significantly between groups.

The Paired samples t-test was employed to compare the average haemoglobin (Hb) values at the time of intervention, after 1-, 3-, 6- and 12-months, carried out pairwise. The null hypothesis indicates that the average Hb values vary slightly among two follow-up time points and is assumed if the 0.05 p-value is exceeded. In the instance of a p-value less than 0.05, assumption of the alternative hypothesis is taken, which stipulates that the average Hb values fluctuate substantially. The Fisher's exact test was utilised to

analyse the association between two categorical variables; one of these variables was DAPT duration (short, long-term) while the other variable is the outcome experienced (none, bleeding, ischaemia, mortality). No association between these categorical variables is assumed where the p-value is greater than 0.05 (null hypothesis). The alternative hypothesis states that the variation between such variables is significant, and is recognised if the p-value is less than 0.05.

2.10. Dissemination

A research abstract was presented as an Oral Presentation at the European Society of Clinical Pharmacy (ESCP) Spring Workshop held in Antwerp, Belgium, in April 2023, and was published in the International Journal of Clinical Pharmacy.

Chapter 3

Results

3.1. Patient Characteristics

A total of 200 patients were recruited and assessed, where 81% (n=162) were male and 19% (n=38) were female. Most patients were Caucasian (99%, n=197), and 3 patients were of African or Asian ethnicity. The mean age was 66 years, ranging between 37 and 88 years. The average weight was 79.5kg, ranging from 41kg to 142kg. Of the 200 patients, 76% (n=151) were inpatients and 24% (n=49) were outpatients.

3.2. PCI Characteristics

A primary/emergency PCI was the most prevalent (48%, n=96), followed by ad-hoc PCI in 37% (n=74), and elective PCI in 15% (n=30) of patients. The most common reason for PCI was STEMI (64%, n=128), followed by NSTEMI (23%, n=46) and unstable angina (12%, n=24). An average of one stent was deployed per patient on the day of PCI (range 1-3 stents), while the mean total number of stents that a patient had implanted was two (range 1-8). PCI for non-complex coronary lesions was carried out in most patients (91.5%, n=183), with a chronic total occlusion occurring in ten patients and bifurcation in seven patients. The most frequently stented lesions were the left anterior descending artery (63%, n=125) and right coronary artery (22%, n=44).

3.3. Bleeding and Ischaemic Risk Factors

CAD (n=160, 80%), hypertension (n=158, 79%) and dyslipidaemia (n=150, 75%) were the most common patient comorbidities and risk factors predisposing patients to increased risk of bleeding and ischaemia (Figure 3.1).

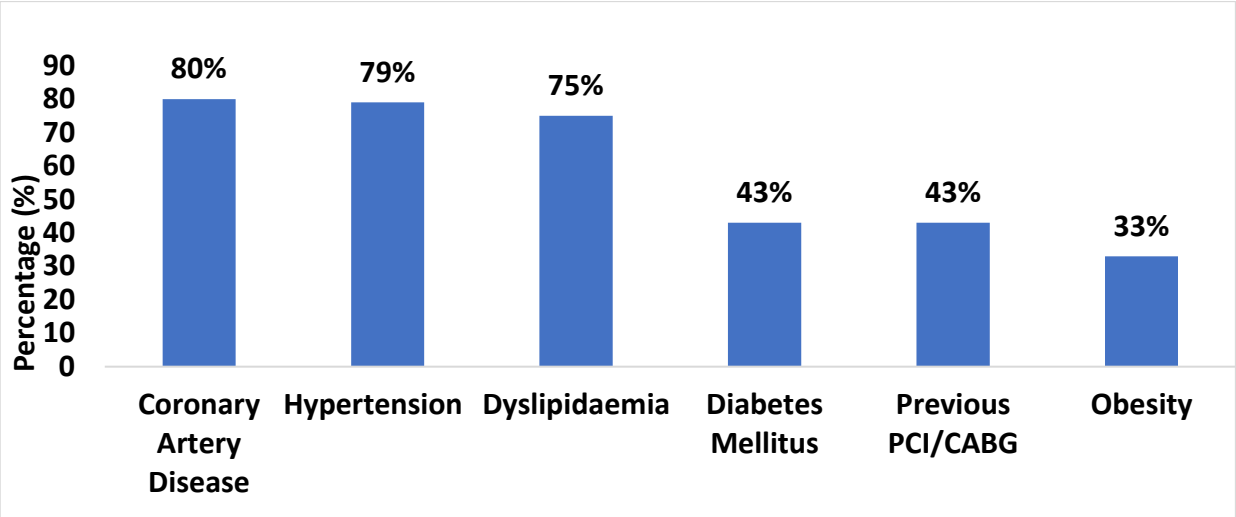

Figure 3.1: Risk Factors (N=200)

Table 3.1 presents other risk factors identified in the patient cohort studied.

Table 3.1: Other Risk Factors (N=200)

Risk Factor	% of patients
Drugs increasing Bleeding Risk	20
Previous MI	18
GORD	16
Heart Failure	13
Atrial Fibrillation	13
Chronic Kidney Disease	9
Anaemia	5
Previous CVA/TIA	5
Malignancy	4
History of Excessive Alcohol Intake/Abuse	4
Major Surgery/Trauma in the past 30 days	1
Acute/Chronic Liver Impairment	1
Prior Bleeding	0.5

3.4. Laboratory Investigations

Mean values for triglycerides and LDL cholesterol were found to be elevated, while mean HDL cholesterol and total cholesterol were within reference range. The mean glycated haemoglobin was above target. Mean body mass index was elevated, classified as overweight. In heart failure patients (n=26), mean LVEF was slightly below reference range. Mean haemoglobin prior to PCI and mean white blood cell count were found to be within reference range. The average serum creatinine was elevated, creatinine clearance was below range, and mean eGFR was above reference limits (Table 3.2).

Table 3.2: Investigations

Parameter	Mean Value
Triglycerides (0.10 – 2.26 mmol/L)	3.18 mmol/L
LDL (1.60 – 1.80 mmol/L)	2.63 mmol/L
HDL (1.15 – 1.68 mmol/L)	1.23 mmol/L
Total Cholesterol (2 – 5 mmol/L)	4.43 mmol/L
HbA1c (4.0 – 5.6 %)	7.36 %
BMI (18.5 – 24.9 kg/m^2)	29 kg/m^2
LVEF (55 – 70 %)	49.37 %
Haemoglobin (Females: 12.0 – 15.5 g/dL) (Males: 13.5 – 17.5 g/dL)	Females: 12.34 g/dL Males: 14.04 g/dL
White Blood Cell Count (4.3 – 11.4x10^9/L)	9.67x10^9/L
Serum Creatinine (45 – 84 µmol/L)	108.54 µmol/L
Creatinine Clearance (88 – 167 mL/min)	68.45 mL/min
eGFR (>60 mL/min/1.73m^2)	78.94 mL/min/1.73m^2

3.5. Bleeding Risk

Most patients (41%, n=82) were categorised as 'high' bleeding risk (Figure 3.2). The mean PRECISE-DAPT score was 23, ranging between 1 and 57.

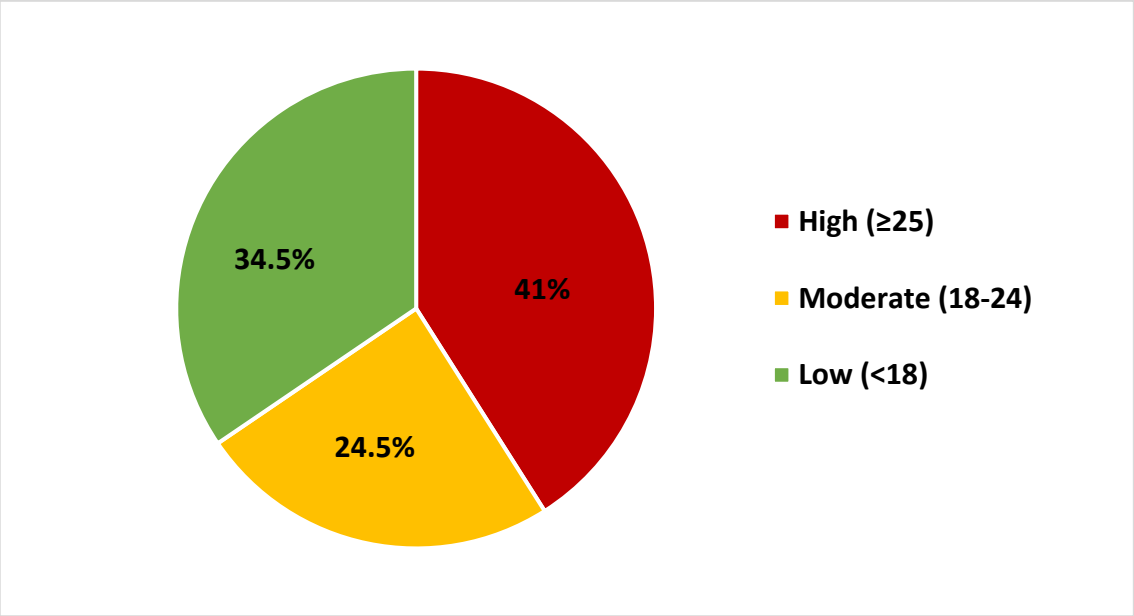

Figure 3.2: Bleeding Risk Category (N=200)

Assessment of bleeding risk pertaining to the PRECISE-DAPT score and risk of 12-months TIMI major or minor bleeding are presented in Table 3.3. Patients having higher PRECISE-DAPT scores have a greater '12 months risk of TIMI major or minor bleeding'.

Table 3.3: 12-months Risk of TIMI Major/Minor Bleeding (N=200)

Bleeding Risk Category	12 months risk TIMI major/minor bleeding	% of patients
Low	0.3 - 1.1%	34.5
Moderate	1.2 - 1.7%	24.5
High	**≥1.8%**	**41.0**

All moderate and high-risk patients and low risk patients on oral anticoagulation therapy, which amounted to 63% (n=126) of the total population, were discussed with the patients' cardiologist for antiplatelet therapy optimisation.

3.6. Antiplatelet Therapy Prescribing

All 200 patients were prescribed DAPT consisting of aspirin and clopidogrel. Patients were prescribed short-term DAPT for ≤6 months (35.5%, n=71) or long-term DAPT for 12 months (64.5%, n=129). Table 3.4 depicts the division of patients prescribed short- or long-term DAPT according to PRECISE-DAPT bleeding risk scores.

Table 3.4: DAPT Duration according to Bleeding Risk (N=200)

Bleeding Risk Category	DAPT Duration	Number of Patients (n)	% of patients
Low	Short-Term	16	8
	Long-Term	53	**26.5**
Moderate	Short-Term	21	10.5
	Long-Term	28	14
High	**Short-Term**	34	**17**
	Long-Term	48	24

The PRECISE-DAPT bleeding score calculated by the researcher was accepted by the cardiologist in 27% (n=53) of the 126 patients discussed, and a short-term DAPT duration was prescribed in these patients. Thirty-six (68%) of the 53 patients in whom the score was used for therapy optimisation were prescribed a DAPT duration of six months. Other short-term DAPT durations opted for by the cardiologists included three months, one month and two weeks. Figure 3.3 represents the various short-term DAPT durations prescribed following discussion with cardiologist with the respective bleeding risk.

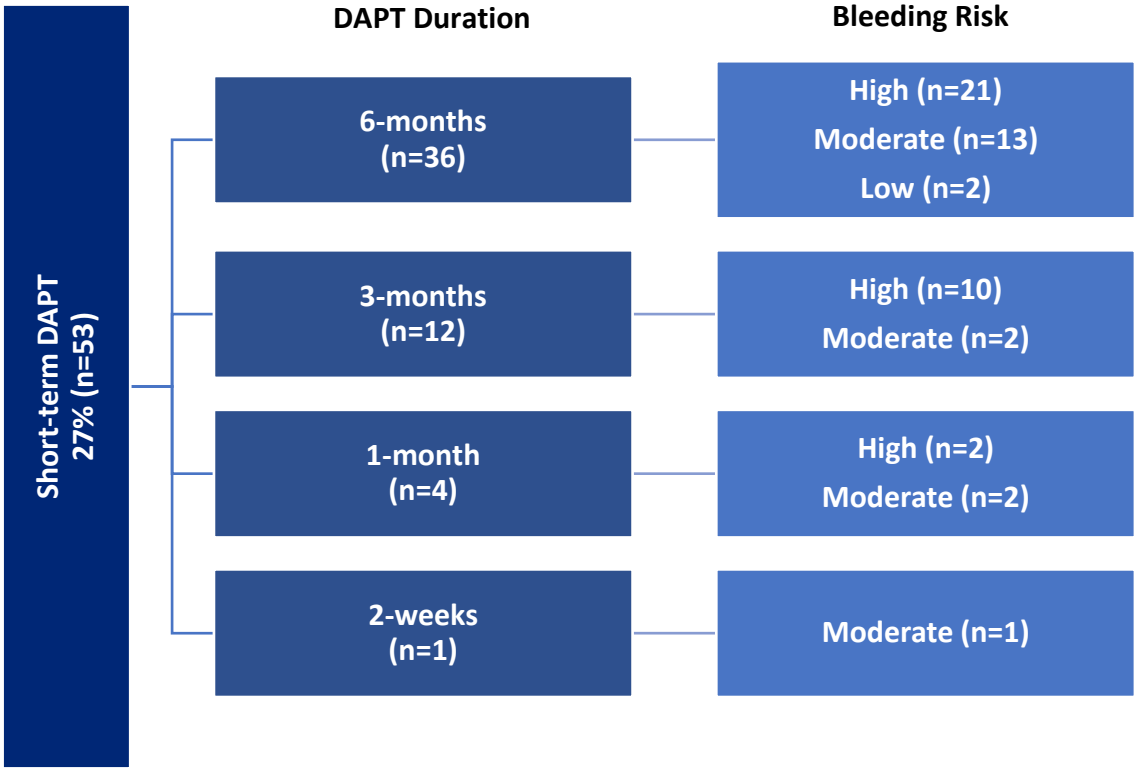

Figure 3.3: Short-Term DAPT Prescribing Guided by PRECISE-DAPT Score (n=53)

The remaining patients (n=147) were prescribed long-term DAPT for 12 months (63%) or short-term DAPT (10%) according to the cardiologist's experience and discretion. Abiding to pre-existing hospital protocols and prescribing DAPT for patients with higher ischaemic risks requiring long-term ischaemic protection were the most common reasons provided by cardiologists for not prescribing short-term DAPT duration recommended by the researcher according to the PRECISE-DAPT score.

The Shapiro Wilk p-values obtained for short-term (p=0.233) and long-term DAPT (p=0.096) exceed the 0.05 level of significance implying that the distribution of the PRECISE-DAPT score is normal, hence, parametric tests were applied. According to the results obtained using the One-Way ANOVA test (Table 3.5), mean PRECISE-DAPT score of the short-term DAPT group (25.76) significantly exceeded the mean score of the long-term group (21.24) ($p<0.05$), implying that patients at higher risk of bleeding (i.e. high PRECISE-DAPT score) were prescribed shorter DAPT duration, compared to patients with lower bleeding risk.

Table 3.5: Mean PRECISE-DAPT Scores for Short/Long Term DAPT Durations (N=200)

DAPT Duration	Mean PRECISE-DAPT Score	Std. Deviation	p-value
Short term (n=71)	25.76	11.948	**0.007***
Long term (n=129)	21.24	10.916	

*p<0.05 – statistically significant

Following DAPT, monotherapy consisting of a single antiplatelet agent was prescribed. Most patients were prescribed monotherapy lifelong (93.5%, n=187), with others (n=13) prescribed pre-determined shorter durations; twelve months (n=5), six months (n=5), three months (n=1), two months (n=1) and one month (n=1). Aspirin was the single antiplatelet agent of choice in 89.5% (n=179) of patients, followed by clopidogrel in 7.5% of patients (n=15).

A small number of patients (12.5%, n=25) were prescribed triple antithrombotic therapy instead of DAPT due to relevant comorbidities requiring an anticoagulant, such as atrial fibrillation. This combination consisted of aspirin, clopidogrel and an oral anticoagulant. In these patients, anticoagulant agents were prescribed as alternative single antithrombotic treatment options instead of single antiplatelet therapy post-DAPT; warfarin (n=3), rivaroxaban (n=2) or apixaban (n=1). All patients were co-prescribed omeprazole as a PPI for the prevention of GI bleeding.

3.7. Outcomes

Outcomes were divided into ischaemic, bleeding and mortality. Ischaemic outcomes occurred in 28.4% of patients, which included coronary revascularisation (12.5% n=25), stent thrombosis (4.5%, n=9), stable/unstable angina (10%, n=20), and myocardial infarction (1.4%, n=3). Minor bleeding, which presented as melaena, haematuria or gingival bleeding, was present in 12.2% (n=24) of patients. Mortality was documented in 2.9% (n=6) of patients.

The variation between short- and long-term DAPT for ischaemic outcomes (p=0.462) and mortality (p=0.554) was not statistically significant. For minor bleeding, a significant difference was observed (p=0.001) among short- and long-term DAPT groups. No major bleeding was observed in both short- and long-term DAPT cohorts. When omitting from the analysis patients (n=40) who were prescribed other drugs known to increase bleeding risk, no significant difference in minor bleeding among short- and long-term DAPT duration was observed (p=0.114), implying that these other drugs could have been contributing to the bleeding experienced (Table 3.6). Table 3.7 presents the drugs known to increase bleeding risk being taken by patients.

Table 3.6: Outcomes over One-Year Follow-up (N=200)

Outcome	Occurrence	% of patients		Fisher's Exact
		Short-Term DAPT	Long-Term DAPT	
Ischaemia	No	86.8%	84.8%	p=0.462
	Yes	13.2%	15.2%	
Minor bleeding	No	91.1%	96.7%	**p=0.001***
	Yes	8.9%	3.3%	
Minor bleeding (excluding drugs increasing bleeding risk)**	No	93.6%	96.7%	p=0.114
	Yes	6.4%	3.3%	
Mortality	No	98.9%	98.2%	p=0.554
	Yes	1.1%	1.8%	

*p<0.05

**Concomitant drugs other than DAPT which increase risk of bleeding: apixaban, citalopram, duloxetine, enoxaparin, escitalopram, paroxetine, prednisolone, rivaroxaban, sertraline, venlafaxine, warfarin

Table 3.7: Drugs Prescribed that Increase Bleeding Risk (n=40)

Drug Class	Agents Prescribed	Number of Patients (n)
Anticoagulants	Apixaban, enoxaparin, heparin, rivaroxaban, warfarin	26
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	Dexketoprofen, diclofenac, ibuprofen	3
Corticosteroids	Prednisolone	2
Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs)	Duloxetine, venlafaxine	3
Selective Serotonin Reuptake Inhibitors (SSRIs)	Citalopram, escitalopram, paroxetine, sertraline	6

Outcomes occurring among short- and long-term DAPT patient cohorts at each follow-up time point are shown in Table 3.8. Most outcomes occurred in the first month following PCI. Ischaemia and minor bleeding were experienced at the greatest frequency one month post PCI at 38.8% and 16.6% respectively. Mortality occurred predominantly one year after stent implantation. Negative outcomes were mostly observed in individuals with PRECISE-DAPT scores ≥25 (high bleeding risk). Minor bleeding was experienced mostly in patients categorised as high bleeding risk (8%, n=16), followed by moderate (2.5%, n=5) and low risk (1.5%, n=3). Twenty percent (n=16) of high bleeding risk patients experienced bleeding at some point throughout the study. Four out of the six patients who died during the study period were categorised as high bleeding risk, and two patients were categorised as low risk. Four out of the six patients who died

during the study were prescribed long-term DAPT duration. No statistically significant difference was detected between mortality and DAPT duration (p>0.05).

Table 3.8: Outcomes at Different Time Points During Follow-up (N=200)

Outcome	% of patients			
	Follow-Up Timepoint	Short-Term DAPT	Long-Term DAPT	Fisher's Exact
Ischaemia	1-month (n=37)	22.5%	16.3%	0.341
	3-months (n=33)	17.1%	16.5%	1.000
	6-months (n=25)	10.0%	14.2%	0.505
	12-months (n=19)	2.9%	13.6%	0.210
Minor bleeding	1-month (n=14)	12.7%	3.9%	0.038*
	3-months (n=11)	10.0%	3.1%	0.056
	6-months (n=6)	5.7%	1.6%	0.189
	12-months (n=11)	7.1%	4.8%	0.528
Mortality	1-month (n=3)	1.4%	1.6%	1.000
	3-months (n=0)	0	0	-
	6-months (n=2)	0	1.6%	0.540
	12-months (n=7)	2.9%	4.0%	1.000

*p<0.05

During follow-up, a modification in DAPT duration was documented in the patient's file for 8.5% of patients (n=17). Of these patients, nine had DAPT duration increased to 12-months for improved ischaemic protection. The remaining eight patients had a decreased duration of DAPT due to tolerability issues, from 12- to 6-months (n=6), 6- to 3-months (n=2) and 3-months to 1-month (n=1). Seven of these 17 patients had a high risk of bleeding, seven patients were moderate risk and three patients were low

bleeding risk. From this patient cohort (n=17), seven patients sustained minor bleeding, four patients experienced angina, three patients underwent coronary revascularisation and one patient experienced stent thrombosis.

The average haemoglobin levels recorded during follow-up 1-, 3-, 6- and 12-months post-PCI were 12.96, 13.16, 13.37, 13.32 g/dL respectively. Table 3.9 shows the pairwise comparison of haemoglobin levels at the time of PCI and after each follow-up timepoint. Haemoglobin levels decreased from the time of PCI to each follow-up interval. The variation between each interval was statistically significant ($p < 0.05$) at each timepoint.

Table 3.9: Haemoglobin Levels at Follow-up (N=200)

	Mean Haemoglobin (g/dL)	**Standard Deviation**	**p value Paired Sample t Test**
Hb at time of PCI	13.56	2.300	0.000
Hb 1-month	12.96	2.418	
Hb at time of PCI	13.62	2.461	0.001
Hb 3-months	13.16	2.200	
Hb at time of PCI	13.73	2.232	0.001
Hb 6-months	13.37	1.945	
Hb at time of PCI	13.78	2.184	0.000
Hb 12-months	13.32	2.110	

Chapter 4

Discussion

4.1. Significance of Individualising Antiplatelet Therapy

Identifying individuals who are at high risk of bleeding is important, especially when treating with DAPT (Gragnano *et al.,* 2022). In this regard, this study sheds light on the importance of categorising patients according to bleeding risk, as this aids in translating the most viable treatment option for that patient, considering also ischaemic risk and cardiologist experience. The study adopted a pharmacist-led personalised medicine approach and contributed towards supporting cardiologists in the optimisation of antiplatelet therapy prescribing in the interest of patient safety and outcomes. This study has the potential to help in decreasing the burden on the healthcare system by contributing to prevention of bleeding and ischaemic complications, however further study is warranted.

One of the aspects analysed in the present study was patient characteristics in relation to bleeding and ischaemic risk. The average age of patients recruited in this study was 66 years. It is established that risk of bleeding and ischaemic complications increase with age (Costa *et al.,* 2023). Race and ethnicity play a role in the determination of a patient's risk of bleeding and ischaemia. In this study, the most predominant ethnicity was Caucasian, with only a few patients belonging to other ethnicities, including African and Asian. From the current demographic data, this study cannot be used to analyse risks associated with ethnic or racial differences. However, evidence shows that Caucasians tend to have lower bleeding and ischaemic risks in comparison to Africans and Asians (Víquez Beita & Whayne, 2018; Cho *et al.,* 2020; Garcia *et al.,* 2021; Tse *et al.,* 2021). Research also shows that such populations potentially have different risk to benefit

ratios with regards to the activity of antithrombotic agents, particularly East Asians who exhibit comparatively less effectiveness with respect to clopidogrel therapy in comparison to Western patients, possibly due to genetic variation (Cho *et al.,* 2020; Xi *et al.,* 2022).

According to the 2020 ESC NSTEMI guidelines, several factors in common with the current study predisposed patients to thrombotic complications and other ischaemic or bleeding events. These included previous PCI or CABG surgery, previous MI, CAD and diabetes mellitus (Collet *et al.,* 2020). The present research identified other common risk factors including dyslipidaemia, hypertension, and obesity. The average laboratory parameters assessed prior to PCI were indicative of high risk of ischaemia with regards to dyslipidaemia, owing to the elevated triglycerides and low-density lipoprotein values, despite treatment with lipid lowering drugs such as statins or fibrates. Similarly, HbA1c was found to be elevated, predisposing patients to diabetes. Haemoglobin values were found to be within range, implying that most patients were not suffering from anaemia before PCI. This is significant since anaemia is a risk factor for bleeding. Haemoglobin values decreased significantly from the time of intervention to the time points during follow up, indicating that patients experienced bleeding (Valgimigli *et al.,* 2018; Lindholm *et al.,* 2019; Collet & Thiele, 2020).

Guidelines and other studies highlight that the complexity of the PCI may affect a patient's risk of bleeding or thrombosis (Valgimigli *et al.,* 2018; Collet *et al.,* 2020; Collet & Thiele, 2020). Guidelines state that high risk is associated with bifurcations or chronic

total occlusion, implanting more than three stents, and undergoing PCI in critical lesions such as the left main and the last patent vessel (Collet *et al.* 2020; Dhruva *et al.,* 2020). In the present study, the mean number of stents implanted was fewer (average of one stent), the left anterior descending artery was the most stented vessel, and bifurcation or chronic total occlusion only occurred in a few patients, hence patients in the present study were not at such high thrombotic risk when evaluating PCI characteristics.

Selection of the optimal DAPT combination and duration is a subject of ongoing debate worldwide. Patients who underwent PCI are typically prescribed DAPT comprising of aspirin with a $P2Y_{12}$ inhibitor. DAPT provides a more potent platelet inhibition effect than monotherapy, which results in minimisation of the likelihood of thrombotic occurrences post-PCI, yet bleeding is possible (Lee *et al.,* 2017). The DAPT combination prescribed in the current study was aspirin with clopidogrel. Clopidogrel was the sole agent of this class prescribed since it is the only one available for free on the government formulary in Malta. A potent antiplatelet agent is one of the fundamental constituents of DAPT. Guidelines recommend prasugrel or ticagrelor since they are more potent $P2Y_{12}$ inhibitors, bringing about more predictable platelet inhibition and are more effective in controlling heightened thrombotic risks in ACS (Valgimigli *et al.,* 2018; Kang *et al.,* 2023b). Ticagrelor and prasugrel are more advantageous than clopidogrel in preventing outcomes of ischaemic origin, while clopidogrel is associated with lower overall bleeding (Zhou *et al.,* 2018; Ziada & Moliterno, 2019; Schnorbus *et al.,* 2020; Collet *et al.,* 2021; Jurisic *et al.,* 2021; Lee *et al.,* 2022).

All moderate to high bleeding risk patients along with patients at low bleeding risk prescribed anticoagulants were discussed with the cardiologist, where the researcher presented the calculated PRECISE-DAPT bleeding score for each individual patient. The score was used to help the cardiologist during the decision-making process. In cases where the score was accepted, treatment duration was selected to best suit the patient's needs, i.e. short-term DAPT duration. In instances where the score was not accepted, prescribing was carried out according to the cardiologist's experience and discretion. The discussion strengthened the cardiologist-pharmacist relationship, which continues to encourage interprofessional collaboration and may lead to medication optimisation and personalisation, safeguarding appropriate and safe use of drugs. Pharmacists play a role in detecting and resolving potential issues such as drug interactions and contraindications, allowing for enhanced patient safety and patient outcomes and improved medication adherence, which are at the heart of seamless care (Reeves *et al.,* 2017; Omboni *et al.,* 2019; Zhang *et al.,* 2022).

Long-term DAPT duration was prescribed in most patients in the current study. It can be noted that the local scenario somewhat deviates from current guidelines and clinical trials which are advocating for shorter DAPT duration of one- to three-months, especially in high- bleeding risk patients (Luo *et al*., 2020; Wernly *et al.,* 2020; Watanabe *et al.,* 2022; Costa *et al.,* 2023). Results from the 'Safety of 6-month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndromes (SMART-DATE)' (Hahn *et al.,* 2018; Choi et al., 2020), 'Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing

Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE)' (Hahn *et al.,* 2019), 'GLOBAL-LEADERS' (Vranckx *et al.,* 2018) and 'Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT)' (Mehran *et al.,* 2019), among other studies, have shown that bleeding and ischaemic occurrences decreased with a reduction in DAPT duration (Collet *et al.,* 2021; Jurisic *et al.,* 2021).

However, it can be noted that most patients in the current study who were prescribed long-term DAPT (26.5%) were in the low bleeding risk category, while the greatest cohort prescribed short-term DAPT (17%) were associated with high bleeding risks. Short-term DAPT has been reported to benefit patients since it enhances medicines management by reducing exposure to unnecessary adverse drug reactions, providing better adherence to therapy, while adequately preventing further ischaemic events (Andreotti *et al.,* 2023). Cardiologists in the present study opted for shorter DAPT durations in specific instances. An example of such an occasion included prescribing of triple antithrombotic therapy owing to comorbid disease states such as atrial fibrillation or venous thromboembolism. Utilising three antithrombotic agents concurrently, including aspirin with a $P2Y_{12}$ inhibitor in addition to an oral anticoagulant, presents difficulties and challenges owing to a raised risk of bleeding complications. This further stresses the importance of balancing the requirements for optimal antithrombotic efficacy with the risk of bleeding. Personalisation of treatment is critical, in addition to close monitoring and compliance to guideline recommendations to safeguard the optimal risk to benefit ratio for patients (Angiolillo *et al.,* 2021; Collet *et al*., 2021; Andreotti *et al.,* 2023).

Following DAPT completion post-PCI, secondary prevention of ischaemic episodes is of utmost importance. This is generally carried out with antiplatelet monotherapy. Owing to a multitude of studies and inconsistent results, the type and duration of long-term monotherapy is still an ongoing debate (Lee *et al.,* 2017; Koo *et al.,* 2021; Rout *et al.,* 2022). Lifelong or long-term antiplatelet monotherapy therapy is recommended, either with a $P2Y_{12}$ inhibitor or aspirin (Collet *et al.,* 2021; Lee *et al.,* 2022). $P2Y_{12}$ inhibitors, especially clopidogrel, are correlated with lesser bleeding risk and fewer major ischaemic outcomes than aspirin (Tan *et al.,* 2023). However, guidelines still generally recommend long-term monotherapy with aspirin (Collet *et al.* 2021; Lee *et al.,* 2022). Aspirin is typically the antiplatelet agent of choice for monotherapy post-DAPT, while $P2Y_{12}$ inhibitors, such as clopidogrel, are reserved for patients with aspirin hypersensitivity or who have experienced substantial gastrointestinal adverse reactions with aspirin (Suh, 2020). According to Tan et al. (2023), the differences in death and major bleeding between these two types of antiplatelet groups was not significant, and myocardial infarction and stent thrombosis, among other ischaemic endpoints, were comparable. Aspirin is almost always maintained indefinitely following DAPT in persons with CAD (Koo *et al.,* 2021; Murphy *et al.,* 2021; Tan *et al.,* 2023). This has also been seen in a research study by Sim et al. (2020) where aspirin was preferred to clopidogrel by Korean physicians, even though there appeared to be no major variations in adverse outcomes at one year follow up. Lifelong single antiplatelet therapy was the most prescribed duration in the present study, with only a very small percentage of patients prescribed shorter periods. The GLOBAL-LEADERS trial compared monotherapy with ticagrelor for a period of 23-months following short-term DAPT, with one year of aspirin after long-term DAPT. The findings of this study established that the $P2Y_{12}$ inhibitor

strategy was preferred (Feng *et al.,* 2021). Tan et al. (2023) specifically investigated the effects of clopidogrel versus aspirin post-PCI after DAPT was completed. Clopidogrel was found to have decreased significant cardiac complications and stroke, in comparison to aspirin. Major bleeding events, stent thrombosis, MI and death were not correlated with any significant differences (Tan *et al*., 2023).

In the present study, aspirin monotherapy was prescribed for almost all patients, with exceptions made owing to aspirin intolerance or hypersensitivity, as well as additional comorbidities in which antiplatelet agents were contraindicated or not recommended. The reason for this is most likely due to the local government protocols established for the prescribing of free medicines at the time when the study was carried out. Prescribing aspirin could be done for a wider spectrum of disorders and did not have constraining limitations, as did clopidogrel. The protocols in place for clopidogrel permit it to be prescribed by cardiologists for a maximum duration of 12-months, implying that it could not be given for lifelong or longer term durations. It may also be related to the possibility that long-term aspirin is perceived as less costly than long-term clopidogrel treatment, making it a more cost-effective treatment option.

4.2. Outcomes of Short- versus Long-Term DAPT

The results of the present research exhibited no significant difference amongst cohorts prescribed short- or long-term DAPT durations with regards to ischaemic outcomes and mortality, however, minor bleeding was reported to be higher with shorter DAPT

durations. Research shows that bleeding events are possible post-PCI and are most likely to occur within the first month following stent implantation (Ducrocq *et al.,* 2015; Valle *et al.* 2016). Such bleeding may be procedure related or may be spontaneous, especially due to the platelet hyperreactivity associated with atherosclerotic disease (Gawaz *et al.,* 2023). Negative outcomes occurred more commonly in patients with high PRECISE-DAPT scores in this current study, which is comparable to other clinical trials (Choi *et al.,* 2018; Ando *et al.,* 2020; Guedeney & Collet, 2020; Clifford *et al.,* 2021; Wester *et al.,* 2021; Gragnano *et al.,* 2022). Such adverse events were also seen to occur mostly within the first month post-PCI. Hannan et al. (2023) stated that a substantial quantity of early deaths post-PCI take place after patients have been discharged, markedly within lower-risk patient groups and this finding warrants further investigation.

In patients who were not prescribed concomitant drugs that increase bleeding risk, minor bleeding was comparable between DAPT durations and was not considered to be significantly different. In the present study, no major bleeding was documented. Major bleeding in other studies is typically correlated with an abrupt and continuous raised risk of morbidity, such as haemodynamic instability, prolonged hospital stays, MI, stent thrombosis, stroke, or mortality. This is particularly relevant for individuals with high risks of developing or progressing cardiovascular disorders (Valgimigli *et al.,* 2018; Tersalvi *et al.,* 2020; Costa *et al.,* 2023). Major bleeding may indirectly increase healthcare costs due to the need for additional interventions, prolonged hospitalisation, and transfusions. This may have an extensive influence on quality of life, bringing about discomfort, mental distress, and restraints in daily activities. It is for such reasons that a

balance between decreasing ischaemic events and reducing bleeding complications must be maintained (Doble *et al.,* 2018; Kim *et al.,* 2020; Valgimigli *et al.,* 2021).

Multiple studies have correlated shorter DAPT durations with a diminished risk of major bleeding and cardiac outcomes, in comparison to longer durations (Vranckx *et al.,* 2018; Hahn *et al.,* 2019; Mehran *et al.,* 2019; Choi *et al.,* 2020; Jurisic *et al.,* 2021; Watanabe *et al.,* 2022). The STOPDAPT-2 ACS study concluded that shorter DAPT durations consisting of one month are associated with considerable decreased bleeding events. This was offset by a greater risk of significant ischaemic outcomes, which spiked interest and concern regarding the prescribing of short-term DAPT in ACS patients. (Watanabe *et al.,* 2022; Costa *et al.,* 2023). Short-term DAPT durations of one to three months are often correlated with this reduction in major bleeding exclusive of increases in ischaemic outcomes compared to long-term DAPT. When comparing among short-term durations, one month provided an inferior risk to benefit ratio than three months, as the longer duration offered better stent stabilisation (Rout *et al.,* 2022). Other studies have concluded that although patients at high bleeding risk mostly experienced ischaemic risk characteristics, shortened DAPT still provided overall clinical benefit (Núñez-Gil *et al.,* 2018; Costa *et al.,* 2019; Costa *et al.,* 2023). The MASTER DAPT trial, which investigated one month versus five months of DAPT among high bleeding risk patients, demonstrated that length of DAPT did not affect outcomes in high bleeding risk patients (Valgimigli *et al.,* 2021; Watanabe *et al.,* 2022). Research carried out in diabetics undertaking a PCI with drug eluting stents revealed that the benefit of short-term DAPT prevailing over longer DAPT durations was not statistically significant (Zhang *et al*., 2020; Gangwani *et*

al., 2022). This was similar to the results obtained in the current study. Such results highlight the importance and the need for personalising DAPT combination and duration centred around patient characteristics, ischaemic and bleeding risk (Wernly *et al.,* 2020; Kinlay *et al*., 2023).

Analogous to the research carried out by Dannenberg et al. (2021), the present study aimed to assess patients during one year follow-up. Parallel to Dannenberg et al. (2021), TIMI major or minor bleeding, plus major negative adverse cardiac and cerebrovascular outcomes were analysed throughout patient monitoring. While the current study showed that patients with 'high' bleeding risk scores experienced the most bleeding events, Dannenberg et al. (2021) differed in that the majority had a lower overall PRECISE-DAPT score, classifying them as 'moderate' bleeding risk. Minor bleeding experienced by some of these patients could be attributed to triple antithrombotic therapy and further investigation is warranted. Individuals with a PRECISE-DAPT bleeding score greater than 25 were correlated with a greater risk of bleeding and ischaemic events, stroke, MI or death (Clifford *et al.,* 2021). From all twelve patients who died in this study, the majority had a high a PRECISE-DAPT score.

4.3. PRECISE-DAPT Score Predictability

Analysing the predictability of the PRECISE-DAPT bleeding score consisted of investigating individuals who were categorised as high risk and those who experienced bleeding at some point throughout the study. Twenty percent of the patients that were

predicted as high bleeding risk patients by the PRECISE-DAPT score experienced minor bleeding during follow up. The remaining 80% of high-risk patients did not experience bleeding, even though they were predicted to be at a high risk of 12-months TIMI major or minor bleed. This implies that there may be room for improvement with respect to the score's precision and prediction capabilities, as has been stated by Messerli & Ahmed (2022).

A study by Sim et al. (2020) similarly employed the PRECISE-DAPT bleeding score to forecast bleeding risk and deemed the score useful in foreseeing 12-month bleeding in Korean patients administering DAPT, and recommended this algorithm over the DAPT bleeding score (Sim *et al.,* 2020). The PRECISE-DAPT score continues to be recognised as a standardised tool, which has recently been employed to assist and guide clinical decision making in prescribing correct treatment durations (Costa et al., 2017; Ando *et al.,* 2020; García-Rodeja Arias *et al.,* 2022). The score was deemed to have sufficient predictability for bleeding events in Asian patients (Zhao *et al.,* 2021). Larger clinical trials tend to typically consider major bleeding as a primary endpoint when taking the PRECISE-DAPT score into consideration. This outcome was absent in the present study, as only minor bleeding occurred or was reported. Even though the PRECISE-DAPT score successfully predicted actual bleeding in a small percentage of patients in the present study, it was considered a useful asset by cardiologists in the personalisation of antiplatelet therapy prescribing. The PRECISE-DAPT bleeding score is recommended to be implemented in practice to support cardiologists and could be a potential activity that a clinical pharmacist may take up as part of the cardiology firm.

4.4. Study Limitations

It is important to acknowledge the limitations of the present study. One limitation is the small sample size compared to the thousands of patients recruited in randomised controlled trials. The small sample size was expected in view of the local scenario where an average of two PCIs are performed daily. A small population was associated with difficulties in the ability to generalise the study findings and limited subgroup analysis.

Insufficient data documentation was another relevant limitation. During the procedure and throughout follow-up, certain details, such as type of DAPT combination and duration, were not consistently recorded in CVIS. This had to be further discussed with the cardiologists and nurses involved in the patients' care. The cause of bleeding experienced by patients and cause of death post-PCI were not always documented, leading to a lack of information available to the researcher. The type of minor bleeding was not always documented.

During the patient interview in the data collection phase, it was noted that not all patients were aware of their treatment regimens. Some patients did not have prior outpatient appointments hence verification of medication history and current medications was not always possible. Not all patients had follow-up appointments with subsequent haemoglobin levels tested during each follow up stage post-PCI. An additional factor for missing documentation regarding outcomes could potentially be due to patients reporting side effects and adverse outcomes to general practitioners and other healthcare professionals before their follow-up appointments with their

cardiologist, implying that such data would not be documented in the patient's hospital record. Patients did not always attend their scheduled appointments prior to and following PCI implying that certain laboratory parameters were not always close to the date of PCI, so the most recent readings were taken.

4.5. Recommendations for Future Studies

Considering gaps and limitations of a study are important to provide recommendations for improvement in future studies. A larger population size would be beneficial to provide more robust and generalisable data with respect to outcomes. Specific subgroups, such as different ethnicities, could be included. It may be recommended to have an equal number of patients in the short- and long-term DAPT cohorts for better comparison.

In attempt to improve data collection in this study, patient interview could be established by the researcher during follow-up to aid monitoring of patient adherence, identification of adverse drug reactions or negative outcomes that patients may not deem significant to report, and may improve early detection of potential complications or comorbidities. A system may be established in the primary healthcare setting where the pharmacist, in hospital and community settings, may better follow patient treatment and investigations as part of a multidisciplinary team. Together, physicians and pharmacists may implement guidelines and procedures that will be adapted to improve patient-centred care. The documentation process may be improved through

development of an online application or programme to be accessed by all relevant healthcare professionals, in both private and government institutions. In this way, physicians and pharmacists working in hospitals, health centres and community pharmacies may have access to all the data collected for each patient and may follow up patients more efficiently, allowing for improvement in personalisation of treatment.

Since only one $P2Y_{12}$ inhibitor (clopidogrel) was prescribed in the present study, it may be recommended to consider the inclusion of alternative $P2Y_{12}$ inhibitors, such as ticagrelor on the government formulary. Ticagrelor is available on the Maltese market but must be paid out of pocket and is costly. Including alternative $P2Y_{12}$ inhibitors will help in the personalisation of antiplatelet therapy and provide a better comparison with international studies.

4.6. Conclusion

Identifying individuals at high bleeding risk is of critical importance, especially when treating with DAPT. Most patients in this study were identified as high bleeding risk. This study highlighted that pharmacist-led bleeding risk evaluation in patients undergoing PCI was useful in supporting cardiologists to personalise and optimise antithrombotic therapy. Application of the PRECISE-DAPT bleeding risk score was innovative since it is currently not routinely used in local practice. The results of this cohort study demonstrated that outcomes with short-term DAPT were comparable to long-term DAPT, in line with multiple studies.

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List of Publications and Abstracts

Formosa R, Wirth F, Xuereb RG, Azzopardi LM. 'OR01.1: Pharmacist-Led Personalisation of Antiplatelet Therapy and Outcomes after Percutaneous Coronary Intervention'. *European Society of Clinical Pharmacy Spring Workshop, Antwerp, 20–21 April 2023.* International Journal of Clinical Pharmacy (IJCP). 2023;45(3):789. doi: 10.1007/s11096-023-01599-5.

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ıttps://doi.org/10.1007/s11096-023-01599-5

CONFERENCE ABSTRACTS

ESCP Spring Workshop 2023: Advancing clinical pharmacy and care in diabetes and cardiovascular comorbidities – Antwerp,20–21 April 2023

Oral Communications

OR01.1 Pharmacist-led personalisation of antiplatelet therapyand outcomes after percutaneous coronary intervention

R. Formosa[1], F. Wirth[1,*], R. G. Xuereb[2], L. M. Azzopardi[1]

[1]Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta; [2]Department of Cardiology, Mater Dei Hospital, Msida, Malta

Background and Objective: Antithrombotic therapy prescribing after percutaneous coronary intervention (PCI) is challenging and requires consideration of bleeding and ischaemic risk. The aims were to assess bleeding risk, optimise antithrombotic therapy prescribing and evaluate outcomes in patients undergoing PCI.
Setting and Method: This prospective cohort study was undertaken at the Cardiac Catheterisation Suite of an acute general hospital. Patients undergoing PCI and candidates for dual antiplatelet therapy (DAPT) were prospectively recruited by convenience sampling after ethics approval. A data collection sheet was developed, validated and completed via patient interview and hospital records. The PRECISE- DAPT score, presently not routinely used in local practice, was calculated to determine bleeding risk (C 25 high, 18–24 moderate, \ 18 low). Low risk patients on oral anticoagulation and all moderate-high risk patients were discussed with cardiologists for antithrombotic therapy optimisation. Patients were followed up over a 1-year period post-PCI for mortality, bleeding and ischaemic cardiac outcomes (stent thrombosis, stable/unstable angina, myocardial infarction, coronary revascularisation). Descriptive statistics were performed (p \ 0.05 statistically significant).
Main outcome measures: Bleeding risk, antithrombotic therapy optimisation, outcomes of long-term (12 months) versus short-term (B 6 months) DAPT duration.
Results: The 137 patients recruited (82% male, mean age 66 years, 46% primary PCI) were scored as high (42%), moderate (26%) or low (32%) bleeding risk. From the 88 (64%) patients discussed with cardiologists, the score was considered in 37 of them, and short-term DAPT was prescribed. The remaining patients were prescribed long-term (66%) or short-term (7%) DAPT irrespective of score. During the 1-year period post-PCI, most patients (51.8%) experienced negative outcomes (DAPT long-term 32.1%, short-term 19.7%, p = 0.329): Ischaemic (33.6%; long-term 22.6%, short-term 11%, p = 0.413), minor bleeding presenting as melaena, haematuria or gingival bleeding (10.9%; long-term 3.6%, short-term 7.3%, p = 0.013) and mortality (7.3%; long-term 5.8%, short-term 1.5%, p = 0.300). The remaining patients (48.2%) did not experience negative outcomes (long-term 34.3%, short-term 13.9%, p = 0.329).
Conclusion: Pharmacist-led assessment of bleeding risk with the PRECISE-DAPT score supported cardiologists in the personalisation of antithrombotic therapy post-PCI. The majority of patients experienced negative outcomes in the 12 months after PCI. There was no difference in outcomes between long-term and short-term DAPT duration, except for minor bleeding.
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Disclosure of Interest
None Declared.

OR01.3 Pilot-study: Concentration of direct oral anticoagulantsin patients undergoing cardioversion

A. Gavrilova[1,2,*], J. Meisters[3], A. ,Nikitina[1], G. Latkovskis[3,4], I. Urtāne[1]

[1]Riga Stradins University; [2]Riga Stradins University Red Cross Medical College; [3]Pauls Stradins Clinical University Hospital; [4]University of Latvia, Riga, Latvia

Background and Objective: Atrial fibrillation (AF) is the most common cardiac arrhythmia. Most patients with AF receive long-term oral anticoagulation to prevent embolic events. For patients undergoing electrical cardioversion, amiodarone as a pre-treatment is commonly administered to increase efficacy of the procedure. The risk of bleeding increases in patients with higher blood levels of direct oral anticoagulant (DOAC), and amiodarone may interfere with DOAC concentrations. The clinical practice still has uncertainty regarding monitoring DOACs in patients with safety issues. This pilot-study aimed to detect patients with higher-than-expected DOAC concentration levels in the blood.
Setting and Method: This cross-sectional study was conducted at Pauls Stradins Clinical University Hospital, Riga, Latvia, from August to December 2022. Irrespective of time since the intake of the drug one blood sample was taken at the hospital to determine DOAC concentration on the day of cardioversion. Functional anti-Xa assays for rivaroxaban and edoxaban (*Hyphen Biomed*) and anti-IIa assay for dabigatran (*Siemens Healthineers*) were used. Statistical Package for

Appendices

Appendix 1: Data Collection Sheet

Data Collection Sheet

Antiplatelet Therapy Prescribing in Patients with

High Bleeding Risk Undergoing Coronary Stenting

Data Collection Form to be completed by researcher (Raquel Formosa) using information from patient's hospital file, CVIS, iSOFT and patient interview where applicable.

Patient Study Number: _____

Cardiologist: _____

Section 1: Patient Details *(From patient hospital file, CVIS)*

Age[6]: _____ years

Weight: _____ kg

Sex: Male ☐ Female ☐ Other ☐

Patient Admission: Inpatient ☐ Outpatient ☐

Patient Ethnicity: Caucasian ☐ Other:_____

Section 2: PCI Details *(From CVIS)*

Date of PCI: _____

Type of PCI: Elective ☐ Primary ☐ Ad-Hoc ☐

Reason for PCI: STEMI ☐ NSTEMI ☐ Unstable Angina ☐

Stable Angina ☐ Other:_____

[6] Actual age of patient at last birthday required to calculate PRECISE-DAPT score

Number of Diseased Vessels: 1 ☐ 2 ☐ 3 ☐ >3 ☐

Procedure: Bifurcation ☐ Chronic Total Occlusion ☐

Non-Complex Coronary Lesion ☐

Culprit Lesion/s:

Vessel	**Yes (✓)**
Left Anterior Descending Artery	
Left Circumflex Artery	
Right Coronary Artery	
Left Main Artery	
Grafts	
Other:	

Section 3: Past Medical History (From patient hospital file, CVIS)

Ischaemic Risk Factors	**Yes (✓)**
Smoking	
Hyperlipidaemia	
Previous Myocardial Infarction	
Obesity (BMI ≥30kg/m^2)	
History of Excessive Alcohol Intake/Abuse	
Bleeding Risk Factors	
Anaemia	
Medications[7]	
Ischaemic and Bleeding Risk Factors	
Diabetes Mellitus	
Hypertension	
Atrial Fibrillation	
Prior Bleeding[8]	
Previous CVA/TIA	
Previous PCI / CABG	
Major Surgery/Trauma in the past 30 days	
Coronary Artery Disease	
Congestive Heart Failure	
Malignancy	
Acute or Chronic Liver Impairment	
Chronic Kidney Disease (Reduced kidney function expressed as eGFR <60mL/min per 1.73m^2)	
Other: E.g. Peptic Ulcer Disease	

[7] Refer to Annex

[8] History of spontaneous bleeding requiring medical attention, defined according to TIMI definitions. TIMI major bleeding; intracranial haemorrhage or bleeding with a haemoglobin decrease of >5 g/dl or haematocrit decrease of >15%. TIMI minor bleeding; dependent on identifiable source of blood loss.

Section 4: Medications[9]

Drug Allergies: Yes *(Iva)* ☐ No *(Le)* ☐

If Yes, which drugs? *(Jekk Iva, liema mediċina/i?)*_____

_____

_____

_____

Relevant Drug History with regards to Bleeding:

Are you aware of any medication that has been stopped due to bleeding? *(Taf b'xi mediċina/i li ġiet/ġew imwaqqfa minħabba li kkawzat/aw dmija?)* _____

_____

_____

_____

_____

[9] Past and present drugs prescribed are to be verified by the researcher with the patient via interview in English or Maltese.

Current Medications:

Generic Name	Dose	Dosage Regimen	Start Date (if known)

Section 5: Laboratory Investigations *(from patient hospital file, iSOFT)*

The most recent data closest to date of PCI shall be recorded.

Test Parameter	Result	Date
Haemoglobin (Hb) (M: 13.5-17.5g/dL; F: 12.0-15.5 g/dL)		
White Blood Cell Count (WBC) (4.3-11.4 x10^9/L)		
Left Ventricular Ejection Fraction (LVEF) (55-70%)		
Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73m^2)		
Serum Creatinine (SCr) (45-84 μmol/L)		
Triglycerides (TG) (0.10-2.26 mmol/L)		
HDL Cholesterol (HDL-C) (1.15-1.68 mmol/L)		
Total Cholesterol (TC) (2.0-5.0 mmol/L)		
LDL Cholesterol (LDL-C) (1.60-1.80 mmol/L)		
HbA1c (4.0-5.6%)		

Calculated Parameter	Result
Creatinine Clearance (CrCl)[10] (88-137 mL/min)	
Body Mass Index (BMI) (18.5-24.9 kg/m^2)	

[10] Calculated using the Cockcroft-Gault Equation = (140 – age) × (weight, kg) × (0.85 if female) / Cr

Section 6: Bleeding Risk Determination

The PRECISE-DAPT score is used to assess and predict each patient's risk of bleeding when treated with DAPT. It is calculated via a web-calculator[11], providing a numerical value and assigning a bleeding risk score to each patient, i.e. high, moderate or low. This score takes 5 factors into account; age, prior bleeding, Hb, WBC count and CrCl.

PRECISE-DAPT Score	Bleeding Risk	
1-17	Low	☐
18-24	Moderate	☐
≥25	High	☐

Section 7: Dual Antiplatelet Therapy

Patients at **moderate and high bleeding risk** are discussed with the cardiologist. Ischaemic risk factors are also addressed in the discussion. The cardiologist's clinical judgement and the outcome of the discussion are noted.

DAPT Prescribed: Yes ☐ No ☐

If yes, which combination?_____

If no, what antithrombotic therapy is prescribed? _____

Planned DAPT Duration : 1 month ☐ 3 months ☐ 6 months ☐ 12 months ☐

Planned single antiplatelet agent to be prescribed after DAPT and duration: _____

_____

[11] Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT). Webcalculator [Internet]. Italy: PRECISE-DAPT; 2017 [cited 2021 Mar 12]. Available from: http://www.precisedaptscore.com/predapt/webcalculator.html

Proton Pump Inhibitor (PPI) Prescribed: Yes ☐ No ☐

If Yes, which PPI, dose, duration?_____

If No, reason why: _____

Oral Anticoagulant (OA) Prescribed: Yes ☐ No ☐

If Yes, which OA, dose, duration?_____

_____

Section 8: Outcomes

Bleeding and ischaemic outcomes are monitored (Ibanez *et al.,* 2018; Collet *et al.,* 2020).

Patient follow-up is undertaken 1, 3, 6 and 12 months after PCI. Hb levels are recorded at each follow-up. Any action taken regarding DAPT (e.g. DAPT shortening, DAPT de-escalation, monotherapy prescribed) is recorded.

Outcome	**Months After PCI**			
	1	**3**	**6**	**12**
None				
Major/Minor Bleeding[3]				
Coronary Revascularisation				
Stent Thrombosis				
Myocardial Infarction				
CVA/TIA				
Unstable Angina				
Death				
Other Relevant Observations:				

	Months After PCI			
	1	**3**	**6**	**12**
Hb (g/dL)				

Action taken in relation to antiplatelet therapy if applicable and any other relevant observations:

References of Data Collection Form

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Annex to Data Collection Form

Drugs Known to Cause Bleeding:

Drug class	Specific Agents	Yes (✓)
Anticoagulants	Enoxaparin, heparin, rivaroxaban, warfarin Others:	
NSAIDs	Low risk: celecoxib, diclofenac, ibuprofen, meloxicam High risk: etoricoxib, naproxen Others:	
Corticosteroids	Dexamethasone, methylprednisolone, prednisolone Others:	
SNRIs	Duloxetine, venlafaxine Others:	
SSRIs	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline Others:	

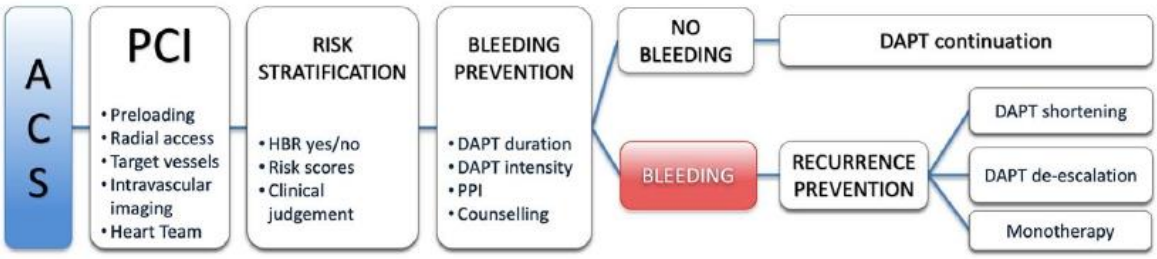

Figure 1: Critical points in decision making for DAPT prescribing.

Reproduced from: Tersalvi G, Biasco L, Cioffi GM, Pedrazzini G. Acute Coronary Syndrome, Antiplatelet Therapy, and Bleeding: A Clinical Perspective. Journal of Clinical Medicine. 2020; 9 (7): 1-20.

Appendix 2: Ethics Approval

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Ref No: FRECMDS_2021_065

8 March 2021

Ms Raquel Formosa
21, Rockfort,
Sir Walter Scott Street,
Naxxar. NXR4112

Dear Ms Formosa,

With reference to your application submitted to the Faculty Research Ethics Committee in connection with your research entitled:

Antiplatelet Therapy Prescribing in Patients with High Bleeding Risk Undergoing Coronary Stenting

The Faculty Research Ethics Committee granted ethical approval for the above mentioned application reviewed on 24 February 2021 following the submission and approval of amendments.

Yours sincerely,

Professor Pierre Mallia
Chairman
Faculty Research Ethics Committee