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Are We Optimizing the Use of Dual Antiplatelet Therapy in Patients Hospitalized with Acute Myocardial Infarction?

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ARE WE OPTIMIZING THE USE OF DUAL ANTIPLATELET THERAPY IN PATIENTS HOSPITALIZED WITH ACUTE MYOCARDIAL INFARCTION?

A Masters Thesis Presented

BY

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ABSTRACT

Background: Dual antiplatelet therapy (DAPT) is a mainstay treatment for hospital survivors of an acute myocardial infarction (AMI). However, there are extremely limited data on the prescribing patterns of DAPT among patients hospitalized with AMI.

Objective: To examine decade-long trends (2001-2011) in the use of DAPT versus antiplatelet monotherapy and patient characteristics associated with DAPT use.

Methods: The study population consisted of 2,389 adults hospitalized with an initial AMI at all 11 central Massachusetts medical centers on a biennial basis between 2001 and 2011. DAPT was defined as the discharge use of aspirin plus either clopidogrel or prasugrel. Logistic regression analysis was used to identify patient characteristics associated with DAPT use.

Results: The average age of the study population was 65 years, and 69% of them were discharged on DAPT. The use of DAPT at the time of hospital discharge increased from 49% in 2001 to 74% in 2011; this increasing trend was seen across all age groups, both sexes, types of AMI, and in those who underwent a PCI. After multivariable adjustment, older age was the only factor associated with lower odds of receiving DAPT, while being male, receiving additional evidence-based cardioprotective therapy and undergoing cardiac stenting were associated with higher odds of receiving DAPT.

Conclusions: Between 2001 and 2011, the use of DAPT increased markedly among patients hospitalized with AMI. However, a significant proportion of patients were not discharged on this therapy. Greater awareness is needed to incorporate DAPT into the management of patients with AMI.

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LIST OF SYMBOLS, ABBREVIATIONS, OR NOMENCLATURE

AMI, acute myocardial infarction

ASA, aspirin

CABG, coronary artery bypass graft

DAPT, dual antiplatelet therapy

GFR, glomerular filtration rate

GI, gastrointestinal

PCI, percutaneous coronary intervention

STEMI, ST segment elevation myocardial infarction

NSTEMI, non-ST segment elevation myocardial infarction

PREFACE

Coronary artery disease has been the leading cause of death over the past decade. With the advancement of the management for this disease, several treatment modalities have been emerging that are contributing to better outcomes and quality of life, particularly among survivors of acute myocardial infarction. Dual antiplatelet therapy is a mainstay treatment for hospital survivors of an acute myocardial infarction, and guidelines are consistent in their recommendations for this therapy specially in recent years. In fact, dual antiplatelet therapy has been shown to reduce major adverse cardiovascular outcomes among survivors of acute myocardial infarction compared to antiplatelet monotherapy. However, there are extremely limited data on the prescribing patterns of dual antiplatelet therapy among patients hospitalized with acute myocardial infarction during recent years. Considering this, it is crucial to continuously monitor the implementation of evidence-based medicine by looking at trends in the use of cardioprotective drug therapies, such as DAPT, and examine patient characteristics that are associated with the receipt of this kind of therapy to enhance physicians' awareness for subjects that may be undertreated with this therapy.

CHAPTER I. INTRODUCTION

Despite advances in the management of patients with acute and chronic forms of coronary artery disease, this disease remains a leading cause of morbidity and mortality worldwide (1). Antiplatelet medications are a mainstay therapy for the secondary prevention of an acute coronary syndrome as these therapies have been consistently shown to reduce cardiovascular morbidity and mortality (2, 3). Moreover, dual antiplatelet therapy (DAPT), where aspirin (ASA) is combined with the use of a P2Y12 receptor inhibitor (clopidogrel, prasugrel or ticagrelor), provides stronger platelet inhibition than a single antiplatelet medication. Use of DAPT has been shown to lead to a greater reduction in recurrent major adverse cardiovascular events in patients with an acute coronary syndrome as well as among those undergoing a percutaneous coronary intervention with stable coronary artery disease compared with aspirin monotherapy (4-9).

Currently, American College of Cardiology/American Heart Association (10) and European Society of Cardiology guidelines (11) recommend dual antiplatelet therapy for effective secondary prevention among hospital survivors of an acute coronary syndrome, regardless of the revascularization intervention implemented. It remains of importance to continuously monitor the use of evidence-based therapy with antiplatelet medications, most notably DAPT, for the management of survivors of an acute coronary event. However, there are limited published data in the United States that has described changes over time in the use of, and factors associated with, DAPT in patients hospitalized with an acute myocardial infarction (AMI) (12).

The primary objective of this observational study was to describe changes over time in the use of, and factors associated with, DAPT in residents of central Massachusetts hospitalized for

an initial AMI at all 11 metropolitan Worcester medical centers on a biennial basis between 2001 and 2011. Our secondary study objective was to describe the characteristics of patients treated with DAPT versus aspirin monotherapy during the decade-long period under study and whether there have been changes in the characteristics of patients more or less likely to receive this beneficial therapy.

CHAPTER II. METHODS

Data for this investigation were derived from the Worcester Heart Attack Study (13). This is an ongoing population-based investigation that is examining long-term trends in the incidence, hospital, and post-discharge case-fatality rates of AMI among residents of central Massachusetts hospitalized at all greater Worcester medical centers. The medical records of residents of the Worcester metropolitan area hospitalized for possible AMI were individually reviewed on an approximate biennial basis and a diagnosis of AMI was validated with pre-defined criteria (14).

Data Collection

Demographic, clinical, and in-hospital management data were abstracted from hospital medical records of geographically eligible patients with confirmed AMI by trained study physicians and nurses. Information was collected about patient's age, sex, comorbidities (e.g., diabetes, hypertension, stroke, chronic kidney disease, atrial fibrillation), AMI order (initial versus. prior) and type ((ST-elevation Myocardial Infarction (STEMI) versus non-ST-elevation Myocardial Infarction (NSTEMI)), significant in-hospital AMI-related complications, in-hospital pharmacologic management and receipt of diagnostic/interventional procedures.

Details regarding the antiplatelet regimen (DAPT or monotherapy) given at the time of hospital discharge were also obtained. DAPT was defined as the receipt of a combination of ASA and a P2Y12 receptor inhibitor (clopidogrel or prasugrel) at the time of hospital discharge, while antiplatelet monotherapy was defined as being prescribed either ASA or clopidogrel alone at the time of hospital discharge. Since ticagrelor, another P2Y12 receptor inhibitor, was not approved until 2013, we did not have data about the use of this drug in our study population. Because we

wanted to compare the characteristics of patients who received DAPT versus monotherapy, we excluded patients who did not receive any form of antiplatelet therapy. Moreover, since current clinical guidelines recommend DAPT for up to 12 months after a PCI with stent implantation before switching to monotherapy (10), we only included patients with an initial episode of AMI. In addition, because the addition of DAPT to oral anticoagulation therapy leads to a two to three-fold increase in bleeding risk (15), patients who were also treated with anticoagulant therapy were excluded from the present investigation. Moreover, we excluded subjects who had coronary artery bypass graft (CABG) in this study due to their high risk of bleeding. Moreover, we collected data on the type of hospital that the patients were admitted to (teaching vs. non-teaching) as well as receipt of evidence-based medical therapy (beta blockers, statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers). This study was approved by the Institutional Review Board at the University of Massachusetts Medical School.

Data Analysis

Differences in the distribution of demographic, medical history, and clinical characteristics between patients with AMI who received DAPT versus monotherapy were examined using chi-square and t tests for discrete and continuous variables, respectively. The significance of changes over the decade-long study period in the use of antiplatelet therapy was examined using chi-square tests for trends. A logistic multivariable logistic regression approach was used to examine the association between several demographic and clinical characteristics with the receipt of DAPT during the patient's index hospitalization for an initial AMI. Stratified analyses by type of AMI (STEMI vs. NSTEMI) and receipt of PCI was also done. Regression diagnostics were performed,

and all the models reported were deemed fit. All statistical analyses were performed with the use of STATA MP software, version 13.1, and a two-sided p-value of 0.05 or less was considered to indicate statistical significance.

CHAPTER III. RESULTS

Study Population Characteristics

The study population consisted of 2,389 hospital survivors of an initial, independently validated AMI at all 11 central Massachusetts medical centers. In this population, 1,657 patients (69.4%) were discharged from participating central Massachusetts hospitals on DAPT (Table 1). Patients who received DAPT at the time of hospital discharge were younger, more likely to be male, who developed a STEMI, and who underwent a cardiac catheterization and a PCI (Table 1). On the other hand, a smaller percentage of patients who received DAPT developed important hospital complications of AMI including heart failure. A greater proportion of patients who received monotherapy were previously diagnosed with various co-morbid medical, experienced a longer hospital stay, were less likely to be treated at teaching hospitals or receive evidence-based medical therapy for AMI and received thrombolytic therapy during their hospitalization (Table 1).

Trends in the use of DAPT among hospital survivors of AMI

The proportion of patients who presented with an initial AMI and received DAPT at the time of hospital discharge increased steadily over time from 49% in 2001 to 74% in 2011 (Figure 1). This increase was seen across all age groups, in both sexes, in patients with a STEMI or an NSTEMI, and in those who underwent a PCI (Figure 1). After controlling for several demographic factors, comorbid conditions, hospital revascularization procedures, and complications of AMI, the odds of receiving DAPT at the time of hospital discharge significantly increased during the

years under study (Table 2). This trend was also seen after stratifying for the type of AMI and the receipt of a PCI (supplementary tables 1 and 2).

In examining possible changing trends in DAPT use across different patient groups (Table 3), the utilization of DAPT significantly decreased with advancing age, and was less often prescribed to women as compared with men. There was a significant increase during the years under study in the use of DAPT among patients with a STEMI or a NSTEMI, with different previously diagnosed co-morbidities, among those with and without prior antiplatelet use, and among those who underwent a PCI.

Factors Associated with Receipt of DAPT at the Time of Hospital Discharge

In the fully adjusted logistic regression model, patients who were between the ages of 65 and 74 years were at significantly lower odds for receiving DAPT at the time of hospital discharge, while being male, receiving evidence-based medical therapy and undergoing a cardiac catheterization and a PCI were associated with a higher odds of receiving DAPT; undergoing a PCI was the strongest predictor of DAPT use (Table 4). Similar results were seen after stratifying for type of AMI (supplementary Table 3). However, after stratifying the data according to whether or not patients underwent a PCI, none of these demographic or clinical factors were associated with DAPT use among those who had PCI during their hospitalization (supplementary Table 4).

CHAPTER IV. DISCUSSION

Platelet adhesion and activation and subsequent aggregation represent the key targets for the secondary prevention of an acute coronary event. At the cellular level, aspirin and thienopyridines inhibit platelet activation through different mechanisms, and prior studies have shown the synergistic effects of DAPT on decreasing platelet activity and improving anti-inflammatory effects compared with monotherapy alone in high-risk populations (16). Inasmuch, adding a thienopyridine to aspirin therapy has well-established benefits in the setting of an acute coronary syndrome, including patients who developed a STEMI or a non-STEMI (5, 17) and among those who underwent a PCI (9, 18), by reducing the risk of stent thrombosis, recurrent AMI, and cardiovascular mortality compared with aspirin alone. Hence, current guidelines recommend DAPT for at least 12 months among patients with an acute coronary syndrome regardless of the type of coronary revascularization procedure performed (10, 11).

Trends in the use of DAPT among hospital survivors of AMI

To the best of our knowledge, there are very limited data and comparable studies describing trends in the use of different antiplatelet regimens for patients with AMI in the U.S. (19). The results of the present study demonstrate that the use of DAPT among residents of central Massachusetts hospitalized at all 11 greater Worcester medical centers for a first AMI has steadily increased during the decade-long period under study. This was seen among patients of different ages, both sexes, with different comorbidities, and after adjusting for several demographic factors, comorbid medical conditions, other hospital management practices, and occurrence of several

clinically important complications. This finding may reflect an increased awareness among clinicians to prescribe DAPT over monotherapy, and more optimal patient management practices.

Data from several cardiovascular disease registries report overall usage of DAPT among patients discharged after an acute coronary syndrome in Europe and Canada to be between 60 and 80%, depending in part on the characteristics of the study population, period under observation, and the type of acute coronary event examined (20, 21). Similar to our study, increases in the use of DAPT among hospital survivors of an AMI has also been seen in studies from Denmark and Sweden (22, 23), In one study of 28,449 patients who survived a first AMI between 2009 and 2012 in Denmark, there was a slight increase in the proportion of patients who received DAPT from 68% in 2009 to 73% in 2012 (22). Similar findings have been observed in a retrospective cohort study which used data from a Swedish national registry of patients hospitalized with AMI (24). In this investigation, there was a decrease in the proportion of patients not receiving DAPT, from 33% in 2009 to 25% in 2013.

Factors Associated with the Receipt of DAPT

In examining differences in the characteristics of patients who received either DAPT or monotherapy, those who were treated with monotherapy appeared to be a sicker group of patients as reflected by their older age and presence of more co-morbid conditions; they also were less likely to be treated at teaching hospitals or receive evidence-based medical therapy for AMI. This may reflect suboptimal adherence to recommended guidelines at those hospitals included in the study, where subjects are not discharged on recommended therapies like DAPT. Moreover, we showed that being a man and undergoing cardiac catheterization and a PCI was associated with a

higher odds of being prescribed DAPT. Factors such as being a woman, of advanced age, and having chronic kidney disease have been associated with a higher risk for bleeding after an AMI (25-27). In addition, patients with a history of GI bleeding were less likely to have received DAPT during their acute hospitalization This is likely explained by the fact that antiplatelet therapy increases the risk of GI bleeding, and the risk of GI bleeding is further increased in patients on DAPT, likely due to prostaglandin inhibition by aspirin and decreased platelet aggregation by both aspirin and P2Y12 inhibitors (28). However, the resumption of antiplatelet therapy following an episode of GI bleeding has been shown to decrease mortality and the risk of recurrent ischemic events, despite increasing the risk of episodes of minor or major bleeding (29). Inasmuch, antiplatelet therapy, particularly DAPT, should be considered among patients who are at risk for adverse events or have a history of GI bleeding, and the use of proton pump inhibitors should be strongly considered in these patients since these agents have been shown to reduce the risk of GI bleeding in patients on DAPT and has been strongly recommended as a Class I indication(10, 30). Inasmuch, the reasons for not prescribing DAPT to certain patient groups may have been based on physicians' judgment given the high risk of bleeding among sicker patients, due to failing DAPT while in the hospital secondary to bleeding, medication costs, or less likely, to suboptimal care for these patients, as seen by the differences in receipt of evidence-based cardioprotective therapies.

Despite the encouraging trends in increased use of DAPT over time, a considerable percentage of patients with a confirmed AMI failed to receive DAPT. In fact, we observed significant age and gender disparities in the use of DAPT as we noted that older patients and

women were less likely to be prescribed this therapy than respective comparison groups. This is of particular concern since women and older individuals who develop an AMI have a worse prognosis and are at greater risk for developing a recurrent AMI compared with men and their younger counterparts (31, 32). Disparities in age and sex with respect to the management of AMI survivors have also been reported in other studies which have shown that women and older individuals were less likely to receive antiplatelet therapy and other cardio-protective medications than men and younger individuals (33).

Despite the fact that the most recent year under study was 2011, there is usually a considerable lag time between guideline updates and widespread adoption of various AMI therapies, including DAPT, in clinical practice, which may explain the suboptimal utilization of DAPT during the period under study. For patients with a NSTEMI, recommendations for long-term DAPT use post discharge have been established since 2002 (34). However, for patients with a STEMI, the recommendations for DAPT use have gained more strength in the last 5-10 years. Since the publication of the 2004 guidelines for the treatment of patients with a STEMI (35) that recommended DAPT only among those who received a stent, 2 trials have provided data supporting the expansion of the use of DAPT to those with a STEMI, irrespective of the type of reperfusion therapy utilized (36, 37). Not until 2007 did the ACC/AHA guidelines recommend the continued and long-term use of DAPT post discharge among survivors of an STEMI, regardless of revascularization therapy (Class IIa; Level of Evidence: C)) (38); this recommendation became more solid and with a higher class recommendation (Class I) and level of evidence (B) in the 2009

ACC/AHA guidelines for the management of STEMI (39) and has been maintained in the most recent guidelines (10).

Study Strengths and Limitations

The current study has several strengths. First, we included patients from a well characterized urban community in central Massachusetts hospitalized with an independently validated first AMI at all hospitals in central Massachusetts. Moreover, this is the first U.S. study to examine trends in the discharge use of DAPT among a large number of patients hospitalized with AMI over a decade-long period who resided in a defined community. Additionally, we were able to control for a number of potentially confounding factors in examining patient characteristics associated with the receipt of DAPT in patients hospitalized with AMI.

The limitations of our study include that the absence of data on the duration of DAPT for subjects who took it, which is the major area of debate in the recent years. In addition, we did not have data for use of the newest P2Y12 inhibitor, ticagrelor, as the drug was not approved until 2013. Data on adherence to the regimen or switch between different antiplatelet medications, which is another topic that is still heavily researched (40), is also absent.

CHAPTER V. CONCLUSION

In conclusion, the use of DAPT for the secondary prevention of AMI among patients with an AMI has increased over time, reflecting enhanced prescribing of evidence-based therapy. Despite the significant benefits on patient survival that have been observed with the use of DAPT compared with antiplatelet monotherapy, we observed that a significant proportion of patients discharged from the hospital after an AMI were not prescribed DAPT. Inasmuch, it is crucial to continuously monitor the implementation of evidence-based medicine by looking at trends in the use of cardioprotective drug therapies, such as DAPT, and examine patient characteristics that are associated with the receipt of this kind of therapy to enhance physicians' awareness for subjects that may be undertreated with this therapy. Therefore, it is crucial to increase awareness among physicians to incorporate DAPT in the management of vulnerable group of patients, while varying the duration of DAPT according to the risk of bleeding in the context of current guidelines.

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TABLES AND FIGURES

Table 1. Baseline characteristics of hospital survivors of an initial acute myocardial infarction according to the receipt of antiplatelet therapy at the time of hospital discharge

Characteristic	**DAPT (n = 1,657)**	**Monotherapy (n = 732)**	**p-value**
Age, mean (SD), years	61.8 (13.5)	70.9 (13.7)	<0.001
Male (%)	66.2	48.4	<0.001
White (%)	88.3	88.8	0.72
ST-segment elevation myocardial infarction (%)	46.7	25.4	<0.001
Medical history (%)			
Chronic kidney disease	9.7	15.7	<0.001
Chronic obstructive pulmonary disease	8.3	17.6	<0.001
Diabetes mellitus	25.5	30.9	<0.01
Heart failure	5.7	16.0	<0.001
Hyperlipidemia	58.6	50.6	<0.001
Hypertension	62.3	69.1	<0.01
Peripheral vascular disease	9.7	13.2	<0.05
Percutaneous coronary interventions	7.6	6.8	0.5
Stroke	4.2	9.2	<0.001
GI Bleeding	1.9	4.8	<0.001
Peptic Ulcer Disease	2.2	4.9	<0.001

Antiplatelet therapy	29.7	33.6	0.056
Hospital length of stay, days, mean (SD)	3.9 (3.1)	5.9 (4.5)	<0.001
Teaching hospital	97.65	86.8	<0.001
Evidence-based medical therapy	57.9	27.3	<0.001
Laboratory Data			
Serum cholesterol mg/dL, mean, (SD)	181.5 (43.0)	180.0 (48.0)	0.53
Serum triglycerides mg/dl, mean (SD)	148.7 (110.7)	136.6 (97.2)	<0.05
Serum LDL mg/dl, mean (SD)	111.9 (39.03)	110.0 (44.74)	0.40
Serum HDL mg/dl, mean (SD)	41.4 (11.8)	44.6 (20.73)	<0.001
Serum glucose, mg/dL, mean (SD)	158.5 (72.4)	168.9 (78.9)	<0.01
Hematocrit, %	41.2 (5.1)	40.2 (23.0)	0.10
Troponin I, mean, (SD)	10.5 (54.8)	11.7 (58.7)	0.64
eGFR mL/min/1.73m^2, mean, (SD)	66.1 (19.5)	56.4 (21.3)	<0.001
Diagnostic/Interventional Procedure (%)			
Cardiac catheterization	90.1	48.9	<0.001
Percutaneous coronary intervention	81.4	13.0	<0.001
Thrombolytic therapy	3.7	4.8	0.23
Hospital Complications (%)			
Cardiogenic shock	2.3	2.9	0.40
Heart failure	17.1	36.6	<0.001
Stroke	0.5	1.1	0.09

Table 2. Trends in the receipt of DAPT at the time of hospital discharge among hospital survivors of an initial acute myocardial infarction (Worcester Heart Attack Study)

Study year	Odds ratio (95% confidence interval)*
2001	Reference year
2003	2.27 (1.41; 3.08)
2005	3.34 (2.15; 4.98)
2007	4.75 (2.84; 6.66)
2009	3.70 (2.08; 4.94)
2011	3.50 (2.07; 4.81)

** Adjusted for age, sex, race, previously diagnosed comorbid conditions (hypertension, diabetes, heart failure, chronic kidney disease, peripheral vascular disease, stroke, chronic obstructive lung disease, GI bleeding, peptic ulcer disease), hospital development of a STEMI, coronary revascularization procedure, type of hospital, receipt of evidence-based therapy, and the development of hospital complications (stroke, heart failure, and cardiogenic shock)*

Table 3. Changes over time in the receipt of DAPT at the time of hospital discharge for an initial acute myocardial infarction according to select patient characteristics

Characteristic	**2001/2003 (n=891) % receiving**	**2005/2007 (n=767) % receiving**	**2009/2011 (n=731) % receiving**	**p for trend**
Age (years)				
<55	76.1	90.7	88.5	
55-64	67.8	82.5	82.1	<0.001
65-74	60	76.5	66.7	
≥ 75	35.1	62.3	61.0	
Male	65.6	83.9	79.6	<0.001
Female	46.5	66.2	68.3	
White	57.4	76.7	75.3	0.17
Non-White	63.9	76.1	74.2	
STEMI (%)	71.4	85.7	88.1	<0.001
NSTEMI	48.3	70.6	67.8	
Medical history				
Chronic kidney disease	46.2	62.1	64.1	<0.05
Chronic obstructive pulmonary disease	39.5	63.3	57.0	<0.05
Diabetes mellitus	53.1	70.0	73.3	<0.001
Heart failure	21.8	54.0	64.0	<0.001
Hyperlipidemia	63.2	77.2	76.1	<0.001

Hypertension	55.0	73.9	73.3	<0.001
Peripheral vascular disease	45.6	74.0	62.8	<0.05
Percutaneous coronary intervention	49.0	81.4	78.6	<0.05
Prior antiplatelet therapy	52.4	77.3	71.6	<0.001
Stroke	43.1	57.1	53.5	0.37
Prior GI Bleeding	36.3	51.5	58.3	0.18
Peptic Ulcer Disease	46.9	56.2	57.1	0.48
Teaching hospital	61.0	78.1	78.0	<0.001
Evidence-based medical therapy	38.9	21.8	21.9	<0.001
Diagnostic/Interventional Procedure				
Cardiac catheterization	72.9	86.3	83.5	<0.001
Coronary artery bypass surgery	14.1	32.5	12.8	<0.05
Percutaneous coronary intervention	89.2	95.7	95.3	<0.001
Thrombolytic therapy	62.1	75.0	100	0.43
Hospital Complications				
Cardiogenic shock	73.7	65.2	52.9	0.4
Heart failure	40.5	56.5	62.4	<0.001
Stroke	44.4	50.0	60.0	0.86

Table 4. Multivariable-adjusted regression analyses of factors associated with the receipt of DAPT at the time of hospital discharge among hospital survivors of an initial acute myocardial infarction (Worcester Heart Attack Study)

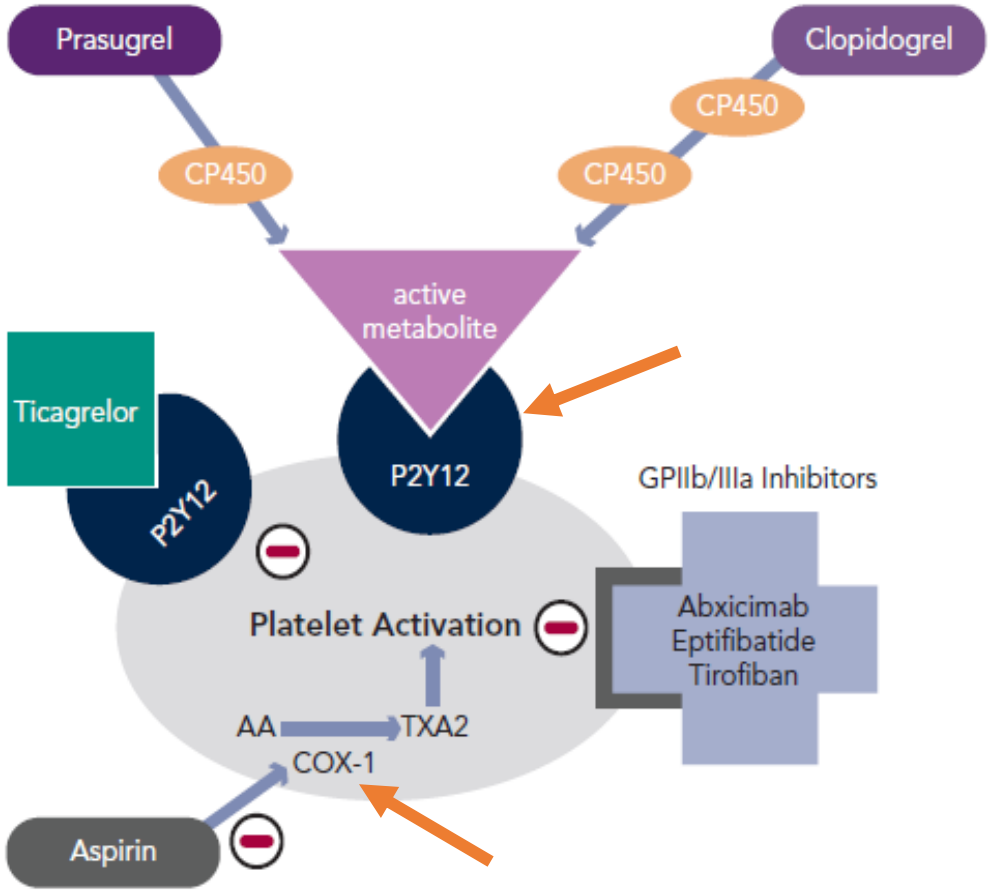
	Model 1 *	**Model 2 †**	**Model 3 ‡**
Characteristics	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Age (years)			
55-64	0.62 (0.46 – 0.84)	0.65 (0.48 – 0.89)	0.76 (0.52 – 1.12)
65-74	0.43 (0.32 – 0.59)	0.48 (0.35 – 0.65)	0.53 (0.36 – 0.80)
≥75	0.25 (0.19 – 0.33)	0.30 (0.23 – 0.40)	0.70 (0.48 – 1.02)
Male	1.52 (1.25 – 1.85)	1.51 (1.24 – 1.84)	1.36 (1.05 - 1.76)
STEMI	2.30 (1.87 – 2.82)	2.14 (1.74 – 2.64)	1.13 (0.85 – 1.50)
Prior chronic obstructive pulmonary disease	-	0.60 (0.45 – 0.80)	0.70 (0.49 – 1.00)
Prior chronic kidney disease	-	0.88 (0.65 – 1.19)	1.36 (0.95 – 1.97)
Prior diabetes mellitus	-	1.03 (0.82 – 1.29)	1.1 (0.83 – 1.45)
Prior heart failure	-	0.61 (0.44 – 0.85)	0.92 (0.60 – 1.40)
Prior peripheral vascular disease	-	1.04 (0.77 – 1.41)	1.24 (0.85 – 1.80)
Prior stroke	-	0.70 (0.48 – 1.04)	0.88 (0.55 – 1.38)
Prior GI Bleeding	-	0.53 (0.31 – 0.90)	0.68 (0.34 – 1.35)
Prior Peptic Ulcer Disease	-	0.69 (0.41 – 1.15)	0.73 (0.37 – 1.45)
Teaching hospital	-	-	1.39 (0.87 - 2.21)
Evidence-based therapy	-	-	1.71 (1.32 - 2.23
Heart Failure post-AMI	-	-	0.80 (0.60 – 1.10)
Stroke post-AMI	-	-	1.46 (0.42 – 5.10)
Cardiogenic Shock	-	-	0.64 (0.29 – 1.40)
Cardiac Catheterization	-	-	2.29 (1.65 - 3.16)
PCI	-	-	14.60 (10.66 - 19.98)

** Model 1: Controlled for age, sex, STEMI, and study year*

† Model 2: Model 1 plus presence of a history of the following co-morbidities: hypertension, diabetes mellitus, chronic kidney disease, heart failure, peripheral vascular disease, stroke, chronic obstructive lung disease, GI bleeding, peptic ulcer disease, type of hospital, receipt of evidence-based therapy

‡ Model 3: Model 2 plus hospital development of a STEMI, coronary revascularization procedure, and the development of hospital complications (stroke, heart failure, and cardiogenic shock)

Figure 1. Mechanism of action of dual antiplatelet therapy



AA = arachidonic acid; COX-1 = cyclooxygenase-1; CYP450 = cytochrome P450; P2Y12 = purinergic receptor P2Y; GPIIb/IIIa = glycoprotein IIb/IIIa; TXA2 = thromboxane A2.

Adopted from: Kandan, Sri Raveen, and Thomas W. Johnson. "Contemporary Antiplatelet Strategies in the Treatment of STEMI using Primary Percutaneous Coronary Intervention." Interventional Cardiology Review 10.1 (2015): 26

Figure 2. Study design flowchart for hospital survivors of AMI in the Worcester Heart Attack study, recruited between 2001 and 2011

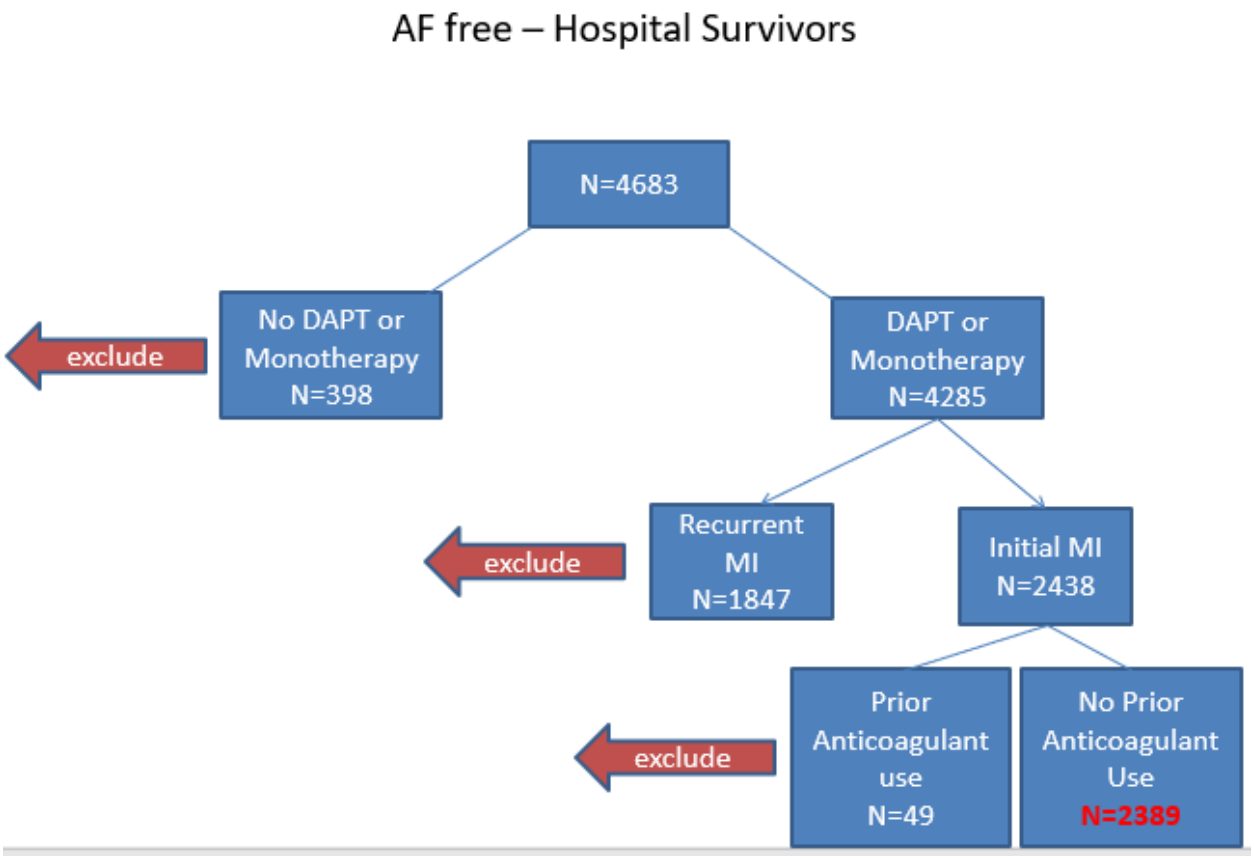
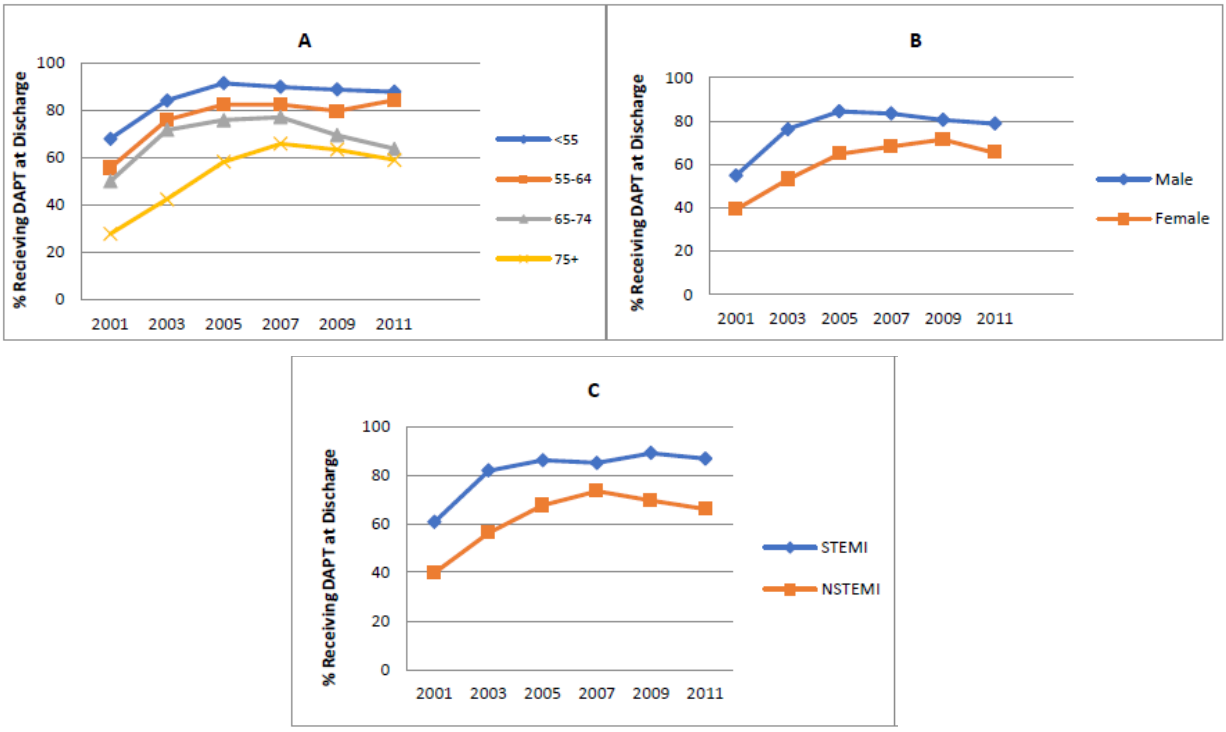


Figure 3. Trends in the receipt of DAPT at the time of hospital discharge among hospital survivors of an initial acute myocardial infarction (Worcester Heart Attack Study). A, by age group; B, by sex; C, by AMI type



SUPPLEMENTARY TABLES

Supplementary Table 1. Changing trends in the receipt of DAPT at the time of hospital discharge among hospital survivors of an initial acute myocardial infarction, stratified according to PCI use (Worcester Heart Attack Study)

Study year	Odds ratio (95% confidence interval) *	
	PCI (+)	No PCI (-)
2001	Reference	
2003	1.77 (0.95; 3.27)	2.19 (1.32; 3.64)
2005	3.01 (1.47; 6.18)	3.48 (2.05; 5.92)
2007	5.48 (2.35; 12.81)	4.12 (2.43; 6.97)
2009	4.09 (1.84; 9.11)	3.01 (1.73; 5.25)
2011	2.64 (1.29; 5.41)	3.46 (2.05; 5.87)

** Adjusted for age, sex, race, previously diagnosed comorbid conditions (hypertension, diabetes, heart failure, chronic kidney disease, peripheral vascular disease, stroke, chronic obstructive lung disease, GI bleeding, peptic ulcer disease), hospital development of a STEMI, coronary revascularization procedure, type of hospital, receipt of evidence-based therapy, and the development of hospital complications (stroke, heart failure, and cardiogenic shock)*

Supplementary Table 2. Changing trends in the receipt of DAPT at the time of hospital discharge among hospital survivors of an initial acute myocardial infarction, stratified according to type of AMI (Worcester Heart Attack Study)

Study year	Odds ratio (95% confidence interval)*	
	NSTEMI	STEMI
2001	Reference	
2003	2.01 (1.23; 3.29)	2.56 (1.30; 5.07)
2005	3.17 (1.88; 5.33)	4.30 (1.89; 8.86)
2007	4.51 (2.67; 7.61)	5.98 (2.59; 13.10)
2009	3.45 (2.05; 5.80)	2.68 (1.14; 6.14)
2011	3.10 (1.86; 5.13)	4.01 (1.74; 9.32)

** Adjusted for age, sex, race, previously diagnosed comorbid conditions (hypertension, diabetes, heart failure, chronic kidney disease, peripheral vascular disease, stroke, chronic obstructive lung disease, GI bleeding, peptic ulcer disease), hospital development of a STEMI, coronary revascularization procedure, type of hospital, receipt of evidence-based therapy, and the development of hospital complications (stroke, heart failure, and cardiogenic shock)*

Supplementary Table 3. Multivariable-adjusted regression analysis of factors associated with the receipt of DAPT at the time of hospital discharge versus antiplatelet monotherapy among hospital survivors of an initial acute myocardial infarction (AMI), stratified according to type of AMI (Worcester Heart Attack Study)

	Odds ratio (95% confidence interval) *	
Characteristics	STEMI	NSTEMI
Age (years)		
55-64	0.76 (0.46 – 1.25)	0.81 (0.42 – 1.54)
65-74	0.51 (0.31 – 0.84)	0.63 (0.32 – 1.27)
≥75	0.69 (0.43 – 1.10)	0.79 (0.39 – 1.60)
Male	1.26 (0.94 – 1.70)	1.79 (1.07 – 2.98)
Chronic obstructive pulmonary disease	0.73 (0.49 – 1.09)	0.63 (0.29 – 1.38)
Prior chronic kidney disease	1.34 (0.90 – 2.00)	1.35 (0.53 – 3.46)
Prior diabetes Mellitus	1.01 (0.73 – 1.40)	1.36 (0.78 – 2.33)
Prior heart failure	0.89 (0.57 – 1.40)	0.54 (0.20 – 2.33)
Prior peripheral vascular disease	1.48 (0.98 – 2.24)	1.89 (0.24 – 1.22)
Prior Stroke	0.76 (0.46 – 1.27)	1.89 (0.62 – 5.84)
Prior GI Bleeding	2.98 (0.56 – 15.8)	0.44 (0.20 – 0.99)
Prior Peptic Ulcer Disease	0.65 (0.18 – 2.45)	0.71 (0.31 – 1.61)
Heart Failure post-MI	0.88 (0.62 – 1.25)	0.62 (0.35 – 1.09)
Stroke post-MI	1.37 (0.31 – 6.0)	2.47 (0.20 – 30.47)
Cardiogenic Shock	0.50 (0.12 – 2.11)	0.87 (0.32 – 2.48)
Cardiac Catheterization	1.94 (1.34 – 2.81)	4.54 (2.26 – 9.12)
PCI	15.35 (10.33 – 22.8)	12.31 (7.20 – 21.04)

** Adjusted for age, sex, race, previously diagnosed comorbid conditions (hypertension, diabetes mellitus, heart failure, chronic kidney disease, peripheral vascular disease, stroke, chronic obstructive pulmonary disease, GI bleeding, peptic ulcer disease), presence of a history of the following co-morbidities: hypertension, diabetes mellitus, chronic kidney disease, heart failure, peripheral vascular disease, stroke, chronic obstructive lung disease, GI bleeding, peptic ulcer disease, type of hospital, receipt of evidence-based therapy and hospital development of a STEMI, coronary revascularization procedure, and the development of hospital complications (stroke,, heart failure, and cardiogenic shock)*

Supplementary Table 4. Multivariable-adjusted regression analysis of factors associated with the receipt of DAPT at the time of hospital discharge versus antiplatelet monotherapy among hospital survivors of an initial acute myocardial infarction, stratified according to the receipt of a PCI (Worcester Heart Attack Study)

	Odds ratio (95% confidence interval) *	
Characteristic	PCI (+)	No PCI (-)
Age (years)		
55-64	1.10 (0.58 – 1.93)	0.59 (0.34 – 0.92)
65-74	0.66 (0.37 – 1.12)	0.42 (0.25 – 0.71)
≥75	0.92 (0.47 – 1.79)	0.41 (0.26 – 0.64)
Male	1.18 (0.74 – 1.89)	1.47 (1.08 – 1.98)
Chronic obstructive pulmonary disease	0.77 (0.36 – 1.63)	0.68 (0.45 – 1.03)
Chronic kidney disease	1.13 (0.48 – 2.63)	1.29 (0.86 – 1.92)
Diabetes mellitus	0.87 (0.53 – 1.43)	1.23 (0.88 – 1.71)
Heart failure	0.67 (0.25 – 1.79)	0.91 (0.58 – 1.41)
Peripheral vascular disease	1.33 (0.58 – 3.02)	1.31 (0.86 – 2.00)
Stroke	0.67 (0.25 – 1.87)	0.98 (0.61 – 1.59)
Prior GI Bleeding	0.96 (0.21 – 4.49)	0.64 (0.29 – 1.43)
Prior Peptic Ulcer Disease	0.45 (0.16 – 1.26)	0.94 (0.42 – 2.11)
Heart Failure post-MI	0.60 (0.34 – 1.07)	0.84 (0.61 – 1.18)
Cardiogenic Shock	1.11 (0.31 – 4.03)	0.41 (0.11 – 1.51)
STEMI	1.24 (0.79– 1.94)	1.07 (0.76 – 1.55)

** Adjusted for age, sex, race, previously diagnosed comorbid conditions (hypertension, diabetes mellitus, heart failure, chronic kidney disease, peripheral vascular disease, stroke, chronic obstructive pulmonary disease, GI bleeding, peptic ulcer disease), presence of a history of the following co-morbidities: hypertension, diabetes mellitus, chronic kidney disease, heart failure, peripheral vascular disease, stroke, chronic obstructive lung disease, GI bleeding, peptic ulcer disease, type of hospital, receipt of evidence-based therapy and hospital development of a STEMI, coronary revascularization procedure, and the development of hospital complications (stroke,, heart failure, and cardiogenic shock)*