VARIATION IN CLINICAL PRACTICE OF PERCUTANEOUS CORONARY INTERVENTION (PCI) AND ITS IMPACT ON PATIENT OUTCOMES

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VARIATION IN CLINICAL PRACTICE OF PERCUTANEOUS CORONARY INTERVENTION (PCI) AND ITS IMPACT ON PATIENT OUTCOMES

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In contemporary clinical practice, percutaneous coronary intervention (PCI) is one of the most common methods to treat ischemic heart disease. It has proven to be very effective in appropriately selected patients. However, clinical discretion among interventional clinicians in the absence of definitive evidence-based guidelines results in significant variation in clinical practice of PCI. The objective of this dissertation research is to study the effect of such variation in three aspects on patient outcomes following PCI: (i) post-discharge statin prescription versus no prescription in the setting of otherwise aggressive medical therapy; (ii) use of multiple stents versus a single stent when either approach is clinically feasible; (iii) use versus no use of stent postdilation.

Patients were evaluated from multiple data sources. The first source included the multi-center National Heart, Lung, and Blood Institute (NHLBI) Dynamic registry recruitment Wave 4 (2004) and Wave 5 (2006). For Aim 1 (post-discharge statin vs. no post-discharge statin), patient eligibility criteria included receipt of aspirin, thienopyridines and at least one type of cardiovascular protective medication (angiotensin-converting enzyme inhibitors, Beta blockers, or Calcium channel blockers) after the PCI procedure, and no in-hospital death. Risk of adverse events was compared between post-discharge statin recipients and non-recipients at one-year follow up. Results showed that post-discharge statin use was associated with a reduced risk of mortality and the composite endpoint of death/MI, death/MI/CABG. These data support the routine use of post-PCI statin therapy in the presence of otherwise aggressive medical therapy.

For Aim 2 (multiple versus single stents), the DEScover Registry, a prospective, multicenter, observational study among 140 clinical centers in the United States, was used. The eligibility criteria for this analysis included: receipt of at least one stent for a lesion treated with PCI and the following characteristics: lesion not previously treated; lesion length of 10 to 32mm (i.e. able to be treated with either a single or multiple stents); and an angiographically successful procedure. Survival analysis over 1-year post-PCI showed that patients who received multiple stents had a similar risk of adverse events compared to patients who received a single long stent for each lesion treated. Thus, this analysis was unable to provide definitive evidence for a preference of single versus multiple stents for lesions in the range of 10 to 32 mm.

For Aim 3 (postdilation versus no postdilation), the Dynamic registry recruitment Wave 4 (2004) and Wave 5 (2006) were used. Patient eligibility criteria for this analysis included receipt of $\geq$1 stent and an angiographically successful PCI procedure. Survival analysis over 1-year post-PCI showed that among PCI patients who presented with acute MI, postdilation appears to significantly increase the risk of death by as much as 3-fold. However, because this finding was observed only among patents with one lesion treated but not among patients with multiple lesions treated, the possibility of a chance finding exists. Moreover, among PCI patients who had no acute MI, lesion postdilation did not appear to be associated with either a benefit or increased risk of adverse cardiac events. Thus, this analysis indicated no obvious clinical benefit associated with postdilation in the setting of PCI patients who had no acute MI, and a potential hazardous effect in the setting of acute MI.

Our study has significant public health importance. Heart disease is the leading cause of mortality in nearly every region of the world, accounting for an estimated 30% of all deaths. Coronary heart disease (CHD) is the principal type of heart disease. The public health significance of our study is that investigating the effect of variation in clinical PCI practice can be a benefit to numerous CHD patients all over the world.

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1.0 DISSERTATION OVERVIEW AND OBJECTIVE

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. Coronary artery disease (CAD) is the principal type of heart disease, and nearly half of all cardiovascular deaths are attributed to CAD worldwide. In 2002 in the United States, approximately 71% of heart disease deaths were attributed to CAD. Thus, the prevention and optimal treatment of obstructive CAD represents a major public health imperative.

Percutaneous coronary intervention (PCI) is one of the most common treatments for CAD in contemporary clinical practice. Detailed guidelines that cover a variety of clinical circumstances in which PCI is performed have been published by the respective professional organizations including the American College of Cardiology (ACC), American Heart Association (AHA), and the Society for Cardiovascular Angiography and Interventions (SCAI). However, as with many surgical procedures, individual operator discretion continues to play a considerable role in the choice of patients deemed suitable for PCI, and how these patients will ultimately be treated with contemporary stent technology and adjunctive pharmacological therapy. Thus, there is significant variation in clinical practice of PCI today, a condition unlikely to change in the near future and one that warrants continuous appraisal and evaluation.

Therefore, the purpose of this dissertation is to evaluate the effect of three different variations in how PCI is being performed in relation to important peri-procedural and post-discharge patient outcomes. Specifically, the following questions are addressed in a series of three research papers:

1. Among patients who undergo successful PCI procedures and receive: (i) aspirin; (ii) thienopyridines; and (iii) one or more cardiovascular protective medications (ACE inhibitors, beta

blockers, or calcium channel blockers), does the addition of post-discharge statin therapy provide additional clinical benefit?

2. What is the effect on patient outcome of the use of single versus multiple stents for atherosclerotic lesions that are of length 10-32 mm and, theoretically, based on lesion length and available stent sizes, can these lesions be treated with a single stent?

3. After initial PCI dilation of one or more obstructive lesions, does stent post-dilation (i.e. for presumed optimal stent expansion) significantly affect patient outcomes? In addition, does the effect of this procedural approach vary among patients who present with acute myocardial infarction (MI) versus those presenting without acute MI?

The first and third investigations were conducted among PCI patients enrolled and followed in the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry of PCI. The second investigation was conducted among PCI patients enrolled and followed in the Cordis-funded DEScover registry. As described in this dissertation, both of these databases include consecutively enrolled PCI patients in "real-world" clinical practice across a variety of clinical centers throughout North America.

2.0 BACKGROUND

Heart disease is the leading cause of morbidity and mortality in the United States. (Rosamond, Flegal et al. 2007) Obstructive coronary artery disease (CAD) is a major cause of heart disease, such as myocardial infarction (MI) and its associated disability and mortality.

Technological advances in the treatment of blocked arteries include the introduction of coronary artery bypass graft surgery (CABG) in the late 1960s, and percutaneous transluminal coronary angioplasty (PTCA), also called balloon angioplasty)), introduced in the late 1970s and now often called percutaneous coronary intervention (PCI). Both CABG and PCI are preceded by cardiac catheterization, which measures the location and extent of coronary artery blockage. The choice of procedure (PCI versus CABG) depends on a number of factors such as location, number, and extent of the obstructive lesions.

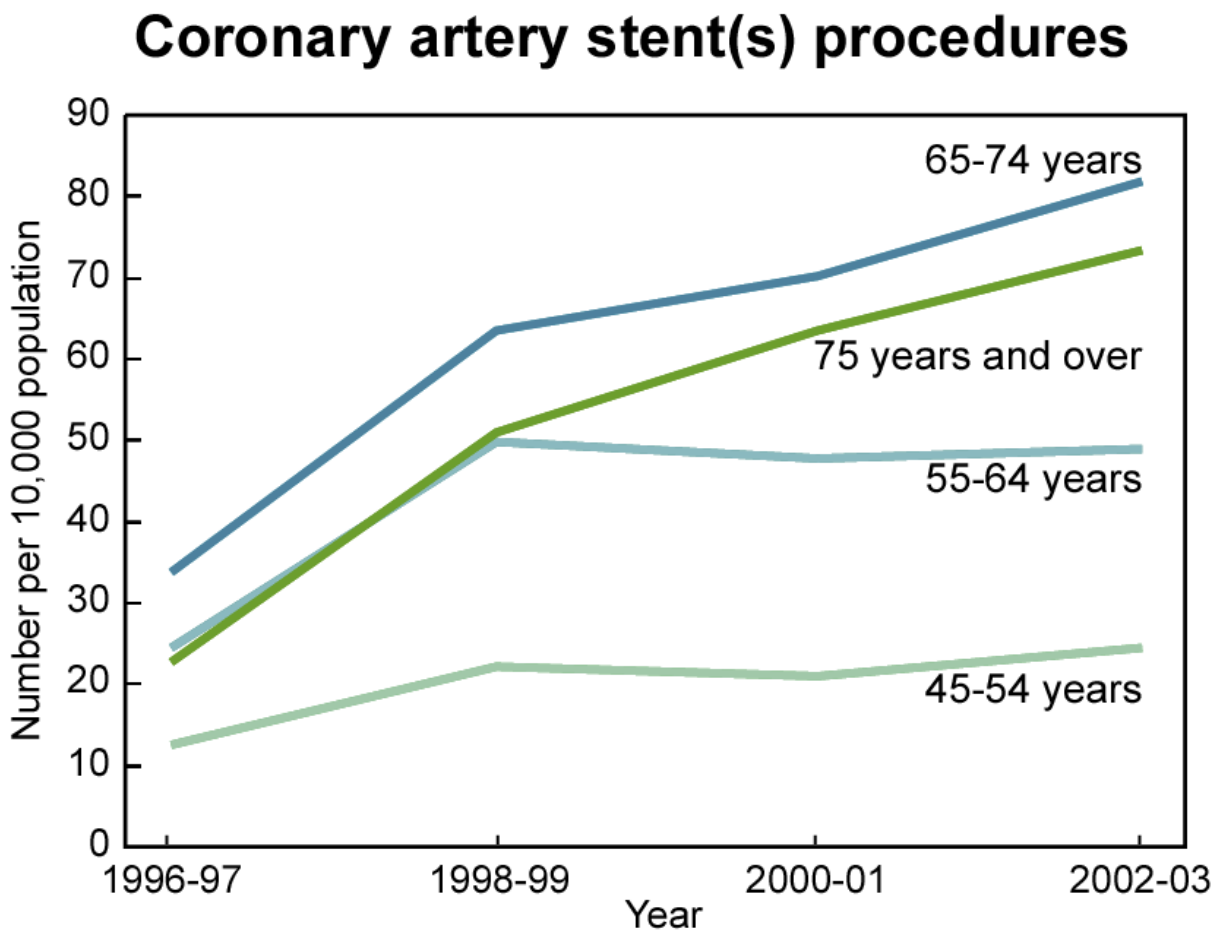
In the practice of PCI, coronary artery stenting was introduced in 1996. A stent is a wire mesh tube used to prop open an artery that has recently been cleared using angioplasty. According to the American Heart Association (AHA), 70–90 percent of PCI procedures involve the implantation of one or more stents.

The practice of PCI continues to grow. According to the National Center for Health Statistics, the rate of coronary stent insertion procedures for adults age 45 years or older doubled from 1996-97 to 2002-03 (from 22 per 10,000 to 49 per 10,000). Moreover, the rate of this procedure tripled for adults ages 75 years and older during the period 1996-97 to 2002-03 (from 23 per 10,000 to 73 per 10,000). (See Figure 1.1)

Developed during the last 30 years, stenting together with other procedures and medical therapy have improved survival after heart attack. It is estimated that around 70 percent of survival improvement in heart attack mortality is contributed by these technologies.

The development of drug eluting stents (DES) has been a milestone in PCI. The rate of restenosis and target vessel revascularization, a hallmark limitation (i.e. "Achilles heel") of treatment with conventional bare metal stents, has been dramatically reduced with the use of DES. This has enabled a broader range of patients with more severe lesions deemed suitable and ultimately selected for PCI. Detailed guidelines that cover a variety of clinical circumstances in which PCI is performed have been published by the respective professional organizations including the American College of Cardiology (ACC), American Heart Association (AHA), and the Society for Cardiovascular Angiography and Interventions (SCAI) (Smith, Feldman et al. 2006). However, operator discretion continues to play a major role in the choice of patients deemed suitable for PCI, and how these patients will ultimately be treated with contemporary stent technology (e.g. bare metal stents versus DES) and adjunctive pharmacological therapy (e.g. routine use of statin therapy). Thus, as with many surgical procedures, there is significant variation in the manner in which PCI is practiced today. This circumstance is likely to remain largely in effect in the near future and hence provides the rationale for continuous appraisal and evaluation.

Despite published guidelines, many variations in PCI practice are not based on evidence-based guidelines, and clearly some of this variance in practice is likely to impact patient outcomes. Thus, it is of considerable public health importance to study important variations in the real-world practice of PCI and how these variations may impact patient outcomes.



SOURCE: Centers for Disease Control and Prevention, National Center for Health Statistics, *Health, United States, 2005*, figure 25.

Figure 1-1 Coronary artery stents procedure from 1996 to 2003

2.1 POST-PROCEDURAL MEDICAL THERAPY

The increasing number of PCI procedures being peformed each year reflects overall excellent acute angiographic results and low rates of restenosis in most patient subgroups. However, with the introduction of DES, in particular, there exists a significant clinical concern -- subacute stent thrombosis (SAT). The occurrence of SAT, which can happen many months or even years after the index PCI, has an alarming case-fatality rate of up to 50%. Thus, considering the increasing number of PCI procedures

being performed, particularly with DES, and the more complex vessel lesions being treated, the role of antiplatelet/anticoagulant therapy (i.e. to reduce the risk of SAT) has become increasingly more important.

2.1.1 Aspirin

It is well established that aspirin prevents ischemic events and prolongs survival among cardiovascular disease patients. It irreversibly blocks the formation of thromboxane A_2, which is a mediator of platelet aggregation.

Theroux et al. conducted a randomized, double-blind, placebo-controlled trial in the 1980s to test the effectiveness of aspirin for treating acute unstable angina. (Theroux, Ouimet et al. 1988) A total of 479 patients with acute unstable angina were randomized to four groups: aspirin (325 mg twice daily), intravenous heparin sodium, both, or neither. The incidence of myocardial infarction was significantly reduced in the groups receiving aspirin (3% vs. 12%; P = 0.01). A larger study, ISIS-2 (Second International Study of Infarct Survival) trial randomized 17,187 patients with onset of suspected acute myocardial infarction within 24 hours into four treatment groups: aspirin therapy (160 mg/d), streptokinase, both, and neither.(1988) The study patients had ST-segment elevation, ST-segment depression, bundle-branch block, or other electrocardiographic abnormalities. Aspirin reduced 5-week vascular mortality by 23% when compared to the neither treatment group (9.4% vs. 11.8%, P<0.00001). Aspirin also significantly reduced non-fatal reinfarction (1.0% vs. 2.0%) and non-fatal stroke (0.3% vs. 0.6%), and was not associated with any significant increase in cerebral hemorrhage or in bleeds requiring transfusion.

A very large meta-analysis of 287 randomized trials involving 135,000 patients showed that aspirin or other antiplatelet therapy reduced the combined outcome of any serious vascular event by about one quarter; non-fatal myocardial infarction was reduced by one third, and vascular mortality by one sixth.(Antithrombotic Trialists 2002) The above results firmly support the conclusion that aspirin is

protective for occlusive vascular events in patients with an acute myocardial infarction or ischemic stroke, unstable or stable angina, previous myocardial infarction, peripheral arterial disease, or atrial fibrillation. In short, aspirin is effective in a wide range of ischemic disease. (1994)

According to the AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease, "*Start aspirin 75 to 162 mg/d and continue indefinitely in all patients unless contraindicated*". (Smith, Allen et al. 2006) Thus, aspirin therapy, unless contraindicated, is regarded as a primary treatment for PCI patients.

2.1.2 Clopidogrel and Ticlopidine

Whereas aspirin is a relatively weak anti-platelet agent because it inhibits only one of several platelet aggregation pathways, i.e. thromboxane A_2, the thienopyridines (ticlopidine and clopidogrel) are another type of more potent anti-platelet agents. They block adenosine diphosphate (ADP) and thus irreversibly inhibit platelet aggregation. Importantly, they act additively or synergistically with aspirin through complementary and independent mechanisms. (Sharis, Cannon et al. 1998)

Ticlopidine has been shown to be clinically effective in reducing adverse cardiac events in placebo-controlled studies. However, it has rare but potentially serious adverse effects: neutropenia, thrombotic thrombocytopenic purpura, bone-marrow depression, rash and diarrhea. Clopidogrel is chemically related to ticlopidine. Of note, it is safer and better tolerated than ticlopidine. (Bertrand, Rupprecht et al. 2000) Moreover, its efficacy in preventing subacute stent thrombosis and peri-procedural ischemia is at least as good as ticlopidine. (Bertrand, Rupprecht et al. 2000; Muller, Buttner et al. 2000; Bhatt, Bertrand et al. 2002) Thus, clopidogrel has essentially replaced ticlopidine in this setting. CAPRIE, a randomized, blinded, international trial, was conducted to assess the relative benefit of clopidogrel (75 mg once daily), compared with aspirin (325 mg once daily) in reducing the risk of a composite outcome cluster: ischemic stroke, myocardial infarction, or vascular death. (1996) A total of 19,185 patients with recent ischemic stroke, recent myocardial infarction, or peripheral arterial disease

were recruited over 3 years, with a mean follow-up of 1.91 years. The clopidogrel treatment had a modest yet statistically significant better effect than aspirin in terms of the outcome cluster (5.32% vs. 5.83%, P=0.043). There were no major differences in terms of safety.

With particular relevance to use of DES, the combination of aspirin and clopidogrel is associated with a lower risk of subacute stent thrombosis than a single agent. The results from the Percutanous Coronary Intervention Clopidogrel in Unstable Angina to Prevent Recurrent Events (PCI-CURE) study showed that combination therapy with clopidogrel and aspirin was superior to aspirin alone in terms of the risk of major ischemic adverse events (RR=0.70, 95% CI 0.50-0.97, P=0.03). There was no significant difference in major bleeding between the groups (p=0.64). (Mehta, Yusuf et al. 2001) In contrast, the CURE study reported 38% more major bleeding in the Clopidogrel group than in the placebo group (3.7% vs. 2.7%, P=0.001) (Yusuf, Zhao et al. 2001). Thus, although combination therapy with aspirin and clopidogrel reduces the risk of adverse cardiac events following PCI, there is also the potential for a higher incidence of major bleeding with this treatment regimen.

On the basis of available evidence, the AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease state: "*Start and continue clopidogrel 75 mg/d in combination with aspirin for up to 12 months in patients after acute coronary syndrome or percutaneous coronary intervention with stent placement (≥1 month for bare metal stent, ≥3 months for sirolimus-eluting stent, and ≥6 months for paclitaxel-eluting stent*)". (Smith, Allen et al. 2006) Whether long clopidogrel and aspirin therapy following PCI (i.e. 1 year and beyond) results in improved patient outcomes is currently under investigation.

2.1.3 Beta Blockers

Numerous secondary prevention studies have shown that beta blockers reduce the risk of death, and re-infarction after myocardial infarction. It is also hypothesized that beta blockers provide a complementary benefit after successful PCI procedures. Chan et al. investigated the effect of beta blockers on mortality

after successful elective PCI among of 4,553 patients in the Cleveland Clinic Foundation registry. Using propensity analysis, beta blockers had an independent protective effect for one-year survival after PCI (hazard ratio=0.63, 95% CI: 0.46-0.97, p=0.0054). Results also showed that beta blockers are associated with improved survival in most subgroups. (Chan, Quinn et al. 2002)

From a national cohort of 115,015 patients aged 65 years or older who survived hospitalization with a confirmed acute MI from 1994 to 1995, 45,308 patients did not have contraindications to beta blockers. Of these patients, 50% had beta blockers prescribed at discharge. After adjusting for potential confounders, beta blockers were associated with a 14% lower risk for one-year mortality. The protective effect was present in subgroups defined by age, gender, left ventricular ejection fraction. (Krumholz, Radford et al. 1998)

Although most studies have shown a beneficial effect of beta blockers among most subgroups of patients, (Krumholz, Radford et al. 1998; Chan, Quinn et al. 2002) some studies have shown that beta blockers reduce cardiac output and thus decrease renal blood flow. (Wilkinson 1982)

Despite the compelling clinical evidence for the beneficial effect of beta blocker therapy, a surprisingly low prescription at discharge has been reported. (Krumholz, Radford et al. 1998) In addition, variation in beta blocker use by state is very large, ranging from 30.3% to 77.1%. Demographic and clinical variables appear to explain little of this variation. Regarding the AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease, the recommendation for beta blocker therapy is: "*Start and continue indefinitely in all patients who have had myocardial infarction, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. Consider chronic therapy for all other patients with coronary or other vascular disease or diabetes unless contraindicated.*"

2.1.4 ACE Inhibitors

Angiotensin-converting enzyme inhibitors (ACE inhibitors) have been shown to be one of the most important treatments for cardiovascular disease. ACE inhibitors attenuate the progressive process of left ventricular (LV) remodeling and thus improve survival. These agents are associated with improved clinical outcomes in a broad spectrum of patients with preserved left ventricular dysfunction. (Investigators 1992; Pfeffer, Braunwald et al. 1992; Kober, Torp-Pedersen et al. 1995)

The Heart Outcomes Prevention Evaluation (HOPE) study examined the effect of an ACE inhibitor, ramipril, versus placebo in patients who were at high risk for cardiovascular events but who did not have left ventricular dysfunction or heart failure. A total of 9,297 patients were recruited in the study – all had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and were not known to have a low ejection fraction or heart failure. They were randomly assigned to receive ramipril (10 mg once per day orally) or matching placebo for a mean of five years. Treatment with ramipril resulted in lower rates and risks of: (i) death from cardiovascular causes (6.1% vs. 8.1%, RR, 0.74; P<0.001); (ii) myocardial infarction (9.9% vs. 12.3%, RR, 0.80; P<0.001); (iii) death from any cause (10.4% vs. 12.2%, RR, 0.84; P=0.005); (iv) revascularization procedures (16.3% vs. 18.8%, RR, 0.85; P<0.001); (v) cardiac arrest (0.8% vs. 1.3%, RR, 0.62; P=0.02); and (vi) heart failure (9.1% vs. 11.6%, RR, 0.77; P<0.001). (Yusuf, Sleight et al. 2000) These data provide compelling evidence for the effectiveness of ACE Inhibitors. Regarding the AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease, the recommendation for beta blocker therapy is: "*Start and continue indefinitely in all patients with left ventricular ejection fraction ≤ 40% and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated. Consider for all other patients. Among lower-risk patients with normal left ventricular ejection fraction in whom cardiovascular risk factors are well controlled and revascularization has been performed, use of ACE inhibitors may be considered optional.*"

2.1.5 Statins

Statins are a group of drugs that reduce LDL cholesterol in the blood by inhibiting HMG-CoA reductase. The Scandinavian Simvastatin Survival Study was the first clinical trial to demonstrate conclusively that long-term statin use substantially reduced the risk of death from all causes, as well as from cardiac events (Strandberg, Pyorala et al. 2004). Subsequent trials, including LIPID, CARE, WOSCOPS, AFCAPS HPS, indicate the tolerability of long-term daily statin therapy and efficacy for a broad range of cardiovascular diseases (1998; Downs, Clearfield et al. 2001; Forster, Stewart et al. 2002; Heart Protection Study Collaborative 2002; Shepherd, Blauw et al. 2002).

The efficacy of statins on secondary prevention after PCI has also been investigated. Serruys et al. carried out a randomized trial to assess whether treatment with fluvastatin reduced risk of major adverse cardiac events (MACE) for patients who had undergone PCI.(Serruys, de Feyter et al. 2002) A total of 1,677 patients with stable or unstable angina or silent ischemia following successful completion of their first PCI, and having baseline total cholesterol levels between 135 and 270 mg/dL (3.5-7.0 mmol/L) and fasting triglyceride levels of less than 400 mg/dL (4.5 mmol/L) were randomly assigned to receive fluvastatin (80 mg/d), or matching placebo (n = 833) at hospital discharge for 3 to 4 years. Fluvastatin treatment significantly increased MACE-free survival time (P =0.01). Specfically, the risk of at least one MACE was decreased from 26.6% to 21.4% (RR, 0.78; 95% confidence interval, 0.64-0.95; P =0.01). This protective effect was consistent among different baseline total cholesterol levels (above and below the median). These results strongly support the conclusion that fluvastatin significantly reduces the risk of major adverse cardiac events in patients with average cholesterol levels undergoing their first successful PCI. There is no specific recommendation about statins in AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease. But the goal for lipid control becomes higher than before: "*LDL-C should be <100 mg/dL; Further reduction of LDL-C to <70 mg/dL is reasonable.If baseline LDL-C is 100 mg/dL, initiate LDL –lowering drug therapy. If on-*

treatment LDL-C is 100 mg/dL, intensify LDL –lowering drug therapy (may require LDL –lowering drug combination)."

2.1.6 Summary

Therefore, on balance, the five classes of drugs reviewed above provide strong evidence of efficacy for primary or secondary intervention of CVD events. However, considerable variability in clinical practice still exists among patients receiving PCI. Of the 5 classes of drugs reviewed, specific AHA/ACC clinical guidelines exist for four of the 5 (aspirin, thienopyridines, beta blockers, ACE inhibitors). At present, the greatest degree of variability and uncertainty appears to exist with respect to universal versus selected use of statins following PCI, and in the presence of aggressive secondary prevention with other classes of medical therapy. Thus, this important clinical issue was selected for investigation in this dissertation. To reiterate, the primary research question investigated was:

Among patients who undergo successful PCI procedures and receive: (i) aspirin; (ii) thienopyridines; and (iii) one or more cardiovascular protective medications (ACE inhibitors, beta blockers, or calcium channel blockers), does the addition of post-discharge statin therapy provide additional clinical benefit?

2.2 TREATMENT WITH MULTIPLE STENTS VS. A SINGLE LONG STENT

When more than one stent is implanted into the coronary arteries, the distal part of the stents can be either overlapped or not overlapped. The scenarios that typically require stent overlapping are excessive lesion length, incomplete lesion coverage, or endoluminal injury or marginal dissection requiring additional stent scaffolding beyond the margins of the initial stent. Thus, stent overlapping may be performed for both lesion morphology (i.e. lesion length) and suboptimal PCI dilation results with the initial stent

placed. When overlapping is performed, there are no strict rules about the length, usually about 2-4 mm in contemporary clinical practice.

There is large variation in the rate of stent overlapping across different clinical sites or countries, ranging from 15% to 36%. (Schofer, Schluter et al. 2003; Kereiakes, Wang et al. 2006; Qiao, Hou et al. 2006) Of note, there are little data available to explain the reasons or consequences for this large variation. The characteristic of patients, physicians, hospitals, and clustering of districts may all be possible explanations. The pros and cons of stent overlap have been under debate since the bare metal stent era and continue today, as summarized below.

2.2.1 Bare Metal Stent

Each type of stent device, whether bare metal or drug-eluting, has its metal platform and polymer. It is not clear whether they have same effect in terms of short and long clinical outcomes. Ellis et al. assessed the risk of restenosis after placement of Palmaz-Schatz stents in the early 1990s. (Ellis, Savage et al. 1992) The results discouraged placement of multiple/overlapping stents. Restenosis occurred at 64% of sites when multiple stents were implanted, while only 30% of sites had restenosis for single stent placement. One limitation of this study was that the follow up was only an average of 5 months. Another relatively short (6-month) follow-up study reported a higher rate of restenosis among patients with overlapping stent treatment when compared with one single long stent (35% vs. 29%, $p>0.05$). (De Scheerder, Wang et al. 1998) A study by Kastrati et al, including 2,736 consecutive patients treated with bare metal stent placement, assessed six-month and one-year event rates. (Kastrati, Elezi et al. 1999) Results showed that overlapping of stents is a risk factor of restenosis and late lumen loss, independent of lesion length and number of stents ($p=0.006$ for restenosis; $p=0.002$ for late lumen loss).

In contrast, Lee et al. reported a comparable effect for stent overlapping. (Lee, Jang et al. 2004) Thirty-two patients received two overlapping stents, and 32 patients received one long stent. The two groups had a similar rate of MACE (36% vs. 29%, $p=0.56$) and six-month restenosis (39% vs. 41%,

p=0.91). Thus, with respect to bare metal stents, some but not all studies suggest that multiple overlapping stents may be associated with a higher risk of restenosis and MACE. What is unknown is whether this higher risk, if present, is due to strategy of overlapping *per se* or because stent overlap with multiple stents was performed because of suboptimal result with the initial stent placed.

2.2.2 Drug Eluting Stents (DES)

With the introduction of DES, assessment of the merit (or hazard) of overlapping stents becomes even more complicated. Specifically, for DES, the overlapped stent metal can serve as a stimulus for neointimal proliferation. On the other hand, the drug elution based on the stents will suppress the neointimal growth. Animal studies have shown that overlapped segments exhibit delayed healing when compared with proximal and distal nonoverlapping segments for both drug-eluting stents and bare-metal stents. (Finn, Kolodgie et al. 2005) Kereiakes et al, pooled five clinical trials (SIRIUS, E-SIRIUS, C-SIRIUS, DIRECT, SVELTE). (Kereiakes, Wang et al. 2006) A total of 575 patients were treated with overlapped stents (337 sirolimus-eluting stent, 238 bare metal stent) and a total of 1,162 patients were treated with single stents (697 sirolimus-eluting stent, 465 bare metal stent). Analyses were stratified on the two stent types. Results showed that stent overlap was associated with a greater late lumen loss. The risk of target vessel revascularization was significantly higher in both overlapped stent groups (29.4% vs. 19.8%, $p<0.01$ for bare metal stent; 9.5% vs. 5.0% for sirolimus-eluting stent).

However, other studies have shown that overlapping-stents is as feasible and effective as non-overlapping stents. Chu et al. compared the clinical outcomes among 55 patients who received overlapping and 39 patients who received non overlapping sirolimus-eluting stents. (Chu, Kuchulakanti et al. 2006) Results showed that event-free survival rate was similar between the two groups (P=0.87). No difference was found between the two treatment groups for 30-day and 6-month revascularization, death, Q-wave MI, Non-Q-wave MI, and stent thrombosis. The in-hospital complication rate was also similar except for a higher rate of Non-Q-wave MI with overlapped-stent treatment (7.7% vs. 23.6%, p=0.04).

This higher rate of myonecrosis is due to periprocedural side branch compromises, including side branch occlusion (19.4% vs. 5.8%, p=0.01), narrowing (61.3% vs. 29.2%, p<0.001), and TIMI flow reduction (54.8% vs. 19.0%). Kereiakes et al. also reported overlapping sirolimus-eluting stents provided similar magnitude of restenosis benefit as observed for single-stent-treated patients. (Kereiakes, Wang et al. 2006) An ultrasound study of eight patients did not find any significant quantitative changes in intravascular measurements within the overlapped segment at 1-year follow-up. (Munoz, Abizaid et al. 2004)

Thus, similar to bare metal stents, the use of multiple overlapping DES has yielded mixed results in terms of risk of restenosis and MACE. On balance, there is little to no persuasive evidence indicating a clinically favorable effect of stent overlapping despite the fact that it occurs relatively frequently in real-world clinical practice of PCI.

2.2.3 Heterogeneous Overlapping

When overlapping DESs are implanted, the drug dose would be expected to double at the overlapping location. If different types of DES are overlapped, the different drug can interact with each other through the same or different mechanisms.

Kang et al. performed a study among 47 consecutive patients receiving two DESs for diffuse long lesions. (Kang WC 2007) A total of 14 patients received two sirolimus and paclitaxel-eluting stents; 13 patients received two sirolimus-eluting stents; 20 patients received two paclitaxel-eluting stents. The endpoint was neointimal hyperplasia at the overlapping site based on 9-month follow-up angiographic and IVUS examination. The results showed that overlapping of different DES had a similar effect on the suppression of neointimal hyperplasia as compared to overlapping of two of the same DES. The conclusion arrived at is the same as a study conducted by Burzotta et al. (Burzotta, Siviglia et al. 2007) However, their results also showed that overlapping of DES and BMS should be avoided because this combination results in a higher rate of MACE as compared to an approach of overlapping of two.

2.2.4 Summary

In summary, results are mixed on the effect of overlapping stents. Some studies suggest an adverse effect; others indicate no effect, and a few may suggest a favorable effect. More definitive analyses are needed, particularly with respect to whether the use of stent overlapping appears to be a planned (a priori) strategy as opposed to a consequence (ad hoc response) to lesion dilation complications. Thus, this important clinical issue was selected for investigation in this dissertation. To reiterate, the primary research question investigated was:

What is the effect on patient outcome of the use of single versus multiple stents for atherosclerotic lesions that are of length 10-32 mm and, theoretically, based on lesion length and available stent sizes, can be treated with a single stent?

2.3 POSTDILATION

During the evolution of stent delivery systems, "semi-compliant" balloons have been increasingly used for stent deployment. This enables a higher pressure during the implantation than earlier generation "compliant" balloons. Therefore, use of postdilation has concomitantly decreased when compared to the era of balloon-expandable stents, which were delivered through compliant balloons. However, researchers soon learned that postdilation may still be needed in order to decrease the risk of target vessel revascularization and thrombosis, and possibly other long term clinical outcomes.

In common clinical practice, PCI procedures are guided by coronary angiography. With this approach, a catheter is inserted into the femoral or radial artery, and the degree of narrowing is visually identified from an X-ray image. More recently, with the introduction of intravascular ultrasound (IVUS), researchers can assess the post-procedural stenting with two powerful measures: minimal stent area (MSA) and minimal stent diameter (MSD). It is well established that larger post-procedural stent

dimensions are associated with lower rates of restenosis and target vessel revascularization. (Kuntz, Safian et al. 1992; Hoffmann, Mintz et al. 1998; Kasaoka, Tobis et al. 1998; de Feyter, Kay et al. 1999; Sonoda, Morino et al. 2004) In the SIRIUS IVUS study, a substudy of the SIRIUS trial, MSA was highly correlated with minimum lumen area (MLA) at 8-month follow up for both SES and BMS (r=0.8 for SES, p<0.0001; r=0.65 for BMS, p<0.0001). (Sonoda, Morino et al. 2004) Thus, the extent to which larger post-procedural stent dimensions can be obtained from PCI, whether visualized or guided by coronary angiography and IVUS, remains a desired clinical goal.

2.3.1 Postdilation and Restenosis

The CRUISE (Can Routine Ultrasound Influence Stent Expansion?) study, a substudy of the Stent Anti-thrombotic Regimen Study (STARS), randomized 497 patients to either IVUS-guided stent implantation or standard stent implantation. The IVUS-guided group performed postdilation with noncompliant balloons at high pressures and used large balloons when needed. The IVUS-guided group had a larger minimal lumen diameter (2.9±0.4 versus 2.7±0.5 mm, p<0.001), a larger minimal stent area (7.78±1.72 versus 7.06±2.13 mm^2, p<0.001), and lower risk of target vessel revascularization (8.5% versus 15.3%, p<0.05). These data indicate the clinical value of IVUS above and beyond conventional coronary angiography despite the fact that IVUS is infrequently used in clinical practice.

Nonetheless, even though the use of DES has dramatically reduced the incidence of restenosis, target vessel revascularization still occurs in 5% of patients or more. Even with this relatively low background incidence, some studies have shown that postdilation provides supplemental benefit after implantation of DES. (Kuntz, Safian et al. 1992; Hoffmann, Mintz et al. 1998; Kasaoka, Tobis et al. 1998; de Feyter, Kay et al. 1999; Sonoda, Morino et al. 2004)

2.3.2 Postdilation and Thrombosis

Stent under-expansion remains the major factor associated with stent thrombosis, a catastrophic clinical event. Cheneau and colleagues analyzed 7,484 consecutive patients without acute myocardial infarction who received stent treatment and underwent IVUS imaging during the intervention. Inadequate postprocedure lumen dimensions were significantly associated with subacute stent thrombosis. (Cheneau, Leborgne et al. 2003) Fujii et al, carried out a matched case-control study. (Fujii, Carlier et al. 2005) A total of 15 patients who had stent thrombosis after SES implantation were matched with 45 control patients who did not have stent thrombosis after SES implantation. The stent thrombosis group had statistically significant smaller MSA (4.3 vs. 6.2 mm^2, $p<0.001$), less stent expansion (0.65 vs. 0.85, $p<0.001$), and more residual stenosis in the proximal/distal reference vessel (67% vs. 9%, $p<0.001$). The MSA and stent expansion were independent predictors for stent thrombosis. In addition, Uren and colleagues reported that under-expansion was associated with ultrasound abnormal finding. (Uren, Schwarzacher et al. 2002)

2.3.3 Size and Pressure

The dilation force a balloon exerts against a lesion or against a stent may be related to both the balloon size and the inflation pressure.

Researchers assessed the effect of different inflation pressure on stent expansion. A porcine coronary model of 30 pigs assessed the effect of different deployment pressure: 4 atm (group one), 8 atm (group two), 14 atm (group three). (De Scheerder, Wang et al. 1998) Imperfect stent alignment was found in 8 coronary arteries: 7 in group one, 1 in group 2, 0 in group 3. Cheneau and colleagues assessed the relationship between delivery pressure and expansion for sirolimus-eluting stents (Cypher). (Cheneau, Satler et al. 2005) Stent expansion was 72% after 14 atm balloon inflation, 90% after 20 atm balloon

inflation, and 90% at the end of procedure with optional postdilating with 0.5 mm larger balloon. The degree of expansion may impact the late occurrence of restenosis.

Despite the lack of randomized clinical trial to support that aggressive dilation is effective in preventing restenosis, stent thrombosis, and long-term adverse clinical outcomes, evidence from many observational studies suggest this possibility. However, in practice, due to physician strategy, imaging technique used (e.g. coronary angiography), complexity of some lesions being treated, and clinical circumstances of the patient (e.g. acute MI), very few patients actually receive optimal stent dilation. Indeed, Cheneau et al. reported that only 15% of patients treated with the SES delivery system achieved optimum stent deployment (MSA/RLA>80%) by IVUS measurements. (Cheneau, Satler et al. 2005)

2.3.4 Summary

In summary, there is considerable variation in the use of postdilation after stent implantation, and moreover, whether this strategy appreciably influences patient outcomes. Thus, this important clinical issue was selected for investigation in this dissertation. To reiterate, the primary research question investigated was:

After initial PCI dilation of one or more obstructive lesions, does lesion post-dilation (i.e. for presumed optimal stent expansion) significantly impact patient outcomes? In addition, does the effect of this procedural approach vary among patients who present with acute myocardial infarction (MI) versus those presenting without acute MI?

3.0 POST-DISCHARGE STATIN FOR PREVENTION OF CARDIAC EVENTS FOR PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

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(Manuscript in Preparation)

3.1 ABSTRACT

Background: Statins have proven to be effective in reducing mortality and cardiac events for a broad range of cardiovascular patients. However, evidence about their efficacy for routine use among patients undergoing percutaneous coronary intervention (PCI) is still limited. The rapid advancement in PCI technology and introduction of new adjunctive medicine make it necessary to assess the effect of statin therapy on adverse cardiac events among patients undergoing PCI procedure and receiving adjunctive medicine.

Methods: Patients were evaluated from the National Heart, Lung, and Blood Institute (NHLBI) Dynamic registry recruitment Wave 4 (2004) and Wave 5 (2006), which is a multi-center prospective observational study. Patient eligibility criteria for this analysis included receipt of aspirin, thienopyridines and cardiovascular protective medications (angiotensin-converting enzyme inhibitors, beta blockers, or calcium channel blockers) after PCI procedure with at least one stent implanted. Baseline characteristics, procedure and lesion information were collected. Adverse cardiac event risks, including death, MI, repeated PCI, CABG, stent thrombosis, repeated PCI/CABG, death/MI, death/MI/CABG, MACE, were compared at one-year follow up between patients receiving post-discharge statin and those who did not.

Results: From Dynamic Registry Wave 4 and Wave 5, a total of 3270 patients were included in this analysis. Of these 3270 patients, 2782 patients (85%) were taking post-discharge statin, and 488 patients (15%) were not taking post-discharge statin. At one-year follow up, post-discharge statin treatment was significantly associated with lower risk of death (HR=0.51, 95% CI: 0.30-0.86, p=0.01), death/MI (HR=0.60, 95% CI: 0.40-0.92, p=0.02), and death/MI/CABG (HR=0.64, 95% CI: 0.44-0.94, p=0.02). The association between postdischarge statin and MACE was of borderline statistical significance (HR=0.76, 95% CI: 0.59-1.00, p=0.05). No significant association was found between post-discharge statin and MI (HR=0.72, 95% CI: 0.38-1.37, p=0.32), repeat PCI (HR=0.85, 95% CI: 0.60-1.19, p=0.33), CABG (HR=0.99, 95% CI: 0.41-2.44, p=0.99), stent thrombosis (HR=0.54, 95% CI: 0.14-2.02, p=0.36), or repeat PCI/CABG (HR=0.86, 95% CI: 0.62-1.19, p=0.36).

Conclusions: Among patients who already received aspirin, thienopyridines and cardiovascular protective medications (ACE inhibitors, beta blockers, or calcium channel blockers) after PCI procedure, post-discharge statin treatment was associated with a significantly reduced risk of death, death/MI and death/MI/CABG, but not significantly associated with reduced risk of other adverse events. These results support routine use of statin therapy after PCI.

Key words: Percutaneous coronary intervention, statin, mortality, adjunctive medication, stent

3.2 INTRODUCTION

Percutaneous coronary intervention (PCI) has proven to be very effective in treating ischemic symptoms due to coronary atherosclerotic narrowing [1, 2]. In the United States, more than one million PCI procedures are performed annually, 70–90 percent of which involve implantation of a stent according to American Heart Association (AHA).

Although PCI achieves immediate symptoms relief in 9 of 10 properly selected patients, these patients remain at increased risk for cardiac events. It is estimated that 40% of patients have major adverse cardiac events (MACE) in 5 years after PCI procedure and 66.7% have MACE in 10 years after PCI procedure [3]. Therefore, most patients also receive adjunctive medicine after PCI procedure, for example, aspirin, thienopyridines (clopidogrel or ticlopidine) and cardioprotective medications, such as angiotensin-converting enzyme (ACE) inhibitors, beta blockers, or calcium channel blockers.

Secondary prevention trials of statins (HMG-CoA reductase inhibitors) have shown a 25% to 30% reduction in ischemic cardiovascular events at long-term follow up [4-6]. However, few data are available to assess whether routine use of statins provide complementary benefit for patients who are receiving other adjunctive medication treatment after PCI.

To evaluate the effect of post-discharge statin treatment among patients who already received aspirin, thienopyridines and at least one type of cardiovascular protective medication (ACE inhibitors, beta blockers, or calcium channel blockers) after undergoing PCI, we evalauetd patients in Dynamic Registry recruitment Wave 4 (2004) and Wave 5 (2006) cohorts to compare one-year outcomes between patients who received a statin prescription after PCI and those who did not receive a statin prescription after PCI.

3.3 METHODS

3.3.1 Patient Selection and Data Collection

The National Heart, Lung, and Blood Institute (NHLBI) Dynamic registry includes 14 sites in Wave 4, and 16 sites in Wave 5 as well as a data coordinating center at University of Pittsburgh. Patients undergoing PCI by Dynamic Registry investigators were enrolled consecutively. Wave 4 recruited 2112 patients. Wave 5 recruited 2158 patients. Consecutive enrollment at each site ended when 125 white men had been enrolled at the site or 1,600 white patients were enrolled across all sites. Consecutive enrollment of women and minorities continued at each site until 200 white patients had been enrolled at the site or 1,600 white patients were enrolled across all sites. Consecutive enrollment of minority patients, men and women, continued until 2,000 patients had been enrolled across all sites. Informed consent was obtained to collect information after hospital discharge. To be eligible for this analysis, the patients had to receive at least one stent, receive aspirin, thienopyridines and at least one type of cardiovascular protective medications (ACE inhibitors, beta blockers, or calcium channel blockers) after PCI procedure.

On-site research coordinators were trained before the recruitment wave started. Data were collected using standard forms. The Dynamic Registry database management system used front-end data entry software developed by the data coordinating center. Data were verified and monitored after entry. The data were imported into an SAS database to search for logical, chronologic, and data accrual inconsistencies. Reports were sent to sites, where corrections might be made after verification.

Successful lesion dilation was defined as an absolute reduction of at least 20% in lesion severity and a final stenosis of <50% (diameter reduction). Partial angiographic success was defined as some but not all lesions were successfully treated; total angiographic success was defined as all attempted lesions were treated successfully. Procedural success was defined as partial or total angiographic success without in-hospital death, myocardial infarction, or emergency coronary artery bypass graft surgery. Myocardial infarction was defined by evidence of ≥2 of the following: (1) typical chest pain > 20 minutes, not

relieved by nitroglycerin; (2) serial electrocardiograms showing characteristic ST-T changes and/or Q waves in ≥2 contiguous leads; (3) serial electrocardiograms showing characteristic ST-T changes and/or Q waves in ≥2 contiguous leads; (4) serum enzyme elevation of creatine kinase-MB is more than 5% of total creatine kinase. Repeat PCI was categorized according to whether the index lesion (target lesion revascularization) or artery (target vessel revascularization) was attempted. Definite stent thrombosis was defined as the presence of angiographic thrombus in a stent that had been previously successfully deployed accompanied by an acute coronary syndrome. Angiographic thrombus was defined as complete occlusion with a stent diameter stenosis <30% or evidence of flow-limiting thrombus within or immediately adjacent to the stent.

3.3.2 Statistical Methods

Patients were categorized into 2 groups according to whether statin therapy was prescribed at discharge. Intergroup differences of continuous variables were analyzed with Student's t test. Intergroup differences of categorical variables were analyzed with chi-square tests. Kaplan-Meier analysis was used to estimate the 1-year cumulative incident proportion of each adverse event in each group. Patients were censored at the last known date of contact or after the first occurrence of the event of interest. Cox proportional hazards regression was used to compare the risk of adverse events between treatment groups during one-year follow-up. Three subgroup analyses were carried out to assess the effect of post-discharge statin therapy including: (i) patients who only received Beta Blocker among the three cardiovascular protective medications; (ii) patients who received beta blocker, ACE inhibitor, but no calcium channel blockers; and (iii) patients who were not in the above two subgroups.

A propensity score model was fit by use of logistic regression to adjust for the bias inherent to the decision to prescribe post-discharge statin therapy [7-12]. A candidate list of baseline variables was included in the propensity score model (refer to Appendix A). A backward approach was used for variable selection with p value of 0.40. Inter-group balances on potential confounders were tested again

after adjustment for the propensity score. If balance was not achieved for certain covariates, the propensity model was refitted by including these covariates in the model. The propensity score was a single covariate that was included in the Cox proportional hazards model to control for confounding related to imblances in the primary exposure variable. One-year cumulative incident proportions were estimates from the Kaplan-Meier analysis for each adverse event in each treatment group. Estimates from crude Cox proportional hazards model were used to plot curves of unadjusted cumulative incident proportion of death by treatment group. Estimates from the Cox proportioanal hazards model, weighted with inverse probability weights (IPW), were used to plot the curve of the weighted cumulative incident proportion of death by treatment group. Specifically, each patient was weighted by sw_i ($sw_i=f(x_i)/f(x_i|z_i)$; $f(x_i)$, marginal probability of receiving the exposure observed; $f(x_i|z_i)$, probability of receiving the exposure observed conditional on observed covariates) [13]. The proportional hazards assumption of constant relative risk over follow-up was evaluated by testing the interaction between time and the primary exposure. All statistical analyses were performed using the SAS program, version.9.1 (SAS Institute, Cary, NC).

3.4 RESULTS

During the study period, a total of 4270 patients were enrolled in Dynamic Registry recruitment Wave 4 and Wave 5. Of these 4270 patients, 45 patients (1.1%) died before discharge, 159 patients (3.7%) did not receive aspirin description or had missing information, 186 patients (4.4%) did not take clopidogrel or ticlopidine at discharge or had missing information, 372 patients (8.7%) did not take any cardiovascular protective medications (ACE inhibitors, beta blockers, or calcium channel blockers) or had missing information. A total of 3280 patients (77%) were included in this analysis. Of these 3280 patients, 2970 patients (85%) were taking post-discharge statin, and 540 patients (15%) were not taking post-discharge statin. The median follow-up among all patients was 8 months and 79% of patients had at least 6-month

follow-up. The proportional hazards assumption of constant relative risk over follow-up was found to be upheld.

Table 3.1 shows the patient demographic, disease history and angiographic characteristics in the two treatment groups. Important differences existed between the two groups. Patients receiving post-discharge statin treatment were more likely to have chest pain at admission (72.2% vs. 66.1%), history of hypercholesterolemia (79.2% vs. 66.8%). They were also less likely to be female (31.5% vs. 39.3%), have prior CABG (17.2% vs. 20.7%), severe non-cardiac disease (34.7% vs. 39.7%), history of congestive heart failure (8.5% vs. 14.9%), and history of hypertension (78.0% vs. 82.6%) or be known to have hypercoagulable status (1.7% vs. 4.2%).

Procedure and lesion characteristics are shown in Table 3.2. Statin recipients were more likely to have Acute MI (30.7% vs. 23.8%), be at urgent (32.4% vs. 25.2%) or emergent procedure (12.4%vs. 9.4%), receive IIb/IIIa receptor antagonist (35.0% vs. 25.1%). The lesion characteristics were similar in the two groups except that statin recipients were more likely to have thrombus evidence (16.2% vs. 9.4%).

The variables to predict the propensity score from the logistic model are shown in Appendix A. The c statistic of the propensity model was 0.69, indicating a probability of 0.69 that a randomly selected post-discharge statin recipient has a larger propensity score than a randomly selected patient who did not receive post-discharge statin. The mean propensity score in the statin group was slightly higher than the no statin group (0.86 vs. 0.78). The distribution of propensity scores among the two treatment groups is shown in Figure 3.1.

Cumulative incident proportions for each adverse event at one-year follow up were estimated with Kaplan-Meier method (Table 3.3). Patients receiving post-discharge statin had lower proportions of each adverse event than patients who did not (death, 2.7% vs. 6.9%; MI, 2.2% vs. 3.1%, repeat PCI, 10.2% vs. 11.1%; CABG, 1.6% vs. 1.8%; stent thrombosis, 0.4% vs. 0.6%) and composite endpoints (repeat PCI/CABG, 11.5% vs. 12.3%; death/MI, 4.7% vs. 9.5%; death/MI/CABG, 6.0% vs. 11.0%; MACE, 14.6% vs. 19.8%). Figure 3.2 is the curve of death incidence in the two treatment groups

produced from crude Cox proportional hazards model, estimated as 1- the estimated survival probability. Post-discharge statin group had a lower death incidence than the no post-discharge statin group. Figure 3.3 is the curve of death incidence produced from Cox proportional hazards model weighting with IPW, which shows the adjusted incidence of death among statin group, estimated as 1- adjusted survival probability, was lower than among no statin group. The estimated hazard ratios from Cox proportional hazards model are shown in Table 3.3. After adjustment with propensity scores, post-discharge statin treatment was significantly associated with reduced risk of death (HR=0.51; 95% CI, 0.30-0.86, p=0.01), composite endpoints of death/MI (HR=0.60; 95% CI, 0.40-0.92, p=0.02), composite endpoints of death/MI/CABG (HR=0.64; 95% CI, 0.44-0.94, p=0.02). The association between postdischarge statin and risk of MACE is of borderline significance (HR=0.76; 95% CI, 0.59-1.00, p=0.05). It is also non-significantly associated with a lower risk of MI, repeat PCI, CABG, stent thrombosis, and repeat PCI/CABG.

Results of subgroups analysis among patients who took only Beta Blocker, no ACE inhibitor or Calcium channel blockers are shown in Table 3.4. Post-discharge statin use was associated with lower risk of all adverse events, except for a higher risk of CABG. None of these differences is statistically significant.

Results of subgroups analysis among patients who took beta blocker, ACE inhibitor, but no calcium channel blockers are shown in Table 3.5. Post-discharge statin use was associated with lower risk of all adverse events, except for a slightly higher risk of death (HR=1.01, 95% CI: 0.36-2.83, p=0.99). None of these differences is statistically significant.

Results for the remaining patients are shown in Table 3.6. Post-discharge statin use was associated with a significantly reduced risk of death (HR=0.34, 95% CI: 0.15-0.79, p=0.01). Post-discharge statin treatment was non-significantly associated with reduced risk of all adverse events considered, except for a non-significantly higher risk for repeat PCI (HR=1.28, 95% CI: 0.60-2.75, p=0.53) and repeat PCI/CABG (HR=1.42, 95% CI: 0.67-3.03, p=0.36).

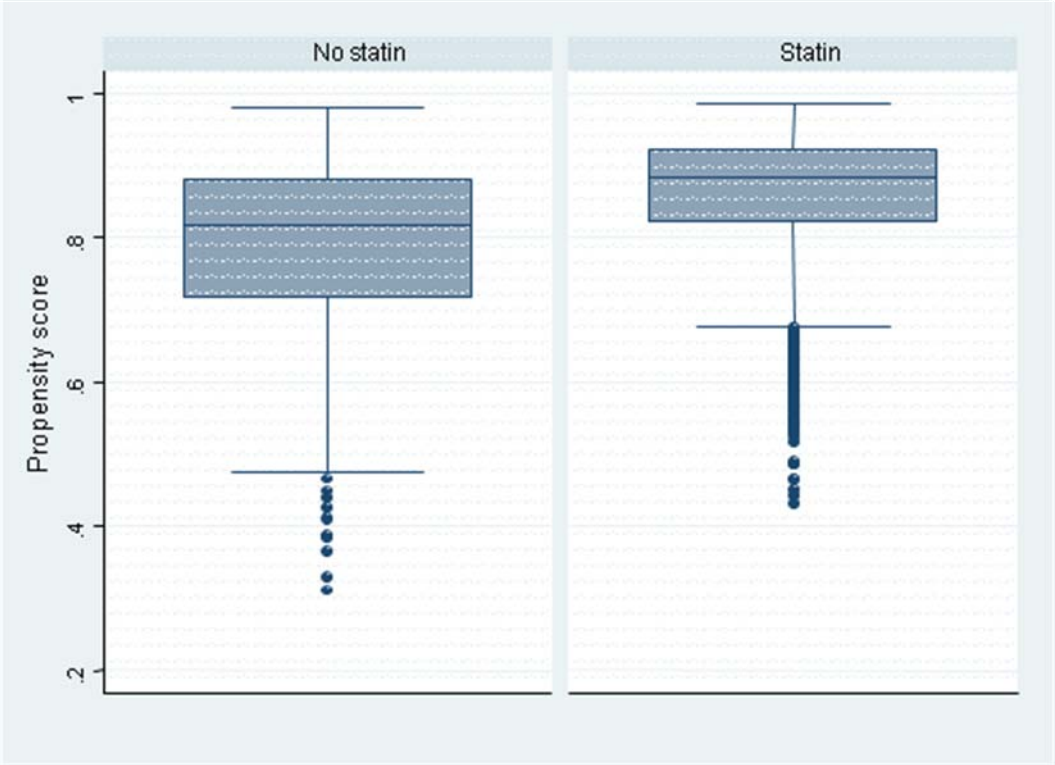

Figure 3.1 Boxplot of propensity scores in no statin group and statin group*

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* The three horizontal lines in the shaded box from bottom to top stand for lower quartile (Q1, $X_{.25}$), median (med, $X_{.5}$), upper quartile (Q3, $X_{.75}$), respectively. Interquartile range (IQR) is defined as Q3-Q1.

Outliers are values which lie more than 1.5*IQR lower than Q1 or 1.5*IQR higher than Q3. The two whiskers below and above the shaded box indicate the smallest and largest values that are not outliers.

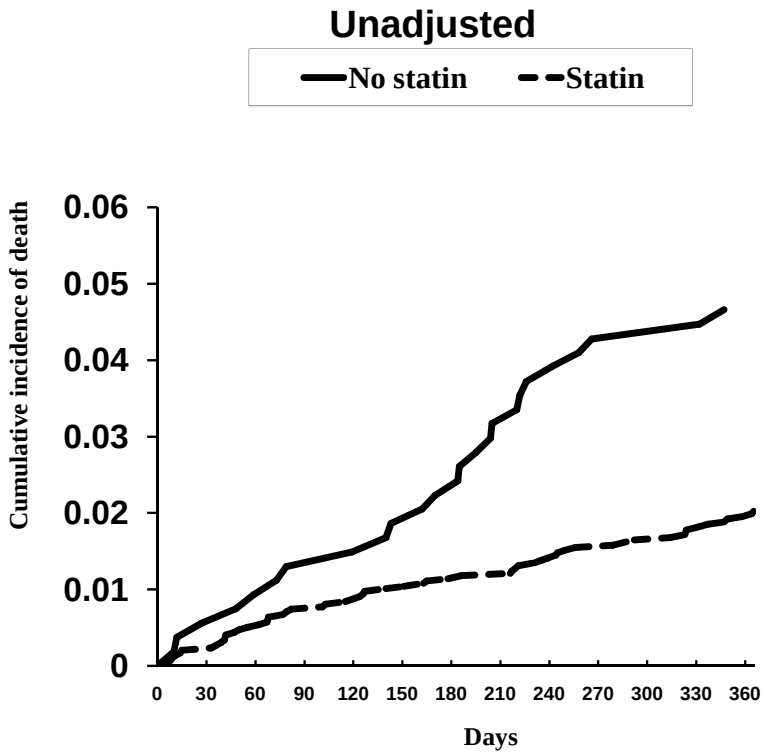

Figure 3.2 Cumulative incidence proporiton of death estimated from crude Cox proportional hazards model for statin group and no statin group

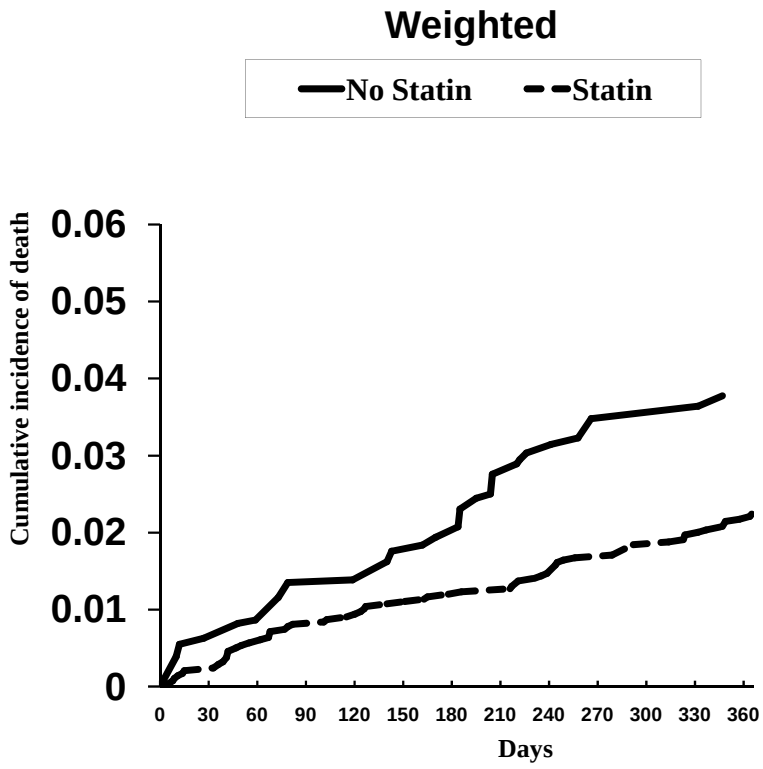

Figure 3.3 Cumulative incidence proportion of death estimated from weighted Cox proportional hazards model for statin group and no statin group

3.5 DISCUSSION

The present study assessed whether post-discharge statin treatment was associated with reduced cardiac adverse event rates for patients already receiving adjunctive medicine after PCI procedure. Results showed that post-discharge statin treatment was associated with lower cumulative incident proportion for each adverse event, including death, MI, repeated PCI, CABG, stent thrombosis, Repeated PCI/CABG, death/MI, death/MI/CABG, MACE. After propensity score adjustment for predictors of statin use, post-

discharge statin treatment was significantly associated with a reduced risk of mortality and composite endpoints of death/MI, and death/MI/CABG. Post-discharge statin use also was associated with lower risk of MACE, but it was of borderline statistical significance. Similar patterns of risk reduction were observed in the three subgroups of patients considered, except for death among patients who took beta blockers and ACE inhibitors, but no calcium channel blockers. In this subgroup, the hazard ratio of death was non-significantly elevated.

It has been well established that statins reduce blood cholesterol level [4-6]. Beyond that, statins also have favorable effects on platelet adhesion [14, 15], stent thrombosis [16-18], endothelial function [19-24], plaque stability and inflammation [25-30]. All these functions can possibly contribute to the mortality benefit among PCI patients. Our finding showed a strong protective effect against mortality at one-year follow up (HR=0.51, 95% CI: 0.30-0.86, p=0.01). The magnitude is comparable to a six-month follow-up study by Chan et al. (HR=0.65, 95% CI: 0.42-0.99, p=0.04)[31]. The difference between the two studies is that Chan et al. assessed the effect of statin administered before PCI procedure, while our study examined the effect of post-discharge statin treatment. They excluded severe patients with acute MI, recent MI (within 7 days of procedure), or cardiogenic shock. Our study excluded patients who did not receive aspirin, or thienopyridines, or cardiovascular protective medications (ACE inhibitors, beta blockers, calcium channel blockers). Kasai et al. also reported a similar magnitude of long-term efficacy of statin treatment at the time of PCI procedure with an average follow-up of 11 years in a Japanese population [32]. Statin treatment was associated with a significant reduction in all cause mortality (HR=0.54, 95% CI: 0.29-0.99, p=0.048) and cardiac death (HR=0.24, 95% CI: 0.07-0.80, p=0.02). Some previous clinical trials with small sample size did not find a statistically significant association between statin and mortality risk [33, 34].

No studies until today have confirmed the efficacy of routine use of statins on restenosis after PCI procedure, although lab experiments provided some evidence that statins prohibit smooth muscle proliferation. The PREDICT trial was a multicenter, randomized, double-blind trial between 1992 and 1994, aiming to assess restenosis benefit with pravastatin (40 mg/day) for 6 month after successful

balloon angioplasty (PTCA) [34]. Minimal lumen diameter, assessed by quantitative coronary angiography, was not different at 6-month follow-up (pravastatin 1.54±0.66mm vs placebo 1.47±0.62mm). The restenosis rate was 39.2% in pravastatin group and 43.8% in placebo group (p=0.26). The Fluvastatin Angiographic Restenosis (FLARE) was another trial designed to evaluate restenosis benefit of statin among patients undergoing successful PTCA (no stent use) [35]. The study was between 1992 and 1995, similar to PREDICT. Patients were randomized to either placebo or fluvastatin 40mg twice daily, which started 2-4 weeks before the procedure. There was no difference in late lumen loss (fluvastatin 0.23±0.49mm vs. placebo 0.23±0.52mm, p=0.95), which was measured by quantitative coronary angiography. Also no difference was found in angiographic restenosis rate (fluvastatin 28% vs placebo 31%, p=0.42). Another earlier trial, Lovastatin Restenosis Trial, reported that lovastatin (40 mg orally twice daily) before coronary angioplasty did not prevent or delay restenosis in the first six months after the procedure [33]. We did not find a statistically significant association between post-discharge statin treatment and repeated PCI (HR=0.85, 95% CI: 0.60-1.19, p=0.33), or repeated PCI/CABG (HR=0.86, 95% CI: 0.62-1.19, p=0.36). This could be due to the fact that DES decreases the risk of repeat PCI to the extent that the event rate is too small to detect a clinically importance effect of postdischarge statin on the risk of this event.

Previous studies reported beneficial effect of statin on composite endpoints among PCI patients. FLARE trial reported a lower incidence of death/MI in fluvastatin group when compared to placebo group (1.4% vs. 4.0%, log rank P=0.025), but not for death/MI/CABG or death/MI/CABG/repeated PTCA [35]. Serruys et al. reported that post-discharge statin treatment was associated with a significant reduction in composite endpoint of cardiac death, nonfatal myocardial infarction or reintervention procedure (HR=0.78, 95% CI: 0.64-0.95, p=0.01) [36]. After excluding reinterventions from the composite endpoint, the protective effect became stronger (HR=0.67, 95% CI: 0.54-0.84, p<0.001). Our study found a significant protection effect for composite endpoints of death/MI, death/MI/CABG.

There are limitations for our study. First, the present study design is a prospective observational study. Although we adjusted for a wide array of factors associated with statin use, it is still possible that

unknown confounders (residual confounding) may have biased risk estimates. Second, the number of some types of adverse cardiac events, such as stent thrombosis and CABG surgery, was small, and we had limited power to detect clinically important effects for these events. Third, only prescription information was collected without knowing patient adherence to the regimen. Crossover between the two groups might also occur. However, we do not have reason to believe the crossover is differential. Both poor adherence and non-differential crossover tend to underestimate the association between post-discharge statin and adverse cardiac events.

3.6 CONCLUSIONS

Among patients who already received aspirin, thienopyridines and cardiovascular protective medications (ACE inhibitors, beta blockers, or calcium channel blockers) after PCI procedure, post-discharge statin treatment was associated with a significantly reduced risk of death, death/MI, death/MI/CABG, and MACE, but not significantly associated with reduced risk of other adverse events. These results support routine use of statin therapy after PCI.

Table 3.1 Patient demographics, disease history, and angiographic characteristics between the two treatment groups

Characteristics	No statin (n=488)	Statin (n=2782)	P†	P‡
Female, %	39.3	31.5	<0.01	0.97
Age in years	65.6(12.2)	63.3(11.9)	<0.01	0.98
Race, %				
White	78.5	79.2	0.05	0.25
Black	17.0	16.1		
Asian	1.4	3.0		
Other	3.1	1.7		
Insurance				
Medicare	41.4	35.0	0.04	0.98
Other public	15.8	15.8		
Private	39.9	45.5		
None/self-pay	2.9	3.8		
Hispanic, %	7.0	5.0	0.07	0.06
Prior intervention, %	34.4	32.4	0.38	0.93
Prior CABG	20.7	17.2	0.06	0.93
Prior MI	21.7	24.6	0.17	0.96
Severe non-cardiac disease	39.7	34.7	0.03	0.71
History of diabetes	36.3	33.5	0.24	0.69
History of chest pain	55.3	53.7	0.51	0.22
Chest pain at admission	66.1	72.2	<0.01	0.90
History of CHF	14.9	8.5	<0.01	0.93
CHF at admission	8.0	5.9	0.07	0.82
History of hypertension	82.6	78.0	0.02	0.69
History of hypercholesterolemia	66.8	79.2	<0.01	0.97
Known hypercoagulable state	4.2	1.7	<0.01	0.45
Dominance				
Left	5.9	8.3	0.15	0.96
Right	87.0	83.8		
Balanced	7.1	8.0		
Vessel disease				
Single	35.1	35.7	0.25	0.71
Double	29.9	32.8		
Triple	35.1	31.5		
Cardiac Protective Medications				
Only ACE	7.4	7.1	<0.01	0.32
Only beta blocker	38.7	32.8		
Only calcium channel blocker	3.7	2.4		
ACE+beta blocker	32.0	43.1		
ACE+calcium channel blocker	3.5	1.7		
beta blocker + calcium channel blocker	8.4	6.3		
ACE + beta blocker + calcium channel blocker	6.4	6.7		

Table 3.1 continued

Amenable with CABG	74.0	77.5	0.09	0.96
Amenable with PCI	90.2	89.4	0.63	0.97

CABG indicates coronary artery bypass graft surgery; CHF congestive heart failure; MI myocardial infarction; PCI percutaneous coronary intervention; ACE angiotensin-converting enzyme inhibitors.

Categorical variables are presented as column percentages, continuous variables as mean±SD.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 3.2 Procedure and lesion characteristics between the two treatment groups

Characteristics	No statin (n=488)	Statin (n=2782)	P value†	P value‡
Cause of procedure				
Acute MI	23.8	30.7	<0.01	0.99
Unstable angina	34.0	34.2		
Stable angina	20.3	19.8		
Asymptomatic CAD	15.4	11.1		
Other	6.6	4.2		
Procedure circumstance				
Elective	65.4	55.2	<0.01	0.89
Urgent	25.2	32.4		
Emergent	9.4	12.4		
Procedure site	74.2	76.5	0.26	0.49
No. of lesions attempted				
1	73.2	73.8	0.41	0.95
2	22.8	21.0		
3 or more	4.1	5.3		
IIb/IIIa receptor antagonist	25.1	35.0	<0.01	0.62
Any lesion >25mm	15.4	15.6	0.90	0.96
Any lesion previously treated	5.9	6.7	0.56	0.58
Any evidence of thrombus	9.4	16.2	<0.01	0.46
Any calcification	30.3	27.0	0.13	0.96
Any ulcerated lesion	13.1	13.6	0.78	0.91
Any ostial lesion	9.4	8.3	0.41	0.58
C type AHA/ACC classification	29.1	27.5	0.47	0.97
Angiographic success				
Yes	93.0	93.1	0.97	0.99
Partial	2.7	2.8		
No	4.3	4.1		

CAD indicated coronary artery disease; AHA American Heart Association; ACC American College of Cardiology.

Categorical variables are presented as column percentages, continuous variables as mean±SD.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 3.3 One-year cumulative incident proportions (K-M) and hazard ratios of 1-year outcome comparing post-discharge statin treatment to no post-discharge statin treatment

Event	N*	Cumulative incident proportion		Hazard Ratio†	95% CI	P value
		No statin (n=488)	Statin (n=2792)			
Death	74	6.9%	2.7%	0.51	0.30-0.86	0.01
MI	62	3.1%	2.2%	0.72	0.38-1.37	0.32
Repeat PCI	260	11.1%	10.2%	0.85	0.60-1.19	0.33
CABG	46	1.8%	1.6%	0.99	0.41-2.44	0.99
Stent thrombosis	14	0.6%	0.4%	0.54	0.14-2.02	0.36
Repeat PCI/CABG	299	12.3%	11.5%	0.86	0.62-1.19	0.36
Death/MI	131	9.5%	4.7%	0.60	0.40-0.92	0.02
Death/MI/CABG	169	11.0%	6.0%	0.64	0.44-0.94	0.02
MACE	387	19.8%	14.6%	0.76	0.59-1.00	0.05

MI indicates myocardial infarction; PCI percutaneous coronary intervention; CABG coronary artery bypass graft surgery; MACE major adverse cardiac event, consited of death, MI, repeat PCI and CABG; CI confidence interval.

* Number of events
† Adjusted with propensity score as continuous variable in Cox proportional hazards model

Table 3.4 One-year cumulative incident proportion (K-M) and hazard ratios of 1-year outcome comparing statin use to no statin use among patients who took only beta blockers, no ACE inhibitor or calcium channel blockers

Event	N*	Cumulative incident proportion		Hazard Ratio†	95% CI	P value
		No statin (n=189)	Statin (n=913)			
Death	16	5.7%	1.4%	0.37	0.13-1.05	0.06
MI	14	2.9%	1.7%	0.59	0.17-2.01	0.39
Repeat PCI	87	14.1%	10.2%	0.66	0.39-1.11	0.11
CABG	12	0.6%	1.5%	2.18	0.26-18.29	0.47
Repeat PCI/CABG	98	14.7%	11.5%	0.71	0.43-1.17	0.18
Death/MI	30	8.5%	3.1%	0.45	0.21-1.00	0.05
Death/MI/CABG	40	9.0%	4.2%	0.56	0.27-1.16	0.12
MACE	119	21.5%	13.4%	0.63	0.41-0.97	0.04

MI indicates myocardial infarction; PCI percutaneous coronary intervention; CABG coronary artery bypass graft surgery; MACE major adverse cardiac event, consisted of death, MI, Repeat PCI, CABG; CI confidence interval.

* Number of events
† Adjusted with propensity score as continuous variable in Cox proportional hazards model.

Table 3.5 One-year cumulative incident proportion (K-M) and hazard ratios of 1-year outcome comparing statin use to no statin use among patients who took beta blockers, ACE inhibitor, but no calcium channel blockers

Event	N*	Cumulative incident proportion		Hazard Ratio†	95% CI	P value
		No statin (n=156)	Statin (n=1198)			
Death	34	3.9%	3.5%	1.01	0.36-2.83	0.99
MI	25	2.8%	2.1%	0.75	0.24-2.30	0.61
Repeat PCI	115	12.5%	10.6%	0.88	0.50-1.54	0.65
CABG	22	2.1%	1.7%	0.76	0.21-2.68	0.67
Stent thrombosis	8	1.3%	0.6%	0.36	0.07-1.87	0.22
Repeat PCI/CABG	133	14.9%	11.8%	0.80	0.48-1.35	0.41
Death/MI	57	6.6%	5.3%	0.83	0.39-1.79	0.64
Death/MI/CABG	73	8.0%	6.6%	0.78	0.39-1.53	0.46
MACE	167	18.5%	15.1%	0.83	0.53-1.32	0.44

PCI indicates percutaneous coronary intervention; CABG coronary artery bypass graft surgery; MI myocardial infarction; MACE major adverse cardiac event, consisted of death, MI, CABG and repeat PCI; CI confidence interval.

* Number of events
† Adjusted with propensity score as continuous variable in Cox proportional hazards model.

Table 3.6 One-year cumulative incident proportion (K-M) and hazard ratios of 1-year outcome comparing statin use to no statin use among patients other than in Table 3.4 and 3.5

Event	N*	Cumulative incident proportion		Hazard Ratio†	95% CI	P value
		No statin (n=143)	Statin (n=671)			
Death	24	11.2%	2.8%	0.34	0.15-0.79	0.01
MI	23	3.7%	3.4%	0.82	0.29-2.28	0.70
Repeat PCI	58	5.7%	9.5%	1.28	0.60-2.75	0.53
CABG	12	2.7%	1.7%	0.87	0.18-4.18	0.86
Repeat PCI/CABG	68	6.6%	11.0%	1.42	0.67-3.03	0.36
Death/MI	44	13.5%	5.9%	0.55	0.29-1.07	0.08
Death/MI/CABG	56	16.1%	7.6%	0.60	0.33-1.10	0.10
MACE	101	18.5%	15.4%	0.90	0.54-1.49	0.67

PCI indicates percutaneous coronary intervention; CABG coronary artery bypass graft surgery; MI myocardial infarction; MACE major adverse cardiac event; CI confidence interval.

* Number of events
† Adjusted with propensity score as continuous variable in Cox proportional hazards model.

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4.0 EFFECT OF TREATMENT WITH MULTIPLE STENTS VS. ONE STENT ON PATIENT OUTCOMES

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4.1 ABSTRACT

Background: The efficacy of treatment with multiple stents or single long stent for long lesions has been a topic under debate for years. It is of clinical importance to assess the effect of multiple stents vs. single stent among shorter lesions, because, unlike longer lesions, shorter lesions do not have to be treated with multiple stents.

Methods: DEScover Registry is a prospective, multicenter, observational study between January-June, 2005. The eligibility criteria for this analysis include: received at least one stent treatment; lesions were not previously treated; lesion length were 10~32mm; procedures were angiographically successful. Baseline characteristics, angiographic characteristics, procedural characteristics and in-hospital events were recorded for participating patients. Follow-up was performed at 1, 6, and 12 months by a central telephone facility for clinical events (death, MI, repeat PCI, CABG, stent thrombosis). For those patients reporting an event, a specially trained research coordinator then obtained additional information about the event. Adverse events, including death/MI, Repeat PCI/CABG, death/MI/CABG, death/MI/thrombosis, death/MI/CABG/thrombosis, were compared between patients receiving multiple stents for any lesion and patients receiving single long stent for every lesion. Patients with one lesion treated were analyzed separately from those with multiple lesions treated.

Results: A total of 2865 patients were included in this analysis. Of these patients, 2282 patients had one lesion treated, and 583 patients had more than one lesion treated during the procedure. In the subgroup of patients with only one lesion treated, the cumulative incident proportions were higher in the patients who received multiple stents treatment than in those who received single stent for death/MI (14.8% vs. 6.4%), death/MI/CABG (15.5% vs. 7.4%), death/MI/thrombosis (15.1% vs. 6.4%), and death/MI/CABG/thrombosis (15.8% vs. 7.5%), lower event rate of repeat PCI/CABG (8.2% vs. 10.5%). In the Cox proportional hazards model, compared with the treatment with single stent, multiple stents

were associated with non-significantly higher risks of death/MI (HR=1.39, 95% CI: 0.80-2.41, p=0.25), repeat PCI/CABG (HR=1.09, 95% CI: 0.66-1.81, p=0.74), death/MI/CABG (HR=1.41, 95% CI: 0.84-2.38, p=0.20), death/MI/thrombosis (HR=1.44, 95% CI: 0.83-2.47, p=0.19), death/MI/CABG/thrombosis (HR=1.45, 95% CI: 0.87-2.42, p=0.15).

Of the 583 patients who had more than one lesion, a total of 474 (81.3%) received a single stent for each lesion, and 109 patients (18.7%) received multiple stents for at least one lesion. Compared to patients with single stents, patients with multiple stents had lower cumulative incident proportion of death/MI (3.0% vs. 7.8%), death/MI/CABG (5.1% vs. 9.0%), death/MI/thrombosis (3.0% vs. 7.8%), and death/MI/CABG/thrombosis (5.1% vs. 9.0%), and a higher cumulative incident proportion of repeat PCI/CABG (12.2% vs. 10.1%). The Cox proportional hazards model showed that treatment with multiple stents was associated with non-significantly lower risk of death/MI (HR=0.50, 95% CI: 0.11-2.24, p=0.37), repeat PCI/CABG (HR=0.98, 95% CI: 0.46-2.10, p=0.96), death/MI/CABG (HR=0.88, 95% CI: 0.29-2.63, p=0.82), death/MI/thrombosis (HR=0.50, 95% CI: 0.11-2.24, p=0.37), death/MI/CABG/thrombosis (HR=0.88, 95% CI: 0.29-2.63, p=0.82).

Conclusion: Treatment with multiple stents may be associated with non-significantly higher risk of adverse events among patients who have one lesion, but may be associated with lower risk of adverse events among patients who have more than one lesion. A specifically designed study with a larger sample size is needed to investigate this question.

Key words: Percutaneous coronary intervention, overlap, multiple stents, adverse cardiac events

4.2 INTRODUCTION

In the practice of percutaneous coronary intervention (PCI), obstructive lesions that are selected for intervention, and are of very long length (i.e. >32mm), nearly always require the use of multiple overlapping stents. In contrast, shorter lesions in the range of 10-32mm can usually be treated with either a single stent or multiple overlapping stents. There is contraversy as to the efficacy of treatment with multiple shorter stents versus a single longer stent from literature. Several investigators have reported similar outcomes between the 2 treatment approaches, [1-5], whereas others have reported that treatment with multiple stents is associated with a higher risk of adverse event rates [6-8].

The lengths of current FDA approved stents in the US market are from 8 to 33mm. Therefore, when obstructive lesions that are targeted for treatment fall within this range, the operator has a choice of using a single versus multiple overlapping stents. Ultimately, full stent coverage of the lesion is the primary goal, while achieving this without excessive stent length in relation to lesion length. This is because previous studies, particularly among bare-metal stented patients, have shown that the risk of restenosis is strongly associated with total stent length [9-11]. In the drug-eluting stent era, the concern over excessive stent length exists, but to a lesser degree compared to bare metal stents [10, 12-15].

Finally, the use of multiple overlapping stents for lesions in the range of 10 to 32mm can occur as an *a priori* (planned) strategy by the operator, or in response to a suboptimal lesion coverage result with the first stent that was used. At present, little if any data exist on evaluating the efficacy of multiple overlapping stents in relation to the reason in which more than one stent was used (i.e. planned approach versus ad hoc response in relation to suboptimal initial result). Therefore, in this study, we investigated the efficacy of treatment with multiple shorter stents versus a single longer stent among lesions of 10 to 32mm in length among patients in the DEScover Registry.

4.3 METHODS

4.3.1 Study Design and Patient Population

The DEScover Registry is a prospective, multicenter, observational study designed to characterize PCI patients treated from a broad sampling of hospitals and practices in the United States. Previous details on the study design and patient population have been published [16, 17]. Briefly, at participating sites (n=140), 7,752 consecutively-enrolled patients underwent PCI between January-June, 2005. The exclusion criteria were minimal: patient refusal or inability to provide written informed consent and/or HIPAA authorization. All interventional strategies, including the use of stents or other devices, stent(s) type and length, number of stents placed, and peri-procedure medications were selected at the operator's discretion. The protocol was approved by a central or individual institutional review board before the study started. Baseline characteristics, angiographic characteristics, procedural characteristics and in-hospital events were recorded for participating patients. Follow-up was performed at 1, 6, and 12 months by a central telephone facility for clinical events.

For the present analysis, patients were included if they received at least one stent, the lesion treated was not previously treated (i.e. not a restenotic lesion), the lesion length was between 10 to 32mm, and the procedure was angiographically successful. The latter was defined as achievement of a minimum stenosis diameter reduction to <50% in the presence of Thrombosis in Myocardial Infarction (TIMI) grade 3 flow. This resulted in an analysis cohort of 2,865 patients (37% of the total cohort).

4.3.2 Data Management and Definitions

Data were collected and submitted online using electronic case report forms. Password protected study codes were used to protect subject identity. An independent contract research organization served as administrator for the study, which is sponsored by Cordis, Johnson & Johnson Company (Miami Lakes,

Fla). The University of Pittsburgh serves as the statistical analysis center. Follow-up was 93.2% complete at 6 months and 89.6% complete at 1 year.

Complete procedural success was defined as achieving angiographic success (as defined above) in all attempted lesions without the occurrence of a major complication, such as myocardial infarction (MI), repeat revascularization during hospitalization, or death. Partial procedural success was defined as angiographic success in at least 1 lesion treated without an in-hospital major complication. Procedural failure was defined as absence of angiographic success in all lesions or occurrence of any in-hospital major complication. All angiographic results were reported on the basis of visual assessment by the individual sites (i.e. not central angiographic laboratory).

Myocardial infarction (MI) was diagnosed by evolutionary ST-segment elevation, development of new Q waves or left bundle-branch block on the ECG or biochemical evidence of necrosis, including a total creatine kinase ≥2 times the normal upper limit with an elevated creatine kinase-MB or a positive troponin. Repeat PCI was categorized according to whether the index lesion (target lesion revascularization) or artery (target vessel revascularization) was attempted. Definite stent thrombosis was defined as the presence of angiographic thrombus in a stent that had been previously successfully deployed accompanied by an acute coronary syndrome. Angiographic thrombus was defined as complete occlusion with a stent diameter stenosis <30% or evidence of flow-limiting thrombus within or immediately adjacent to the stent. Major adverse coronary events were defined as death (all cause), MI, repeat PCI, or coronary artery bypass graft surgery (CABG).

4.3.3 Statistical Methods

Analyses were performed in subgroups of patients according to whether a single lesion (n=2282, 79.7%) was treated (primary analysis) or multiple lesions (n=583, 20.3%) were treated (secondary analysis). The rationale for this was that the primary single lesion analysis was easiest to interpret directly in relation to whether a single or multiple stents were used. In the case of multiple treated lesions, there existed the

possibility of a "partial" approach whereby one lesion was treated with a single stent and a second lesion was treated with multiple stents. On the other hand, the secondary analysis of multiple treated lesions was presumably better able to judge whether multiple stents were used as a planned strategy as opposed to a response to complications with the initial stent. Specifically, if a patient had multiple lesions treated with multiple stents for each lesion, one can infer that this was likely the planned approach rather than a response to suboptimal initial stent result.

For both subgroups, patients were categorized into 2 groups according to whether a single or multiple stents were used to treat a lesion. Differences in continuous variables were compared by student t-tests. Differences in proportions of categorical variables were compared by chi-square tests. The Kaplan-Meier method was used to estimate cumulative incident proportion of each adverse event in each group. Patients were censored at the last known date of contact or after the first occurrence of the event of interest. For each subgroup, a separate propensity score model was fit by use of logistic regression to adjust for the potential selection bias inherent in the decision to dilate the lesion(s) with multiple shorter stents versus a single longer stent [18-24]. A candidate list of baseline variables were included in the propensity score model (refer to Appendix B). A backward selection method was used with a p value of 0.40 to select variables. If balance was not achieved for certain covariates, the propensity model will be refitted by including these covariates in the model. Cox proportional hazards regression was used to estimate the independent effect of the use of multiple overlapping stents versus a single stent on the relative hazard of adverse clinical outcomes. The propensity score was the single covariate that was included in the model to control for confounding in addition to the binary exposure variable of single versus multiple overlapping stents. The proportional hazards assumption of constant relative risk over follow-up was evaluated by testing the interaction between time and the primary exposure (multiple stents/single stent). All statistical analyses were performed using the SAS program, version.9.1 (SAS Institute, Cary, NC).

4.4 RESULTS

Between January and June 2005, 7752 patients were enrolled in DEScover Registry. A total of 2865 patients were eligible in this analysis. Of these patients, 2282 patients had one lesion treated, and 583 patients had more than one lesion treated during the procedure. The proportional hazards assumption of constant relative risk over follow-up was found to be upheld. The analysis results for the two subgroups are shown below.

4.4.1 PATIENTS WHO HAVE ONLY ONE LESION

Among the 2282 patients who have only one lesion, a total of 2002 (87.7%) patients received single stent, and 280 (12.3%) patients receive more than one stent. The median follow up time is 12 month. The median follow-up time among patients who did not have any adverse event is 12 month. Table 4.1 shows the patient demographics, disease history and angiographic characteristics in each treatment group. The practice of single stent or multiple stents differed among regions of US. Patients from North East or West were more likely to receive multiple stents treatment, while patients from South East and South West were more likely to receive single stent treatment. No significant difference was found between the two treatment groups in terms of other patient demographics, disease history, and angiographic characteristics (Table 4.1). After propensity score adjustment, none of the differences was statistically significant.

The primary reason for revascularization and circumstance of procedure was similar between the two treatment groups (Table 4.2). However, patients who received multiple stents tended to have longer lesion than patients who received a single stent (mean length, 22.0 mm vs. 17.7 mm, $p<0.01$). The proportion of occlusion was higher among patients who received multiple stents than among patients who received single stent (16.4% vs. 10.7%, $p=0.01$). After propensity score adjustment, none of these differences was statistically significant.

The variables to predict the propensity score from the logistic model are shown in Appendix B. The c statistic for the propensity score model was 0.74, indicating a probability of 0.74 that for a randomly selected subject receiving multiple stents the propensity score would be higher than for a randomly selected subject receiving single stent. Patients treated with multiple stents had higher average propensity score than patients treated with one stent (0.21 vs. 0.11). The distribution of propensity scores among patients treated with one stent and patients treated with multiple stents is shown in Figure 4.1.

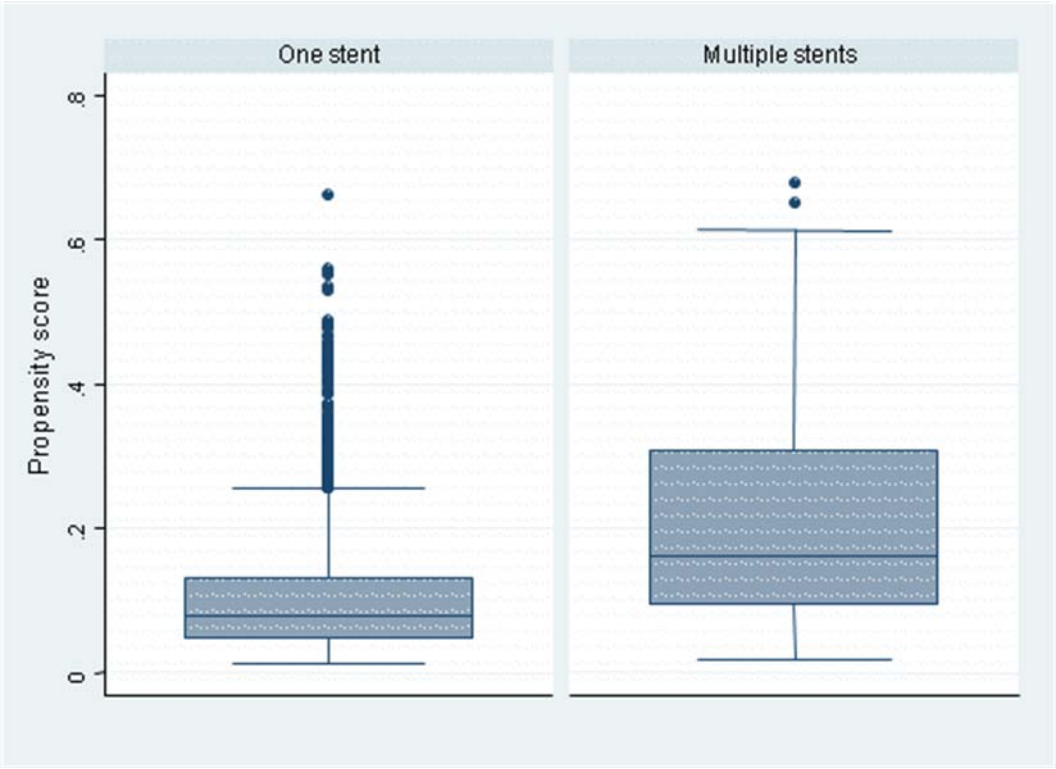

Figure 4.1 Boxplot of propensity score between patients treated with one stent and patients treated with multiple stents (primary analysis)*

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* The three horizontal lines in the shaded box from bottom to top stand for lower quartile (Q1, $X_{.25}$), median (med, $X_{.5}$), upper quartile (Q3, $X_{.75}$), respectively.
Interquartile range (IQR) is defined as Q3-Q1.

Outliers are values which lie more than 1.5*IQR lower than Q1 or 1.5*IQR higher than Q3. The two whiskers below and above the shaded box indicate the smallest and largest values that are not outliers.

Cumulative incident proportions estimated with Kaplan-Meier method are shown in Table 4.3. The cumulative incident proportions were higher in the group treated with multiple stents than in the group treated with single stent for death/MI (14.8% vs. 6.4%), death/MI/CABG (15.5% vs. 7.4%), death/MI/thrombosis (15.1% vs. 6.4%), and death/MI/CABG/thrombosis (15.8% vs. 7.5%), lower cumulative incident proportions of repeat PCI/CABG (8.2% vs. 10.5%). In Cox proportional hazards model, compared with the treatment with single stent, multiple stents were non-significantly associated with higher risk for death/MI (HR=1.39, 95% CI: 0.80-2.41, p=0.25), repeat PCI/CABG (HR=1.09, 95% CI: 0.66-1.81, p=0.74), death/MI/CABG (HR=1.41, 95% CI: 0.84-2.38, p=0.20), death/MI/thrombosis (HR=1.44, 95% CI: 0.83-2.47, p=0.19), death/MI/CABG/thrombosis (HR=1.45, 95% CI: 0.87-2.42, p=0.15) (Table 4.3).

4.4.2 PATIENTS WHO HAVE MORE THAN ONE LESION

Of the 583 patients who had more than one lesion, a total of 474 patients (81.3%) received single stent for each lesion, and 109 patients (18.7%) received multiple stents for at least one lesion. Among all patients the median follow up is 12 months. Among patiens without any adverse events the median follow up is 12 months.

Patient demographics, disease history, and angiographic characteristics are shown for each treatment group in Table 4.4. Patients who received multiple stents were more likely to be female (37.6% vs. 28.5%), less likely to have hypercholesterolemia (71.0% vs. 81.2%), history of hypertension (70.1% vs. 78.6%), or history of prior intervention (22.6% vs. 31.2%). The choice of treatment with single stent or multiple stents was different among different regions of US. Patients from North East were more likely to receive multiple stents for their lesions than patients in other region, and patients from South East and South West were more likely to receive single stent for their lesions than patients in other region. No significant differences were found between the two treatment in terms of other demographic

characteristics, disease history and angiographic characteristics. After propensity score adjustment, none of the differences was statistically significant.

The primary reason for revascularization and circumstance of procedure were similar among the two groups (Table 4.5). Patients receiving multiple stents were more likely to have lesion calcification (78.0% vs. 69.2%, p=0.07). No significant differences were found between the two treatments in terms of other lesion characteristics. After propensity score adjustment, none of the differences was statistically significant.

The variables to predict the propensity score from the logistic model are shown in Appendix B. The c statistic of the propensity model was 0.76, indicating a probability of 0.76 that for a randomly selected subject receiving multiple stents the propensity score would be higher than for a randomly selected subject receiving single stent. Patients treated with multiple stents had higher average propensity score than patients treated with one stent (0.29 vs. 0.15). The distribution of propensity scores among patients treated with one stent and patients treated with multiple stents is shown in Figure 4.2.

Cumulative incident proportion of adverse even estimated with Kaplan-Meier method is shown in Table 4.6. These are defined as 1- estimated probablity of no adverse events. The cumulative incident proportions were lower in the group of multiple stents treatment than in the group of single stent in terms of death/MI (3.0% vs. 7.8%), death/MI/CABG (5.1% vs. 9.0%), death/MI/thrombosis (3.0% vs. 7.8%), and death/MI/CABG/thrombosis (5.1% vs. 9.0%), higher cumulative incident proportion of repeat PCI/CABG (12.2% vs. 10.1%).

In the Cox proportional hazards model, compared with the treatment with single stent, multiple stents were associated with a non-significantly lower risk of death/MI (HR=0.50, 95% CI: 0.11-2.24, p=0.37), Repeat PCI/CABG (HR=0.98, 95% CI: 0.46-2.10, p=0.96), death/MI/CABG (HR=0.88, 95% CI: 0.29-2.63, p=0.82), death/MI/thrombosis (HR=0.50, 95% CI: 0.11-2.24, p=0.37), death/MI/CABG/thrombosis (HR=0.88, 95% CI: 0.29-2.63, p=0.82) (Table 4.6).

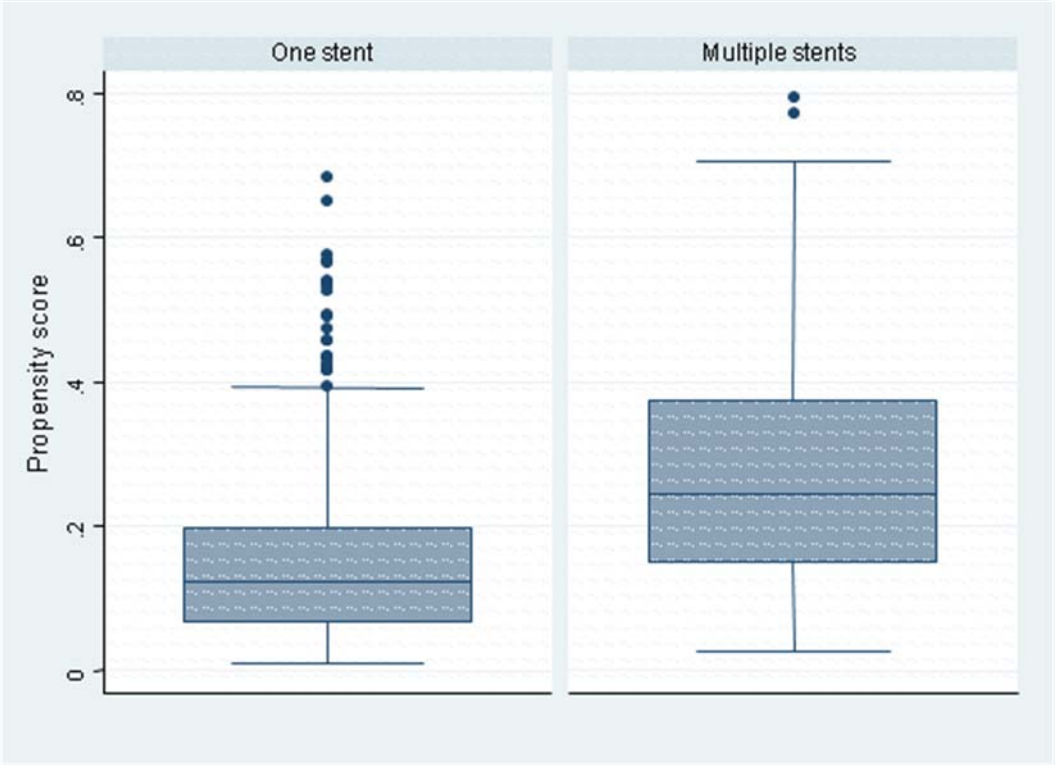

Figure 4.2 Boxplot of propensity score between patients treated with one stent and patients treated with multiple stents (secondary analysis)

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* The three horizontal lines in the shaded box from bottom to top stand for lower quartile (Q1, $X_{.25}$), median (med, $X_{.5}$), upper quartile (Q3, $X_{.75}$), respectively. Interquartile range (IQR) is defined as Q3-Q1.

Outliers are values which lie more than 1.5*IQR lower than Q1 or 1.5*IQR higher than Q3. The two whiskers below and above the shaded box indicate the smallest and largest values that are not outliers.

4.5 DISCUSSION

The present study demonstrates that among patients with one lesion treated treatment with multiple stents for lesions of 10~32mm was associated with non-significantly increased risk of death/MI, repeat PCI/CABG, death/MI/CABG, death/MI/thrombosis, and death/MI/CABG/thrombosis when compared with treatment with single stent. For patients with more than one lesion treated, treatment with multiple stents was associated with non-significantly reduced risk of adverse clinical outcome when compared to treatment with single stent.

The use of multiple stents per lesion has been a subject under debate for a long time[1, 4, 8, 15, 25]. However, interventional cardiologists sometimes can not avoid multiple stenting in a long lesion. The stent lengths are 8~33mm at current US market, although stents of longer length can be obtained under specific request. Therefore, to investigate the efficacy of multiple stents per lesion vs. single long stent among lesions of 10-32 mm in length not only complements to the investigation of long lesions, but also is of clinical importance.

In our study we found treatment with multiple stents was non-significantly associated with higher risk of adverse events among patients with one lesion treated. Previous studies have also reported an adverse effect of multiple stents treatment [6-8, 25]. Some researchers believed the overlapped stent strut served as a stimulus to neointimal hyperplasia [7, 26-28]. A recent study by Kereiakes et al. showed that stent overlap was associated with neointimal proliferation and subsequent late lumen loss regardless of bare metal stent (BMS) or sirolimus-eluting stent (SES) [1]. For drug-eluting stent (DES), the relative importance of stimulus from overlapped stent metal versus the efficacy of stent-based drug to suppress neointimal growth has been under discussion [29]. Kereiakes et al. found that the relative magnitude of restenosis reduction observed in patients treated with single SES versus BMS was maintained in the comparison of patients treated with overlapped SES versus treated with overlapped BMS, indicating sirolimus is effective in reducing high degree of neointimal proliferation and late lumen loss observed in overlapped stents [1]. However, TAXUS-V and VI trials reported a higher incidence of periprocedural

myocardial enzyme elevation among patients treated with overlapped paclitaxel-eluting stent (PES) when compared to patients receiving overlapped EXPRESS stent [12]. The metal platforms are similar between PES and EXPRESS. The difference in the incidence of MI can be related to the polymer and pharmacologic agent on the stent, although a post-hoc angiographic analysis suggested that the reduction in side branch flow in patients treated with overlapped PES could be the reason [30]. Studies also showed that multiple stent per lesion is an independent predictor for stent thrombosis, regardless of BMS or DES [31, 32]. Although stent thrombosis is a rare event, the mortality rate is about 40% and MI rate is very high among survivors.

We found a beneficial effect of treatment with multiple stents compared to single stent among patients having more than one lesion. Several other studies had similar findings. Kereiakes et al. reported that overlapping of multiple SES per lesion is both safe and efficacious in reducing restenosis [1]. Chu et al. also reported that overlapping of SES is feasible and effective for long, native coronary lesions, although it is associated with an increased rate of periprocedural myonecrosis [2]. Kornowski et al. reported that patients treated with multiple stents per lesion had similar target lesion revascularization (TLR) rate and major cardiac event rate (MACE) at one-year follow-up[4]. Hoffmann et al. reported a similar angiographic restenosis rate between treatments with two stents vs. single long stent in long lesion [3]. Pan et al. reported a similar survival at follow-up for multiple stenting and single long stent [5]. Lee et al. reported a similar rate of in-stent restenosis (ISR) between overlapping of multiple stents vs. one long stent in long tortuous or calcified lesions (>20 mm) and long lesions with diameter discrepancy or significant dissection (> 20mm) [33].

Although we do not know the biological reason why patients with one lesion react differently from patients who have more than one lesion, one possible reason could be the treatment strategy. The strategy of treatment with multiple stents can be an *a priori* strategy or can be a measure taken to meet the requirements of unanticipated complications. The complications during procedure include dissection, side branch occlusion, persistent flow reduction, abrupt closure, device malfunction, or others complications. It is reported that up to one-third or more of coronary stent procedures may be complicated by excessive

target lesion length, incomplete target lesion coverage, or stent marginal dissection, which may require multiple stents for full lesion coverage [34-37]. When additional stents are required by the difficult situations during procedure, the adverse effect of treatment with multiple stents we observed here may only be a proxy of the difficult procedural situations. The more it occurred among the patients with one lesion, the higher adverse effect of multiple stent treatment we expect to observe. On the other hand, the beneficial effect of treatment with multiple stents among patients with more than one lesion is not conclusive. Although our results suggested a trend of benefit for each adverse event, the associations are not statistically significant. The sample size and number of events are low in this subgroup.

Our study has its limitations despite prospective study design and detailed information about demographic, procedure, lesion characteristics and high follow-up rate. First, our study is lack of randomization, which makes our conclusion susceptible to unknown factors. Second, we do not know whether the treatment strategy of multiple stents is an *a priori* plan or it is only a measure to account for the unanticipated procedure complications or other difficult circumstance. Third, the sample size is not large enough for each adverse event. The number of patients with more than one lesion is especially low. A specifically designed study with larger sample size is needed to investigate the question.

4.6 CONCLUSIONS

Treatment with multiple stents may be associated with non-significantly higher risk of adverse events among patients who have one lesion, but may be associated with lower risk of adverse events among patients who have more than one lesion. Further specifically designed study with larger sample size is needed to investigate this topic.

Table 4.1 Patient demographics, disease history, and angiographic characteristics among patients having one lesion treated

Characteristics	single stent (n=2002)	Multiple stents (n=280)	P value†	P value‡
Female, %	31.6	31.1	0.87	0.99
Age in year	63.7(11.5)	63.6(11.8)	0.88	0.59
Insurance				
Medicare	42.3	43.5	0.83	0.74
Medicaid	4.0	4.8		
Private Insurance	50.0	47.6		
No insurance	3.7	4.1		
Region				
Middle West	27.7	26.4	0.08	0.99
North East	30.4	36.4		
South East	25.9	20.7		
South West	7.3	5.4		
West	8.7	11.1		
Prior intervention, %	33.3	32.4	0.76	0.98
Prior CABG	17.4	21.0	0.15	0.36
Prior MI	24.7	27.9	0.25	0.96
Severe non-cardiac disease	32.3	34.3	0.51	0.29
History of diabetes	31.1	31.5	0.88	0.99
History of CHF	10.1	12.5	0.23	0.56
History of hypertension	73.9	74.9	0.73	0.89
History of hypercholesterolemia	74.3	74.1	0.93	0.69

CABG indicates coronary artery bypass graft surgery; CHF congestive heart failure; MI myocardial infarction.

Categorical variables are presented as column percentages, continuous variables as mean±SD.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 4.2 Procedure and lesion characteristics among patients having one lesion treated

Characteristics	single stent (n=2002)	Multiple stents (n=280)	P value†	P value‡
Cause of procedure				
Acute MI w/o shock	21.5	23.2	0.38	0.21
Acute MI with shock	1.3	1.4		
Unstable angina	29.3	27.5		
Stable angina	15.1	11.1		
Positive for ischemia study	24.2	25.0		
Other	7.9	11.1		
Unknown	0.6	0.7		
Procedure circumstance				
Elective	63.9	65.7	0.67	0.88
Urgent	24.9	22.5		
Emergent	11.2	11.8		
Lesion length, mm	17.7(4.9)	22.0(5.7)	<0.01	0.65
Occlusion	10.7	16.4	0.01	0.86
Calcification	69.2	70.7	0.61	0.97
Ostial lesion	6.1	5.7	0.80	0.59

MI indicated myocardial infarction.

Categorical variables are presented as column percentages, continuous variables as mean±SD.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 4.3 Cumulative incident proportions of adverse events and hazard ratios comparing multiple stents use to single long stent use among patients having only one lesion treated

Event	Cumulative incident proportion		Hazard Ratio†	Hazard Ratio‡	95% CI	p value
	Single stent (n=2002)	Multiple stents (n=280)				
Death/MI	6.4%	14.8%	1.47	1.39	0.80-2.41	0.25
Repeat PCI/CABG	10.5%	8.2%	0.99	1.09	0.66-1.81	0.74
Death/MI/CABG	7.4%	15.5%	1.43	1.41	0.84-2.38	0.20
Death/MI/thrombosis	6.4%	15.1%	1.53	1.44	0.83-2.47	0.19
Death/MI/CABG/thrombosis	7.5%	15.8%	1.48	1.45	0.87-2.42	0.15

CABG indicates coronary artery bypass graft surgery; CHF congestive heart failure; MI myocardial infarction; PCI percutaneous coronary intervention.

† Crude hazard ratio without adjustment with propensity score in Cox model.
‡ Adjusted hazard ratio with propensity score as continuous variable in Cox model.

Table 4.4 Patient demographics, disease history, and angiographic characteristics among patients who have more than one lesion treated

Characteristics	All single stent (n=474)	Multiple stent (n=109)	P value†	P value‡
Female, %	28.5	37.6	0.06	0.87
Age in year	64.9(11.0)	64.4(12.5)	0.63	0.90
Insurance				
Medicare	45.8	41.2	0.49	0.57
Medicaid	2.5	1.0		
Private Insurance	47.5	54.9		
No insurance	4.2	2.9		
Region				
Middle West	26.6	27.5	0.04	0.99
North East	24.9	38.5		
South East	31.2	22.0		
South West	7.4	3.7		
West	9.9	8.3		
Prior intervention, %	31.2	22.6	0.08	0.97
Prior CABG	17.6	17.9	0.93	0.84
Prior MI	26.6	29.3	0.58	0.95
Severe non-cardiac disease	35.3	32.1	0.52	0.99
History of diabetes	35.0	41.9	0.18	0.87
History of CHF	11.6	13.2	0.63	0.77
History of hypertension	78.6	70.1	0.06	0.97
History of hypercholesterolemia	81.2	71.0	0.02	0.34

CABG indicates coronary artery bypass graft surgery; CHF congestive heart failure; MI myocardial infarction.

Categorical variables are presented as column percentages, continuous variables as mean±SD.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 4.5 Procedure and lesion characteristics among patients who have more than one lesion treated

Characteristics	single stent (n=474)	Multiple stent (n=109)	P value†	P value‡
Cause for procedure				
Acute MI	22.6	16.5	0.31	0.99
Unstable angina	31.2	33.0		
Stable angina	15.8	15.6		
Positive for ischemia study	22.4	21.1		
Other	8.0	13.8		
Procedure circumstance				
Elective	64.8	72.5	0.26	0.90
Urgent	26.2	22.0		
Emergent	9.1	5.5		
More than two lesions	13.9	16.5	0.49	0.97
Any occlusion	8.4	5.5	0.31	0.24
Any calcification	69.2	78.0	0.07	0.86
Any ostial lesion	8.0	11.0	0.32	0.26

MI indicates myocardial infarction.

Categorical variables are presented as column percentages, continuous variables as mean±SD.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 4.6 Cumulative incident proportions of adverse events and hazard ratios comparing multiple stents use to single long stent use among patients having more than one lesion treated

Event	Cumulative incident proportion		Hazard Ratio†	Hazard Ratio‡	95% CI	p value
	Single stent (n=474)	multiple stents (n=109)				
Death/MI	7.8%	3.0%	0.48	0.50	0.11-2.24	0.37
Repeat PCI/CABG	10.1%	12.2%	1.24	0.98	0.46-2.10	0.96
Death/MI/CABG	9.0%	5.1%	0.67	0.88	0.29-2.63	0.82
Death/MI/thromb	7.8%	3.0%	0.48	0.50	0.11-2.24	0.37
Death/MI/CABG/thrombosis	9.0%	5.1%	0.67	0.88	0.29-2.63	0.82

CABG indicates coronary artery bypass graft surgery; CHF congestive heart failure; MI myocardial infarction; PCI percutaneous coronary intervention; CI confidence interval.

† Crude hazard ratio without adjustment with propensity score in Cox model.
‡ Adjusted hazard ratio with propensity score as continuous variable in Cox model.

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5.0 EFFECT OF POSTDILATION AFTER STENT DEPLOYMENT ON PATIENT OUTCOMES

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5.1 ABSTRACT

Background: In percutaneous coronary intervention (PCI), postdilation effectively increases stent dimension. Evidence regarding the long-term efficacy of routine stent postdilation on clinical outcomes is limited, particularly among different patient subgroups.

Methods: Patients were evaluated from the multi-center National Heart, Lung, and Blood Institute (NHLBI) Dynamic registry recruitment Wave 4 (2004) and Wave 5 (2006) cohorts. Patient eligibility criteria for this analysis included receipt of ≥1 stent treatment and an angiographically successful PCI procedure. The analysis was conducted among two subgroups: patient presenting with (N=938) and without (N=2264) acute myocardial infarction (AMI). Among each of the two subgroups, analyses were carried out separately for patients having one lesion treated (N=1629 for patients without AMI, N=713 for acute MI patients) and patients having more than one lesion treated (N=635 for patients without AMI, N=225 for acute MI patients). Baseline, procedure, and lesion information were collected. Adverse cardiac events were compared at one-year follow up by the performance or absence of lesion postdilation.

Results: Among patients without AMI with one lesion treated, postdilation was not associated with adverse cardiac events, although some, but not all, risk estimates were in the direction of a protective effect: death (adjusted HR, 0.81; 95% CI, 0.40-1.59; P=.54), repeat PCI (adjusted HR, 0.87; 95% CI, 0.57-1.33; P=.52), death/MI (adjusted HR, 0.90; 95% CI, 0.56-1.45; P=.67), MACE (adjusted HR, 0.89; 95% CI, 0.65-1.22; P=.46). Similarly, postdilation among patients without AMI with >1 lesion was not associated with adverse cardiac events: death/MI (adjusted HR, 0.81; 95% CI, 0.36-1.81; P=.60), repeat PCI/CABG (adjusted HR, 1.39; 95% CI, 0.82-2.38; P=.22), MACE (adjusted HR, 1.45; 95% CI, 0.91-2.30; P=.12).

Among acute MI patients with one lesion treated, postdilation was associated with a significantly higher risk of death (adjusted HR, 3.46; 95% CI, 1.09-11.03; P=.04). No association was observed for risk

of repeat procedures. Among acute MI patients with >1 lesion treated, postdilation was not associated with death/MI (adjusted HR, 0.79; 95% CI, 0.23-2.73; P=.71), repeat PCI/CABG (adjusted HR, 0.99; 95% CI, 0.36-2.73; P=.98), or MACE (adjusted HR, 0.79; 95% CI, 0.34-1.82; P=.57).

Conclusion: Among PCI patients presenting with acute MI, postdilation is associated with significantly increase the risk of death at 1-year. However, this finding was observed only among patents with one lesion treated and not among patients with multiple lesions treated and may be spurious. Among non-acute MI PCI patients, lesion postdilation does not appear to be associated with trend towards benefit. Further investigation is needed to determine whether a strategy of postdilation among acute MI patients should be discouraged.

Key words: Percutaneous coronary intervention, postdilation, acute MI, adverse cardiac events, stent

5.2 INTRODUCTION

In early-era balloon-expandable stents were delivered with compliant balloons. Postdilation with noncompliant balloons at higher pressure is performed to optimize stent deployment. This results in less acute complications and lower rate of restenosis. Recent stent delivery systems use semicompliant balloons to deploy stents at higher pressure, initially leading to less postdilation after stent deployment. However, studies with intravascular ultrasound (IVUS) showed that only few patients achieved optimal stent expansion with the current stent delivery system [1-3].

Although postdilation with noncompliant balloon increases stent dimensions in the short term [2], there is little evidence about its long term effect on clinical outcomes, especially among Acute MI (AMI) patients who are at higher risk of distal embolization [4-6]. In this study we will assess whether postdilation results in better patient outcomes at one-year follow-up among patients without Acute MI and patients with Acute MI.

5.3 METHODS

5.3.1 Patient Selection and Data Collection

The National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry includes 14 clinical sites in Wave 4, and 16 clinical sites in Wave 5 as well as a data coordinating center at University of Pittsburgh. Wave 4 began in 2004, consecutively recruited 2112 patients. Wave 5 began in 2006, consecutively recruited 2158 patients. Consecutive enrollment at each site ended when 125 white men had been enrolled at the site or 1,600 white patients were enrolled across all sites. Consecutive enrollment of women and

minorities continued at each site until 200 white patients had been enrolled at the site or 1,600 white patients were enrolled across all sites. Consecutive enrollment of minority patients, men and women, continued until 2,000 patients had been enrolled across all sites. Informed consent was obtained. On-site research coordinators were trained before the wave started. Standard forms were used to collect data. For present analysis, patients were included if they received at least one stent, received balloon predilation before stent implantation, and the procedure was angiographically successful. The latter was defined as achievement of a minimum stenosis diameter reduction to <50% in the presence of Thrombosis in Myocardial Infarction (TIMI) grade 3 flow. This resulted in an analysis cohort of 3202 patients.

Successful lesion dilation was defined as an absolute reduction of at least 20% in lesion severity and a final stenosis of <50% (diameter reduction). Partial angiographic success was defined as some but not all lesions were successfully treated; total angiographic success was defined as all attempted lesions were treated successfully. Procedural success was defined as partial or total angiographic success without in-hospital death, myocardial infarction, or emergency coronary artery bypass graft surgery. Myocardial infarction (MI) was defined by evidence of ≥2 of the following: (1) typical chest pain > 20 minutes, not relieved by nitroglycerin; (2) serial electrocardiograms showing characteristic ST-T changes and/or Q waves in ≥2 contiguous leads; (3) serial electrocardiograms showing characteristic ST-T changes and/or Q waves in ≥2 contiguous leads; (4) serum enzyme elevation of creatine kinase-MB is more than 5% of total creatine kinase.

5.3.2 Statistical Methods

Analyses in each subgroup were carried out separately among patients with one lesion treated (primary analysis) and among patients with >1 lesion treated (secondary analysis). The rationale for this was that the primary single lesion analysis was easiest to interpret directly in relation to whether postdilation was used. In the case of multiple treated lesions, a “partial” approach is possible, whereby one lesion was postdilated and a second lesion was not postdilated.

For both subgroups, patients were categorized into 2 groups according to whether postdilation was performed. Differences in continuous variables were compared using t-test. Differences in proportions of categorical variables were compared by chi-square tests. One-year cumulative incident proportion in each group was estimated with Kaplan-Meier method. Patients were censored at one-year follow-up. For each subgroup, a propensity score model was fit by use of logistic regression to adjust for the potential selection bias inherent in the decision to postdilate the stent versus not [7-12]. A backward selection method was used with a p value of 0.40 to select variables for the prediction of propensity score. If balance was not achieved for certain covariates, the propensity model will be refitted by including these covariates in the model. Cox proportional hazards regression was used to estimate the independent effect of the use of postdilation versus not postdilation on the relative hazard of adverse clinical outcomes over 1-year follow-up. The propensity score was the single covariate that was included in the model to control for factors associated with postdilation. The binary exposure variable was postdilation versus not postdilation. The proportional hazards assumption of constant relative risk over follow-up was evaluated by evaluating the exposure by time interaction. All statistical analyses were performed using the SAS program, version.9.1 (SAS Institute, Cary, NC).

5.4 RESULTS

A total of 3202 patients were included in the analysis. Among these, 2264 patients (71%) did not have Acute MI (AMI), and 938 patients (29%) had Acute MI. The proportional hazards assumption of constant relative risk over follow-up was evaluated and found to be upheld. Results are shown separately for each of the two subgroups.

5.4.1 PATIENTS WITHOUT ACUTE MI

PATIENTS WITH ONE LESION TREATED

Among the total 1629 Patients without AMI who had one lesion treated, 1037 patients (64%) did not received postdilation, and 592 patients (36%) received postdilation. The median follow up was 7 months and 77% of patients had at least 6-month follow up.

The patient demographics, disease history and angiographic characteristics are shown in Table 5.1 for two treatment groups. Patients who received postdilation were less likely to have history of CHF (8.2% vs. 11.6%), more likely to be amenable with Coronary Artery Bypass Grafting surgery according to the clinician (78.4%% vs. 71.1%), more likely to be hispanice (6.1% vs. 3.3%), to have private insurance or none insurance (49.8% vs. 43.8% for private insurance, 2.0% vs. 0.9% for none insurance). After propensity score adjustment, none of these differences were statistically significant.

Procedure and lesion characteristics are shown in Table 5.2. Patients who received postdilation were more likely to receive PCI at the same setting as diagnostic catheterization (79.4% vs. 73.3%, $p<0.01$). Patients receiving postdilation were more likely to have, on average, longer lesions (19.1 vs. 15.3 mm, $p<0.01$), calcified lesions (38.0% vs. 25.8%, $p<0.01$), ulcerated lesions (13.3% vs. 9.9%, $p=0.04$), C type of ACC/AHA classification (31.9% vs. 19.0%, $p<0.01$). After propensity score adjustment, none of these differences were statistically significant.

The variables to predict the propensity score from the logistic model are shown in Appendix C. The c statistic of the propensity score model was 0.72, indicating a probability of 0.72 that for a randomly selected subject receiving postdilation the propensity score would be higher than for a randomly selected subject not receiving postdilation. The mean propensity score in the postdilation groups was higher than in the no postdilation group. The distribution of propensity score in the two treatment groups are shown in Figure 5.1.

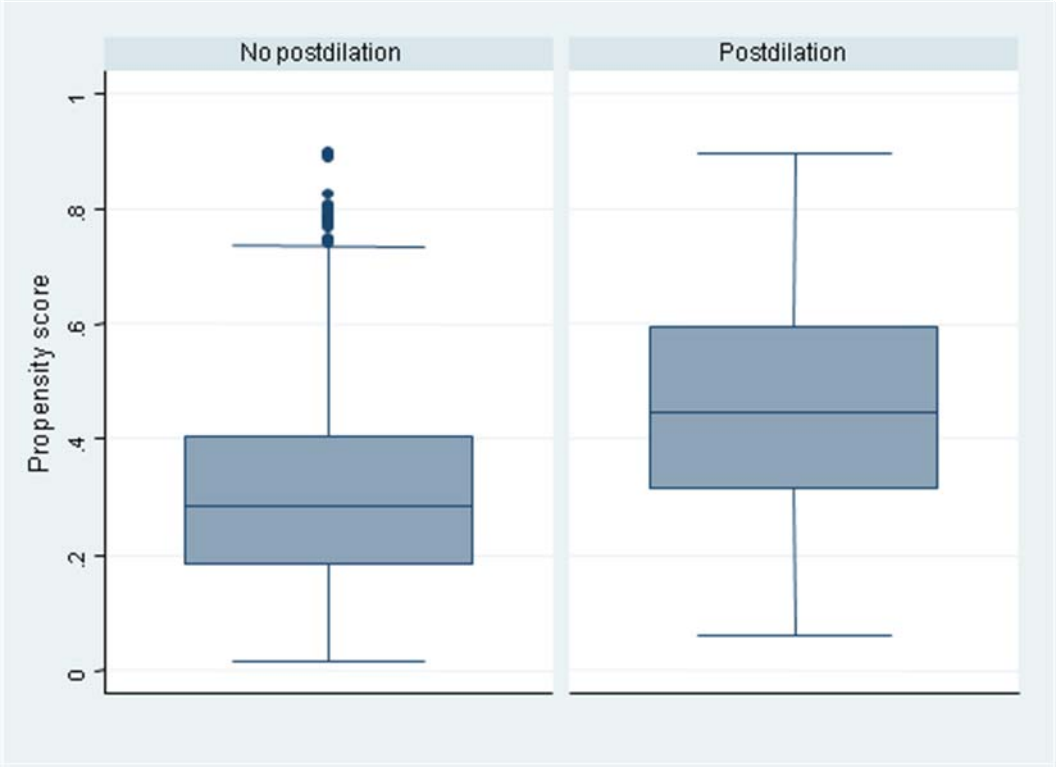

Figure 5.1 Boxplot of propensity scores between two treatment groups among patients without acute MI who had one lesion treated

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* The three horizontal lines in the shaded box from bottom to top stand for lower quartile (Q1, $X_{.25}$), median (med, $X_{.5}$), upper quartile (Q3, $X_{.75}$), respectively. Interquartile range (IQR) is defined as Q3-Q1.

Outliers are values which lie more than 1.5*IQR lower than Q1 or 1.5*IQR higher than Q3. The two whiskers below and above the shaded box indicate the smallest and largest values that are not outliers.

Compared to patients who did not receive postdilation, patients receiving postdilation had non-significantly lower cumulative incident proportion of death, repeat PCI, repeat PCI/CABG, death/MI, death/MI/CABG, MACE, non-significantly higher event rate of MI and CABG (Table 5.3). The hazard ratios from Cox proportional hazards model for each event were all below 1.0 (Death, HR=0.81; repeat PCI, HR=0.87; repeat PCI/CABG, HR=0.95; death/MI, HR=0.90; death/MI/CABG, HR=0.97; MACE, HR=0.89), except a higher risk for CABG (HR=2.23, 95% CI: 0.84-5.96, p=0.11) and a slightly higher hazard ratio for MI (HR=1.27, 95% CI: 0.68-2.36, p=0.45). None of these hazard ratios is statistically significant.

5.4.2 PATIENTS WITHOUT ACUTE MI

PATIENTS WITH MORE THAN ONE LESION TREATED

Among 643 Patients without AMI who have more than one lesion treated, 335 patients (53%) did not receive postdilation, and 300 patients (47%) received postdilation. The median follow up was 7 months and 77% of patients had at least 6-month follow up.

Patient's demographics, disease history, and angiographic characteristics are shown in Table 5.4. Patients who received postdilation were less likely to have history of CABG (16.3% vs. 23.5%), history of hypertension (79.6% vs. 85.6%), be amenable with PCI (87.3% vs. 92.0%). After propensity score adjustment, none of these differences were statistically significant.

Procedure and lesion characteristics are shown in Table 5.5. Patients who received postdilation were more likely to have PCI procedure at the same setting as diagnostic setting (69.7% vs. 62.2%). After propensity score adjustment, this difference was not statistically significant.

The variables to predict the propensity score from the logistic model are shown in Appendix C. The c statistic of the propensity score model was 0.73, indicating a probability of 0.73 that for a randomly selected subject receiving postdilation the propensity score would be higher than for a randomly selected subject not receiving postdilation. The mean propensity score in the postdilation groups was higher than

in the no postdilation group. The distribution of propensity score in the two treatment groups are shown in Figure 5.2.

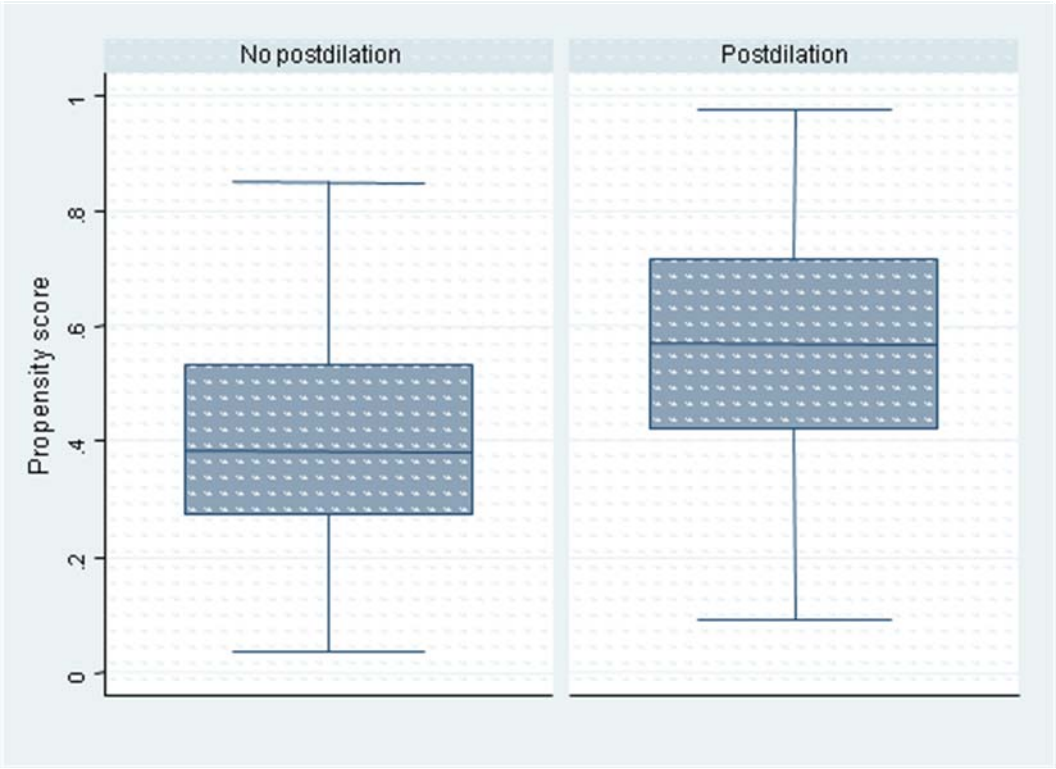

Figure 5.2 Boxplot of propensity scores between two treatment groups among patients without acute MI who had more than one lesion treated

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* The three horizontal lines in the shaded box from bottom to top stand for lower quartile (Q1, $X_{.25}$), median (med, $X_{.5}$), upper quartile (Q3, $X_{.75}$), respectively. Interquartile range (IQR) is defined as Q3-Q1.

Outliers are values which lie more than 1.5*IQR lower than Q1 or 1.5*IQR higher than Q3. The two whiskers below and above the shaded box indicate the smallest and largest values that are not outliers.

One-year cumulative incident proportion estimated with Kaplan-Meier method are shown in Table 5.6. Compared to patients who did not receive postdilation, patients who received postdilation had non-significantly lower cumulative incident proportion of death/MI (5.0% vs. 7.2%), and non-significantly higher cumulative incident proportion of Repeat PCI/CABG (14.9% vs. 12.0%) and death/MI/CABG/thrombosis (20.0% vs. 16.0%). Crude and adjusted hazard ratios from Cox proportional hazards model are shown in Table 5.7. Postdilation was not significantly associated with death/MI (HR=0.81, 95% CI: 0.36-1.81, p=0.60), repeat PCI/CABG (HR=1.39, 95% CI: 0.82-2.38, p=0.22), or death/MI/CABG/thrombosis (HR=1.45, 95% CI: 0.94-2.30, p=0.12).

5.4.3 ACUTE MI PATIENTS

PATIENTS WITH ONE LESION TREATED

Among the total 713 Acute MI patients with one lesion treated, 445 patients (62%) did not received postdilation, and 268 patients (38%) received postdilation. The median follow up was 7 months and 74% of patients had at least 6-month follow up.

Patient demographics, disease history, and angiographic characteristics are shown in table 5.7. Patients who receive postdilation were more likely to be Hispanic (7.5% vs. 3.2%), more likely to be right dominance (88.9% vs. 80.4%). After propensity score adjustment, these differences were not statistically significant.

Procedure and lesion characteristics are shown in Table 5.8. Patients who received postdilation were more likely to have, on average, longer lesions (20.4 vs. 15.8 mm, p<0.01), ulcerated lesion (30.2% vs. 23.2%, p=0.04), ostial lesion (8.2% vs. 4.0%, p=0.02), C type of lesion (36.9% vs. 28.1%, p=0.01). After propensity score adjustment, none of these differences was statistically significant.

The variables to predict the propensity score from the logistic model are shown in Appendix C. The c statistic of the propensity score model was 0.78, indicating a probability of 0.78 that for a randomly selected subject receiving postdilation the propensity score would be higher than for a randomly selected

subject not receiving postdilation. The mean propensity score in the postdilation groups was higher than in the no postdilation group. The distribution of propensity score in the two treatment groups are shown in Figure 5.3.

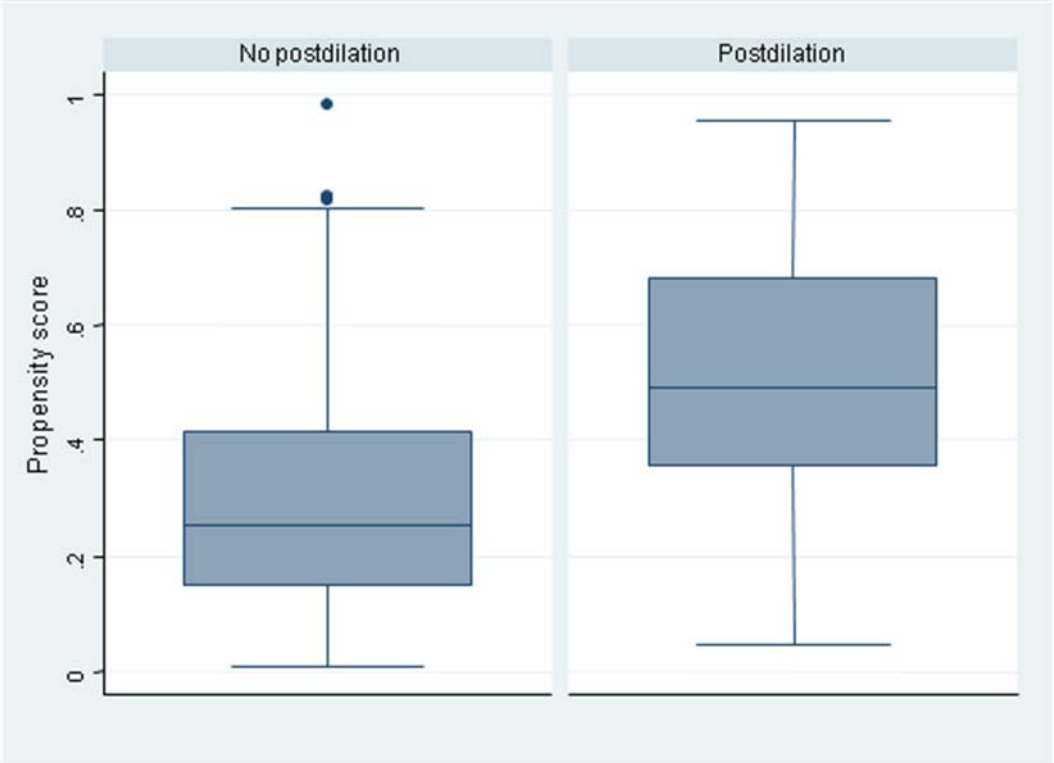

Figure 5.3 Boxplot of propensity scores between two treatment groups among patients with acute MI who had one lesion treated

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* The three horizontal lines in the shaded box from bottom to top stand for lower quartile (Q1, $X_{.25}$), median (med, $X_{.5}$), upper quartile (Q3, $X_{.75}$), respectively. Interquartile range (IQR) is defined as Q3-Q1.

Outliers are values which lie more than 1.5*IQR lower than Q1 or 1.5*IQR higher than Q3. The two whiskers below and above the shaded box indicate the smallest and largest values that are not outliers.

One-year cumulative incident proportion estimated with Kaplan-Meier method are shown in Table 5.9. Compared to patients who did not receive postdilation, patients who received postdilation had higher event rates for each adverse event. After adjustment in Cox proportional hazards model, a significantly higher risk of death was observed (HR=3.46, 95% CI: 1.09-11.03, p=0.04) among patients who received postdilation when compared to patients who did not, non-significant higher risks of all the other adverse events also were observed among patients who received postdilation than among patients who did not.

5.4.4 ACUTE MI PATIENTS

PATIENTS WITH MORE THAN ONE LESION TREATED

Among 225 Acute MI patients who have more than one lesion, 113 patients (50%) did not receive postdilation, 112 patients (50%) received postdilation. The median follow up was 7 months and 77% of patients had at least 6-month follow up.

Patient's demographics, disease history, and angiographic characteristics are shown in Table 5.10. Patients who received postdilation were more likely to have history of MI (30.4% vs. 17.3%). After propensity score adjustment, this difference was not statistically significant.

Procedure and lesion characteristics are shown in Table 5.11. Patients who received postdilation were more likely to have PCI procedure at the same setting as diagnostic catheterization (88.6% vs. 79.0%). After propensity score adjustment, no comparisons were statistically significant.

The variables to predict the propensity score from the logistic model are shown in Appendix C. The c statistic of the propensity score model was 0.85, indicating a probability of 0.85 that for a randomly selected subject receiving postdilation the propensity score would be higher than for a randomly selected subject not receiving postdilation. The mean propensity score in the postdilation groups was higher than in the no postdilation group. The distribution of propensity score in the two treatment groups are shown in Figure 5.4.

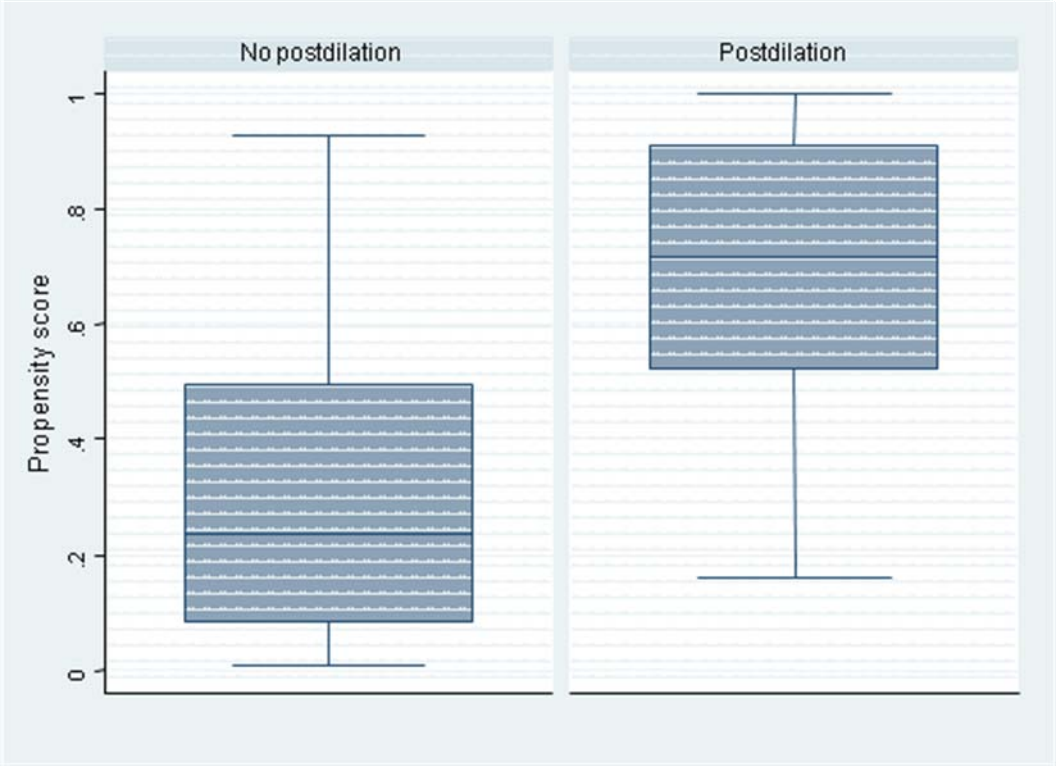

Figure 5.4 Boxplot of propensity scores between two treatment groups among patients with acute MI who had more than one lesion treated

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* The three horizontal lines in the shaded box from bottom to top stand for lower quartile (Q1, $X_{.25}$), median (med, $X_{.5}$), upper quartile (Q3, $X_{.75}$), respectively. Interquartile range (IQR) is defined as Q3-Q1.

Outliers are values which lie more than 1.5*IQR lower than Q1 or 1.5*IQR higher than Q3. The two whiskers below and above the shaded box indicate the smallest and largest values that are not outliers.

One-year cumulative incident proportions estimated with Kaplan-Meier method are shown in Table 5.12. Compared to patients who did not receive postdilation, patients who received postdilation had non-significantly higher cumulative incident proportion of death/MI (9.2% vs. 7.8%), death/MI/CABG/thrombosis (20.9% vs. 18.0%), and almost same cumulative incident proportion of repeat PCI/CABG (13.5% vs. 13.6%). Crude and adjusted hazard ratios from Cox proportional hazards model was shown in Table 5.12. Postdilation was associated with non-significantly lower risk of death/MI, repeat PCI/CABG, death/MI/CABG/thrombosis.

5.5 DISCUSSION

In this study we assessed whether postdilation is associated with either a beneficial effect or higher risk of cardiac adverse events after PCI procedure at one-year follow-up. Results showed minimal evidence of a protective effect among patients without AMI, while apparently no adverse effect associated with this strategy. In contrast, our most compelling finding was an estimate 3-fold adjusted higher risk of death at 1-year when postdilation is performed for a single lesion in the setting of acute MI. However, this finding was not confirmed among acute MI patients with multiple lesions treated, leading to an equivocal interpretation as to the validity of the single lesion finding.

The current stent delivery system uses semi-compliant balloon, which enables higher deployment pressure than previous delivery system using compliant balloon. However, only a few patients achieved optimum stent deployment. The POSTIT (Postdilation Clinical Comparative Study) trial found that only 29% of patients achieved optimum stent deployment (defined as minimal stent diameter ≥ 90% average reference lumen diameter) through current bare metal stent (BMS) delivery system (Boston Scientific NIR, Guidant Tri-Star/Tetra, and Medtronic AVE S670 stents) [2]. Cheneau et al. reported that only 15% of patients achieved optimum stent deployment (defined as minimal stent cross-sectional area (CSA)/reference cross-sectional lumen area > 80%, or >90% if minimal lumen CSA < 9 mm^2) with

current sirolimus-eluting stent (SES) delivery systems and an inflation pressure of 14 atm [3]. The most important reason for suboptimal stent expansion is balloon material. The delivery balloon in contemporary practice is semi-compliant, which are designed to maximize deliverability. As pressure inside the balloon increases, the balloon grows in the areas of less resistance. This results in stretching of the balloon around the lesion, instead of concentrating the force on the lesion. In contrast to semi-compliant stent-delivery balloon, the balloon for postdilation is noncompliant, which change little in volume when inflation pressure increases. It delivers more focal force to the lesion. Deployment pressure is also associated with optimum stent deployment [1-3]. However, only 36% of patients achieved optimum stent deployment even at high deployment pressure of at least 14 atm [2].

Previous studies showed that postdilation with noncompliant balloons can increase the frequency of optimum stent deployment. The POSTIT trial reported that after postdilation with noncompliant balloon minimal stent area (MSA) increased from 6.6 mm^2 to 7.8 mm^2, minimal stent diameter (MSD) increased form 2.6 mm to 2.8 mm and the optimum stent deployment rate doubled increased from 21% to 42% [2]. The CRUISE (Can Routine Ultrasound Influence Stent Expansion) found that IVUS-guided group together with postdilation had larger MSA (7.8 vs. 7.1 mm^2, $p=0.001$) and larger minimal lumen diameter (2.9 vs. 2.7 mm, $p<0.001$) when compared to standard angiography-guided group [13]. Johansson et al. reported 67% of patients got optimum stent deployment (MSA > 90% RLA) among a routine postdilation practice [14].

MSA and stent underexpansion have been shown to be the two most important predictors of restenosis and target vessel revascularization (TVR) [15-20]. Although drug-eluting stent (DES) is effective in reducing the risk of TVR, it still occurs in 5% of patients following the procedure [21, 22]. Studies showed that postdilation with noncompliant balloon reduced the risk of target lesion revascularization (TLR) and TVR [13, 18, 23]. Stent thrombosis is another major concern for PCI procedure [24]. Its case-fatality rate is about 45% and nonfatal MI occurs in most of the survivors [25]. Studies showed that MSA and stent underexpansion are major predictors of stent thrombosis [25-27]. Up to today, there are little data about the relationship between postdilation and stent thrombosis.

Patients presenting with Acute MI usually have plaques that are more thrombotic and ulcerated than those seen in patients who present for PCI for indications other than Acute MI. Distal embolization of thrombotic debris may occur during and after PCI, happening more often when intervening in patients presenting with Acute MI, which leads to impaired microvascular perfusion, which in turn has been associated with MI, and mortality [4-6, 28-30]. We did observe an adverse effect of postdilation compared to no postdilation treatment among Acute MI patients who have only one lesion. The mortality risk among AMI patients receiving postdilation is 3.5 times that among AMI patient not receiving postdilation. The observed effect in our study is biologically plausible. However, we observed an opposite direction of postdilation effect among Acute MI patients who have more than one lesion, although none of these associations are statistically significant. This inconsistency of the postdilation effect among Acute MI patients can be the result of the poorly estimated effect due to the low sample size of Acute MI patients who with multiple lesions treated. However, it can also be a chance finding because the patients who did not receive postdilation had a very low event rate (1.7%, see Table 5.9), even lower than patients without AMI (4.7% for patients receiving no postdilation; 3.4% for patients receiving postdilation, see Table 5.3). Further study with larger sample size is required on this topic.

There are limitations about our study. In our study, patients were not randomized to a strategy of postdilation versus no postdilation. Therefore, we cannot exclude the possibility of residual confounding. With respect to the higher risk of death associated with postdilation among acute MI patients with a single lesion treated, it is possible that unobserved patient or procedural characteristics could explain, at least in part, the apparent difference in risk of death at 1-year. Though we considered an extensive array of factors that may have been associated with the decision of postdilation, it is still possible that one or more important variables were missed. A second limitation is the relatively small sample size among patients with multiple lesions treated, which leads to imprecise risk estimates.

5.6 CONCLUSIONS

Among PCI patients presenting with Acute MI, postdilation may significantly increase the risk of death at 1-year. However, because this finding was observed only among patents with one lesion treated and not among patients with multiple lesions treated, the possibility of a chance finding exists. Among PCI patients without AMI, lesion postdilation does not appear to be associated with either a benefit or increased risk of adverse cardiac events. Further investigation is needed to determine whether a strategy of postdilation among acute MI patients should be discouraged.

Table 5.1 Patient demographics, disease history, and angiographic characteristics among patients without AMI who have one lesion treated

Characteristics	No postdilation (n=1037)	Postdilation (n=592)	P value†	P value‡
Female	31.9	33.5	0.53	0.98
Age in years	64.5(11.3)	63.8(11.6)	0.23	0.84
Race				
White	83.1	82.4	0.95	0.65
Black	13.2	13.9		
Asian	2.2	2.0		
Other	1.5	1.7		
Hispanic	3.3	6.1	<0.01	0.97
Insurance				
Medicare	36.6	31.8	0.02	0.99
Other public	18.8	16.4		
Private	43.8	49.8		
None/self-pay	0.9	2.0		
Prior intervention	37.7	37.3	0.88	0.95
Prior CABG	21.7	20.9	0.72	0.92
Prior MI	27.1	27.6	0.83	0.86
Severe non-cardiac disease	37.1	36.4	0.80	0.51
History of diabetes	35.0	33.1	0.44	0.99
History of chest pain	64.3	62.4	0.45	0.18
Chest pain at admission	64.0	61.2	0.25	0.54
History of CHF	11.6	8.2	0.03	0.84
CHF at admission	5.3	5.1	0.84	0.66
History of hypertension	81.6	78.3	0.11	0.81
History of hypercholesterolemia	84.3	81.0	0.08	0.91
Known hypercoagulable state	1.5	1.9	0.59	0.82
Dominance				
Left	8.8	7.9	0.12	0.99
Right	81.7	85.3		
Balanced	9.5	6.7		
Amenable with CABG	71.1	78.4	<0.01	0.16
Amenable with PCI	88.1	88.7	0.74	0.93

CABG indicates coronary artery bypass graft surgery; CHF congestive heart failure; MI myocardial infarction; PCI percutaneous coronary intervention.

Categorical variables are presented as column percentages, continuous variables as mean±SD.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 5.2 Procedure and lesion characteristics among patients without AMI who have one lesion treated

Characteristics	No postdilation (n=1037)	Postdilation (n=592)	P value†	P value‡
Cause of procedure				
Unstable angina	46.8	46.0	0.90	0.99
Stable angina	29.9	29.7		
Asymptomatic CAD	17.2	17.2		
Others	6.2	7.1		
Procedure circumstance				
Elective	71.7	73.1	0.18	0.99
Urgent	27.7	25.3		
Emergent	0.7	1.5		
Procedure setting	73.3	79.4	<0.01	0.87
Lesion length, mm	15.3(9.4)	19.1(12.8)	<0.01	0.10
Previously treated lesion	7.7	10.5	0.06	0.97
Evidence of thrombus	5.6	7.9	0.06	0.97
Calcification	25.8	38.0	<0.01	0.99
Ulcerated	9.9	13.3	0.04	0.96
Ostial lesion	8.1	10.0	0.20	0.96
C type of ACC/AHA classification	19.0	31.9	<0.01	0.92

CAD indicates coronary artery disease; ACC American College of Cardiology; AHA American Heart Association.

Categorical variables are presented as column percentages, continuous variables as mean±SD.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 5.3 One-year cumulative incident proportions and hazard ratios of adverse event among patients without AMI who have one lesion treated

Event	N*	Cumulative incident proportion		Hazard Ratio†	Hazard Ratio‡	95% CI	P value
		No postdilation (n=1037)	Postdilation (n=592)				
Death	47	4.7%	3.4%	0.78	0.81	0.41-1.59	0.54
MI	49	3.2%	3.6%	1.22	1.27	0.68-2.36	0.45
Repeat PCI	112	9.6%	7.9%	0.93	0.87	0.57-1.33	0.52
CABG	19	1.1%	2.0%	1.99	2.23	0.84-5.96	0.11
Repeat PCI/CABG	127	10.6%	8.8%	0.99	0.95	0.64-1.41	0.80
Death/MI	92	7.9%	6.0%	0.87	0.90	0.56-1.45	0.67
Death/MI/CABG	107	8.8%	7.5%	0.95	0.97	0.63-1.50	0.89
MACE	202	17.3%	13.5%	0.90	0.89	0.65-1.22	0.46

PCI indicates percutaneous coronary intervention; CABG coronary artery bypass graft surgery; MI myocardial infarction; MACE major adverse cardiac event; CI confidence interval.

* number of events
† crude hazard ratio from Cox proportional hazards model
‡ adjusted hazard ratio with propensity score in Cox proportional hazards model

Table 5.4 Patient demographics, disease history, and angiographic characteristics among patients without AMI who have more than one lesion treated

Characteristics	No postdilation (n=335)	Postdilation (n=300)	P value†	P value‡
Female	33.0	31.6	0.70	0.99
Age, y	66.3(11.3)	64.9(10.9)	0.11	0.77
Race, %				
White	80.7	74.6	0.07	0.99
Black	14.3	17.6		
Asian	0.9	3.9		
Other	4.2	3.9		
Hispanic	6.3	7.2	0.64	0.91
Insurance				
Medicare	44.8	41.0	0.80	0.78
Other public	14.9	15.6		
Private	37.6	41.0		
None/self-pay	3.3	2.3		
Prior intervention	35.7	32.6	0.40	0.87
Prior CABG	23.5	16.3	0.02	0.98
Prior MI	22.6	24.0	0.68	0.93
Severe non-cardiac disease				
History of diabetes	36.0	38.8	0.47	0.74
History of chest pain	60.8	59.4	0.73	0.84
Chest pain at admission	60.2	60.6	0.92	0.91
History of CHF	10.2	12.5	0.36	0.65
CHF at admission	4.5	5.9	0.42	0.70
History of hypertension	85.6	79.6	0.05	0.87
History of hypercholesterolemia	79.8	81.5	0.59	0.68
Known hypercoagulable state	1.7	4.4	0.10	0.86
Dominance				
Left	11.6	6.4	0.07	0.89
Right	81.4	84.9		
Balanced	7.0	8.7		
Amenable with CABG	73.8	75.2	0.68	0.92
Amenable with PCI	92.0	87.3	0.05	0.99

CABG indicates coronary artery bypass graft surgery; CHF congestive heart failure; MI myocardial infarction; PCI percutaneous coronary intervention.

Categorical variables are presented as column percentages, continuous variables as mean±SD.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 5.5 Procedure and lesion characteristics among patients without AMI who have more than one lesion treated

Characteristics	No postdilation (n=335)	Postdilation (n=300)	P value†	P value‡
Cause of procedure				
Unstable angina	47.6	48.2	0.67	0.75
Stable angina	28.3	28.3		
Asymptomatic CAD	17.0	18.2		
Other	7.1	5.2		
Procedure circumstance				
Elective	74.3	73.6	0.98	0.62
Urgent	24.9	25.4		
Emergent	0.9	1.0		
Procedure setting	62.2	69.7	0.05	0.98
Device access from femoral	95.5	94.5	0.53	0.14
Number of lesions				
2	85.7	80.5	0.16	0.99
3	12.2	15.6		
4+	2.1	3.9		
Total lesion, mm	29.2	33.6	0.23	0.96
Lesion previously treated	95.8	96.4	0.70	0.99
Evidence of thrombus	1.5	2.3	0.46	0.99
Any calcification	25.9	30.9	0.16	0.96
Any ulcerated	6.3	6.8	0.76	0.96
Any ostial lesion	7.7	7.2	0.78	0.98
Any C type ACC/AHA classification	25.9	31.6	0.11	0.99

CAD indicates coronary artery disease; ACC American College of Cardiology; AHA American Heart Association.

Categorical variables are presented as column percentages.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 5.6 One-year cumulative incident proportions and hazard ratios of adverse event among patients without AMI who have more than one lesion treated

Event	N*	Cumulative incident proportion		Hazard Ratio†	Hazard Ratio‡	95% CI	P value
		No postdilation (n=335)	Postdilation (n=300)				
Death/MI	29	7.2%	5.0%	0.74	0.81	0.36-1.81	0.60
Repeat PCI/CABG	64	12.0%	14.9%	1.31	1.39	0.82-2.38	0.22
Death/MI/CABG/ repeat PCI	85	16.0%	20.0%	1.37	1.45	0.91-2.30	0.12

MI indicates myocardial infarction; PCI percutaneous coronary intervention; CABG coronary artery bypass graft surgery.

* number of events
† crude hazard ratio without adjustment with propensity score.
‡ Adjusted with propensity score as continuous variable.

Table 5.7 Patient demographics, disease history, and angiographic characteristics among Acute MI patients who have one lesion treated

Characteristics	No postdilation (n=445)	Postdilation (n=268)	P value†	P value‡
Female	35.7	35.1	0.86	0.96
Age in years	61.4(13.2)	62.2(12.4)	0.43	0.81
Race				
White	77.1	78.7	0.43	0.85
Black	19.3	16.4		
Asian	2.9	3.0		
Other	0.7	1.9		
Hispanic	3.2	7.5	0.01	0.96
Insurance				
Medicare	30.4	35.6	0.33	0.19
Other public	21.0	16.1		
Private	42.8	42.3		
None/self-pay	5.9	6.0		
Prior intervention	17.5	15.3	0.44	0.94
Prior CABG	9.2	7.8	0.53	0.86
Prior MI	16.1	15.8	0.91	0.95
Severe non-cardiac disease	29.9	34.1	0.24	0.48
History of diabetes	24.7	26.5	0.60	0.97
History of chest pain	30.4	29.5	0.79	0.43
Chest pain at admission	92.8	92.2	0.76	0.51
History of CHF	5.1	7.6	0.18	0.99
CHF at admission	10.3	7.5	0.20	0.96
History of hypertension	67.5	69.3	0.62	0.94
History of hypercholesterolemia	65.7	59.5	0.11	0.92
Dominance				
Left	8.6	4.8	0.01	0.99
Right	80.4	88.9		
Balanced	11.0	6.3		
Amenable with CABG	74.2	78.4	0.21	0.42
Amenable with PCI	92.1	90.7	0.50	0.95

CABG indicates coronary artery bypass graft surgery; CHF congestive heart failure; MI myocardial infarction; PCI percutaneous coronary intervention.

Categorical variables are presented as column percentages, continuous variables as mean±SD.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 5.8 Procedure and lesion characteristics per patient among Acute MI patients who have one lesion treated

Characteristics	No postdilation (n=445)	Postdilation (n=268)	P value†	P value‡
Procedure circumstance				
Elective	22.7	20.9	0.73	0.79
Urgent	38.0	36.9		
Emergent	39.3	42.2		
Procedure site	86.3	89.2	0.26	0.96
Total lesion, mm	15.8(9.0)	20.4(11.8)	<0.01	0.77
Previously treated lesion	3.8	4.1	0.85	0.83
Evidence of thrombus	47.4	53.0	0.15	0.65
Calcification	24.9	28.7	0.27	0.94
Ulcerated	23.2	30.2	0.04	0.71
Ostial lesion	4.0	8.2	0.02	0.93
C type of ACC/AHA classification	28.1	36.9	0.01	0.67

ACC indicates American College of Cardiology; AHA American Heart Association.

Categorical variables are presented as column percentages, continuous variables as mean±SD.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 5.9 One-year cumulative incident proportions and hazard ratios of adverse event among Acute MI patients who have one lesion treated

Event	N*	Cumulative incident proportion		Hazard Ratio†	Hazard Ratio‡	95% CI	P value
		No postdilation (n=445)	Postdilation (n=268)				
Death	15	1.7%	4.5%	2.57	3.46	1.09-11.03	0.04
MI	24	3.3%	5.0%	1.21	1.13	0.45-2.83	0.80
Repeat PCI	47	6.9%	9.0%	1.25	1.41	0.73-2.71	0.30
CABG	14	2.3%	3.0%	1.28	1.22	0.37-4.06	0.74
Repeat PCI/CABG	60	8.8%	11.9%	1.34	1.49	0.83-2.68	0.18
Death/MI	38	4.8%	9.5%	1.70	1.77	0.86-3.64	0.12
Death/MI/CABG	49	6.9%	11.0%	1.51	1.48	0.79-2.81	0.22
MACE	85	12.5%	18.2%	1.41	1.41	0.87-2.29	0.16

PCI indicates percutaneous coronary intervention; CABG coronary artery bypass graft surgery; MI myocardial infarction; MACE major adverse cardiac event; CI confidence interval.

* number of events
† crude hazard ratio from Cox proportional hazards model
‡ adjusted hazard ratio with propensity score in Cox proportional hazards model

Table 5.10 Patient demographics, disease history, and angiographic characteristics among Acute MI patients who have more than one lesion treated

Characteristics	No postdilation (n=113)	Postdilation (n=112)	P value†	P value‡
Female	29.8	32.5	0.67	0.99
Age	63.2(11.5)	62.9(13.7)	0.83	0.88
White	82.5	77.2	0.32	0.97
Insurance				
Medicare	33.3	36.9	0.11	0.27
Other public	14.9	18.0		
Private	48.3	35.1		
None/self-pay	3.5	9.9		
Prior intervention	15.8	21.9	0.24	0.71
Prior CABG	15.8	14.0	0.71	0.66
Prior MI	17.3	30.4	0.02	0.92
Severe non-cardiac disease	32.5	37.7	0.41	0.93
History of diabetes	32.5	35.1	0.67	0.98
History of chest pain	26.1	34.6	0.18	0.98
Chest pain at admission	90.4	91.2	0.82	0.90
History of CHF	7.4	9.0	0.67	0.75
CHF at admission	10.8	7.1	0.33	0.91
History of hypertension	75.0	71.7	0.57	0.53
History of hypercholesterolemia	64.8	63.3	0.82	0.87
Known hypercoagulable state	3.2	3.7	0.87	0.91
Dominance				
Left	8.3	6.1	0.10	0.99
Right	79.8	89.5		
Balanced	11.9	4.4		
Amenable with CABG	77.2	80.7	0.52	0.79
Amenable with PCI	86.8	92.1	0.20	0.94

CABG indicates coronary artery bypass graft surgery; CHF congestive heart failure; MI myocardial infarction; PCI percutaneous coronary intervention.

Categorical variables are presented as column percentages, continuous variables as mean±SD.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 5.11 Procedure and lesion characteristics among Acute MI patients who have more than one lesion treated

Characteristics	No postdilation (n=113)	Postdilation (n=112)	P value†	P value‡
Procedure circumstance				
Elective	25.4	23.7	0.60	0.89
Urgent	48.3	43.9		
Emergent	26.3	32.5		
Procedure setting	79.0	88.6	0.05	0.90
More than two lesions	13.2	21.1	0.12	0.90
Any lesion >25mm	26.3	35.9	0.12	0.91
Any lesion previously treated	98.3	99.1	0.57	0.97
Any evidence of thrombus	14.9	10.5	0.32	0.67
Any calcified lesion	28.1	28.1	1.00	0.93
Any ulcerated lesion	12.3	14.0	0.70	0.57
Any ostial lesion	4.4	9.7	0.13	0.99
C type of ACC/AHA classification	29.0	30.7	0.77	0.74

CAD indicates coronary artery disease; ACC American College of Cardiology; AHA American Heart Association.

Categorical variables are presented as column percentages.
† p value of tests for covariate balance between two treatments before propensity score adjustment
‡ p value of tests for covariate balance between two treatments after propensity score adjustment

Table 5.12 One-year cumulative incident proportions and hazard ratios of adverse event among Acute MI patients who have more than one lesion treated

Event	N*	Cumulative incident proportion		Hazard Ratio†	Hazard Ratio‡	95% CI	P value
		No postdilation (n=113)	Postdilation (n=112)				
Death/MI	16	7.8%	9.2%	1.01	0.79	0.23-2.73	0.71
Repeat PCI/CABG	24	13.6%	13.5%	1.12	0.99	0.36-2.73	0.98
Death/MI/CABG/ repeat PCI	34	18.0%	20.9%	1.09	0.79	0.34-1.82	0.57

PCI indicates percutaneous coronary intervention; CABG coronary artery bypass graft surgery; MI myocardial infarction; MACE major adverse cardiac event; CI confidence interval.

* cumulative incident proportion
† crude hazard ratio from Cox proportional hazards model
‡ adjusted hazard ratio with propensity score in Cox proportional hazards model

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6.0 GENERAL DISCUSSION

6.1 SUMMARY OF FINDINGS

Although the guidelines for PCI procedures have been updated from the American College of Cardiology (ACC), American Heart Association (AHA), and the Society for Cardiovascular Angiography and Interventions (SCAI) periodically, the discretion from clinicians still plays an important role and thus results in significant variation in clinical practice of PCI. The objective of this dissertation research was to study the effect of the variation in three aspects on the patient outcomes, including post-discharge statin prescription, choice of stent number (multiple vs. single stent for each lesion), and postdilation. The results showed that this variation does have a strong impact on the risk of adverse patient outcomes.

Specifically, in *Research Paper 1* post-discharge statin treatment was associated with a significantly reduced risk of death, death/MI and death/MI/CABG, but not significantly associated with reduced risk of repeat PCI. In *Research Paper 2,* treatment with multiple stents per lesion was non-significantly associated with higher risk of Repeat PCI/CABG, death/MI/CABG, death/MI/Thrombosis, death/MICABG/Thrombosis, but it was non-significantly associated with reduced risk of these adverse events among patients who have only one lesion treated among patients who had more than one lesion treated,. In *Research Paper 3,* postdilation was significantly associated with dramatically increased risk of death and death/MI among acute MI patients who have one lesion treated, but this adverse effect was not seen among acute MI patients who have more than one lesion treated. Among patients without AMI, postdilation was not associated with either a benefit or increased risk of adverse cardiac events.

By use of propensity score methodology, our study controlled to a large extent for selection bias that can exist in observational studies. Nonetheless, unobserved factors (residual confounding) may still have existed resulting in potentially biased estimates and impacting the validity of our conclusions. Technically, the randomized clinical trial with a large sample size can solve this potential problem. However, it would be very difficult to carry out, in practice, clinical trials for the 3 topics investigated in this dissertation. For the first topic, post-discharge statin was shown to be effective in our study, and its use among heart disease patients at large, including PCI patients, has been widely accepted (85% among PCI patients in our study). Thus, it may be both unethical and impractical to randomize patients into a placebo group. Patient adherence to treatment assignment may also be a problem. Furthermore, given practical and ethical constraints, we do not see an urgent need for a clinical trial to confirm the observed effect in our study since several large clinical trials have already proven its efficacy among other ischemic heart disease patients. For the second topic, multiple stents per lesion vs. single long stent per lesion, there is insufficient rationale for a clinical trial. Although there are no specific guidelines for the number of stents to treat each lesion, use of a single stent for lesions of 10-32 mm is most common in contemporary practice (in our study, 88% of patients with single lesion treated received single stent and 81% of patients with more than one lesion treated received single stent for each lesion). The choice of multiple stents is the result of complex lesions, or unanticipated circumstances that occur during procedure, which requires additional stent for a full coverage. Even if enough patients could be recruited and randomized, it may be difficult to persuade clinicians to implant more than one stent if the disease and initial lesion result does not appear to warrant the use of more than one stent.

Alternatively, a large carefully done observational study with data on why single or multiple stents were chosen could be helpful. For the third topic, we did observe a very strong adverse effect of postdilation among acute MI patients with one lesion treated. In our study, the risk of death in postdilation treatment was 3.5 times higher than in no postdilation treatment. Again, practical limitations indicate that it would be very difficult to randomize patients into a potentially hazardous practice without the perceive

equipoise of a possible beneficial effect. Thus, on balance, the 3 topics investigated in this dissertation are likely to be adequately addressed within the framework of observational studies only.

6.2 FUTURE RESEARCH

Thrombosis is a rare event. However, the fatality rate is high. It is one major concern for PCI procedure, especially when drug-eluting stents greatly reduce the risk of restenosis. Because of low event numbers, we did not evaluate postdischarge statin, multiple stents vs. single long stent, or postdilation on the risk of thrombosis. In the future research, as the follow-up continues, and study population becomes larger, it is worthwhile to assess the effect of these variations on thrombosis specifically.

For the same reason of small sample size, the effect estimates were not precise among the subgroup of patients who had more than one lesion treated. We do not expect dramatically different effect estimates between patients having one lesion treated and patients having more than one lesion treated. The inconsistent results in Paper 2 and Paper 3 among the two subgroups are very likely the results of small sample size of patients in the second subgroup: patients having more than one lesion treated. In future research the effect of these variations among the small subgroups needs to be reinvestigated to check consistency among the two subgroups.

6.3 PUBLIC HEALTH SIGNIFICANCE

According to the World Health Organization, cardiovascular disease (CVD) is the leading cause of mortality in nearly every region of the world, accounting for an estimated 30% of all deaths. Projections indicate that the proportion of cardiovascular deaths worldwide will increase from 29% in 1990 to 36% in 2020. Coronary heart disease (CHD) is the principal type of heart disease. Worldwide, coronary heart

disease kills more than 7 million people each year. CHD death is about 71% of all heart disease deaths in 2002 in US. Percutaneous coronary intervention (PCI) is the most common treatment for ischemic cardiac disease at contemporary practice. According to the American Heart Association, 70–90 percent of PCI procedures involve the implantation of a stent. About one million coronary artery stenting procedures are performed annually in the United States.

Although guidelines are published and updated periodically from American College of Cardiology and American Heart Association and the Society for Cardiovascular Angiography and Interventions (SCAI), much variation exists in the practice of PCI procedure because the discretion of clinicians plays an important role on patient selection, stent type, number of stent, implantation procedure, et al. Our study showed the existence of these variations and assessed its impact on patient outcome at one-year follow up. It is of great public health significance to find the better practice for each specific type of patients in order to improves the patient outcome and thus improve the survival and quality of life for numerous patients suffering from this number-one killer disease.

APPENDIX A

PROPENSITY SCORE MODELLING FOR PAPER ONE

The list of baseline variables entered in the propensity score model, including demographic information: age (10-year increments), gender, race, ethnity, BMI (<25, 25-30, 30-35, 35-40, ≥40), enrollment time (wave 4/wave 5), disease history: history of coronary intervention, coronary bypass surgery, MI, severe concomitant non-cardiac disease (cerebrovascular, or PVD, or pulmonary disease, or cancer, or renal failure or other), diabetes, chest pain, chest pain at admission, congestive heart failure, congestive heart failure (CHF) at time of hospital admission, hypertension, hypercholesterolemia, known hypercoagulable state (history of hypercoagulability or excessive clotting as diagnosed by a physician or established by objective testing), angiographic characteristics: dominance (left, right, balanced), vessel disease (single, double or triple), evidence of minimal luminal irregularities in major vessels that are not significantly diseased (RCA, LAD, or LCx), the disease amenable to complete revascularization with CABG and percutaneous procedure according to the clinician, RCA ≥50% stenosis, any segment of RCA 100% stenosis, LAD ≥50% stenosis, any segment of LAD 100% stenosis, LCx ≥50% stenosis, any segment of LCx 100% stenosis, any bypass grafts, procedure characteristics: primary reason for revascularization (acute MI, unstable angina, stable angina, asymptomatic CAD, others), cardiogenic shock (yes/no), procedure circumstance (elective, urgent, emergent), device access site (femoral or not), renal-protective medication used (yes/no), IIb/IIIa receptor antagonist, Heparin, Clopidogrel, aspirin used < 24 hours prior to or during procedure (yes/no), procedure angiographically successful (all, partial success or failure),

rotational atherectomy, other atherectomy attempt (yes/no), local drug delivery (yes/no), patient being rejected for surgery (yes/no), lesion characteristics: number of lesions (one, two or more than two), any lesion length greater than 25 mm, number of narrow lesion less than 3 mm in diameter (none, one, more than one), any lesion previously treated, any evidence of thrombus, any calcified lesion, any ulcerated lesion, any lesion receiving collaterals, supplies collaterals, any ostial lesion, any tortuosity lesion, any C type lesion according to ACC/AHA classification, medication at discharge: beta blocker, ACE inhibitor, calcium channel blockers.

Table 6.1 Variables in logistic regression model to predict the conditional probability of receiving post-discharge statin

Variable	Variable label		β	se	P
SEX	gender	Male vs. Female	-0.09	0.06	0.09
age	age	<50 vs. ≥70	0.07	0.11	0.50
		50-60 vs. ≥70	0.14	0.09	0.12
		60-70 vs. ≥70	-0.05	0.09	0.54
PPROC	history of PCI	Yes vs. No	-0.12	0.06	0.04
TYPRO	Procedure circumstance	Elective vs. Urgent	-0.09	0.10	0.36
		Emergent vs. Urgent	-0.11	0.14	0.43
primi	history of MI	Yes vs. No	0.17	0.07	0.02
hxchf	history of CHF	Yes vs. No	-0.26	0.08	0.00
hxhyp	histoty of hypertension	Yes vs. No	-0.19	0.07	0.01
hxcho	history of hypercholesterolemia	Yes vs. No	0.48	0.06	<.0001
hxcoa	know hypercoagulable state	Yes vs. No	-0.47	0.17	0.01
domin	dominance	Left vs. Right	0.20	0.11	0.07
		Balanced vs. Right	-0.14	0.20	0.49
BMI	BMI	<25 vs. ≥40	-0.05	0.11	0.64
		25-30 vs. ≥40	0.16	0.09	0.07
		30-35 vs. ≥40	-0.01	0.10	0.93
		35-40 vs. ≥40	0.15	0.15	0.31
C type lesion	C type according to AHA classification	Yes vs. No	-0.10	0.06	0.10
length >25mm	lesion length	Yes vs. No	0.06	0.08	0.49
EOT	evidence of thrombus	Yes vs. No	0.26	0.10	0.01
CALC	calcified	Yes vs. No	-0.06	0.06	0.29
ULC	ulcerated	Yes vs. No	-0.07	0.08	0.41
BYPG	bypass grafts	Yes vs. No	-0.11	0.09	0.19
DATHN	none evidence of minimal irregularity	Yes vs. No	0.04	0.06	0.48
AMCAB	amenable with CABG	Yes vs. No	-0.08	0.06	0.20
AMPER	amenable with PCI	Yes vs. No	0.08	0.09	0.40
number of lesions	number of lesions treated	1 vs. ≥3	-0.38	0.14	0.01
		2 vs. ≥3	-0.11	0.12	0.35
RCA	RCA 50% stenosis	Yes vs. No	0.07	0.05	0.18
rca100	RCA 100% stenosis	No	-0.09	0.07	0.23
lad100	LAD 100% stenosis	No	0.03	0.08	0.73
acutemi	acute MI	No	0.14	0.09	0.15
unstable	unstable angina	No	0.07	0.08	0.35
stable	stable angina	No	0.14	0.08	0.09
p_at	other atherectomy attempt	No	0.22	0.15	0.13
p_drug	local drug delivery	No	0.22	0.17	0.19

Table 6.1 continued

p_st	stent attempt	1 vs. ≥3	0.21	0.11	0.05
		2 vs. ≥3	-0.06	0.09	0.50
DACE	ACE inhibitors at discharge	Yes vs. No	0.20	0.05	0.00
DBB	beta blockers at discharge	Yes vs. No	0.18	0.08	0.02
MDRA	IIb/IIIa receptor antagonist	Yes vs. No	0.21	0.06	0.00
RENM	renal-protective medication	Yes vs. No	-0.04	0.08	0.61
pclop	clopidogrel prior to procedure	Yes vs. No	0.11	0.08	0.16
diameter <3mm	number of vessels whose diameter<3mm	0 vs. vs. ≥2	-0.10	0.09	0.30
		1 vs. ≥2	-0.17	0.10	0.08

se indicates standard error; P P value.

APPENDIX B

PROPENSITY SCORE MODELLING FOR PAPER TWO

A candidate list of baseline variables were entered in the propensity score model, including demographic information: age (10-year increment), gender, insurance and region; disease history: history of PCI, CABG, congestive heart failure, hypertension, hypercholesterolemia, diabetes, severe concomitant non-cardiac disease (stroke, cancer, PVD, pulmonary, renal insufficiency, other); procedure characteristics: primary indication for intervention, circumstances of procedure (elective, urgent, emergent), procedure sequence, MI type (ST elevation/Non ST elevation/Unknow), time from presentation of MI to intervention (≤12 hours/>12 hours), LV ejection fraction < 40%, use of rotational atherectomy, radiation therapy, and other interventional device; and lesion characteristics: lesion length (measured in mm for patients with one lesion, measured as any lesion longer than 15 mm), any occlusion, any ostial lesion, any bifurcation, any calcification, any previously treated lesion, lesion attempted times, cutting balloon use, medication use before procedure: aspirin, Beta Blocker, GP IIb/IIIa inhibitor, Low-Molecular Weight Heparin, Statin, Direct Thrombin Inhibitor, Plavix and Ticlid. Medication use during procedure: aspirin, Beta Blocker, Planned GP IIb/IIIa inhibitor, Bail-out GP IIb/IIIa inhibitor, ACE inhibitors.

Table 6.2 Variables in logistic regression model to predict the conditional probability of receiving multiple stents (among patients with only one lesion treated)

Variable	Variable label		β	se	P
age_cat	age	55 to 64 vs. <55	0.07	0.12	0.55
		65 to 74 vs. <55	-0.08	0.13	0.51
		75 and older vs. <55	0.04	0.14	0.80
GENDER	gender	Male vs. Female	0.04	0.08	0.65
hxmi	history of MI	Yes vs. No	0.11	0.08	0.18
hxhypertension	history of hypertension	Yes vs. No	-0.07	0.09	0.44
region_char	region	Midwest vs. West	0.12	0.14	0.39
region_char		Northeast vs. West	0.23	0.13	0.07
region_char		Southeast vs. West	-0.45	0.16	0.00
region_char		Southwest vs. West	-0.05	0.25	0.83
PROCSEQU	procedure sequence	staged vs. index	0.45	0.16	0.01
calcification2	calcification	Yes vs. No	0.11	0.08	0.16
occlusion2	occlusion	Yes vs. No	0.19	0.11	0.08
bifurcation2	bifurcation	Yes vs. No	0.17	0.12	0.16
les_attempt	lesion attempt	two vs. one	-0.33	0.40	0.41
lcx	LCx 50% stenosis	Yes vs. No	0.10	0.08	0.22
lcx_graft	LCx graft	Yes vs. No	-0.24	0.25	0.35
PRIMARYTX5	cutting balloon	Yes vs. No	0.47	0.24	0.05
PRIMARYTX7	other device	Yes vs. No	0.20	0.18	0.27
intraprocmeds2	beta blockers during procedure	Yes vs. No	0.06	0.16	0.72
preprocmeds2	beta blockers before procedure	Yes vs. No	-0.05	0.08	0.50
preprocmeds3	IIb/IIIa receptor antagonist	Yes vs. No	0.30	0.14	0.03
preprocmeds6	Coumadin before procedrue	Yes vs. No	0.15	0.22	0.49
preprocmeds7	unfractured heparin before procedure	Yes vs. No	-0.18	0.11	0.09
preprocmeds8	low molecular weight heparin before procedure	Yes vs. No	-0.40	0.16	0.01
preprocmeds9	statin before procedure	Yes vs. No	0.08	0.08	0.32
preprocmeds12	ACE inhibitors before procedure	Yes vs. No	0.02	0.08	0.81
preprocmeds13	no meds before procedure	Yes vs. No	0.11	0.17	0.49
LESLENGTH	lesion length		-0.15	0.01	<.0001

se indicates standard error; P P value.

Table 6.3 Variables in logistic regression model to predict the conditional probability of receiving multiple stents (among patients with more than one lesion treated)

Variable	Variable label		β	se	P
age_cat	age	55 to 64 vs. <55	0.41	0.22	0.06
		65 to 74 vs. <55	0.01	0.21	0.95
		75 and older vs. <55	-0.04	0.24	0.88
GENDER	gender	Male vs. Female	-0.20	0.14	0.16
pci_history	prior PCI	Yes vs. No	-0.35	0.16	0.03
hxmi	history of MI	Yes vs. No	0.24	0.15	0.12
hxhypertension	history of hypertension	Yes vs. No	-0.35	0.15	0.02
diabetes_tx	history of diabetes	1 vs. 0	-0.24	0.13	0.07
indmitype1	MI type	Yes vs. No	-1.02	0.60	0.09
indmitype2	MI timing	Yes vs. No	-0.98	0.52	0.06
REVASCIND_r	cause of procedure	acute MI vs. others	1.37	0.79	0.08
		Unstables angina vs. others	-0.44	0.29	0.12
		stable angina vs. others	-0.32	0.33	0.34
		postive studyvs. others	-0.70	0.32	0.03
region_char	region	Midwest vs. West	0.12	0.25	0.63
		Northeast vs. West	0.68	0.23	0.00
		Southeast vs. West	-0.37	0.27	0.17
		Southwest vs. West	-0.51	0.47	0.28
PROCCIRCUM	procedure circumstance	Elective vs. Urgent	0.46	0.31	0.15
		Emergent vs. Urgent	-0.32	0.49	0.52
lvef_lt40	LVEF<40%	Yes vs. No	-0.47	0.25	0.05
calcification	lesion calcification	Yes vs. No	0.21	0.15	0.17
lcx	LCx 50% stenosis	Yes vs. No	0.16	0.13	0.22
intraprocmeds9	thrombin inhibitor	Yes vs. No	-0.10	0.13	0.45
preprocmeds1	aspirin before procedure	Yes vs. No	-0.41	0.17	0.02
preprocmeds8	low molecular weight heparin before procedure	Yes vs. No	-0.42	0.29	0.15
preprocmeds9	statin before procedure	Yes vs. No	-0.15	0.13	0.25
number of lesions	number of lesion treated	≥3 vs. 2	0.24	0.18	0.17

se indicates standard error; P P value.

APPENDIX C

PROPENSITY SCORE MODELLING FOR PAPER THREE

A list of candidate baseline variables entered to the propensity score model, including demographic information: age (10-year increments), gender, race, hispanic, insurance, BMI (<25, 25-30, 30-35, 35-40, ≥40), enrollment time (Wave 4/Wave 5), disease history: history of coronary intervention, coronary bypass surgery, MI, severe concomitant non-cardiac disease (cerebrovascular, or peripheral vascular disease, or pulmonary disease, or cancer, or renal failure or other), diabetes, chest pain, chest pain at admission, congestive heart failure, congestive heart failure at time of hospital admission, hypertension, hypercholesterolemia, known hypercoagulable state (history of hypercoagulability or excessive clotting as diagnosed by a physician or established by objective testing), angiographic characteristics: dominance (left, right, balanced), vessel disease (single, double or triple), RCA, LAD, or LCx 50% stenosis, the disease amenable to complete revascularization with CABG according to the clinician, the disease amenable to complete revascularization with percutaneous procedure according to the clinician, any bypass grafts, procedure characteristics: cause of procedure (acute MI, unstable angina, stable angina, asymptomatic CAD, others), procedure site (same as diagnostic site), cardiogenic shock (yes/no), procedure circumstance (elective, urgent, emergent), procedure site (same to diagnostic site: yes/no), device access site (femoral or not), rotational atherectomy, other atherectomy, cutting balloon, thrombolytics reperfusion, any drug-eluting stent, renal-protective medication used (yes/no), medication used < 24 hours prior to procedure (IIb/IIIa receptor antagonist, Heparin, Clopidogrel, aspirin: yes/no),

local drug delivery (yes/no), patient being rejected for surgery (yes/no), lesion characteristics: number of lesions (one, two or more than two), any lesion length greater than 25 mm, any lesion previously treated, any evidence of thrombus, any calcified lesion, any ulcerated lesion, any lesion receiving collaterals, supplies collaterals, any ostial lesion, any tortuosity lesion, any C type lesion according to ACC/AHA classification. For patients with one lesion treated, the lesion length (<10mm, 10-15mm, 15-20mm, ≥20mm), vessel diameter (<2.5mm, 2.5-3.0mm, 3.0-3.5mm, ≥3.5mm), stent diameter bigger than vessel diameter (yes/no), number of stent (1, 2, 3 or more).

Table 6.4 Variables in logistic regression model to predict the conditional probability of receiving postdilation (among patients without AMI and had only one lesion treated)

Variable	Variable label		β	se	P
SEX	gender	Male vs. Female	0.07	0.06	0.27
HISPA	hispanic	Yes vs. No	-0.35	0.13	0.01
TYPRO	procedure circumstance	Elective vs. urgent	0.20	0.20	0.33
		Emergent vs. urgent	-0.53	0.38	0.16
HXDB	history of diabetes	Yes vs. No	0.05	0.06	0.38
hxchf	history of CHF	Yes vs. No	0.13	0.10	0.19
hxhyp	history of hypertension	Yes vs. No	0.07	0.07	0.32
hxcho	history of hypercholesterolemia	Yes vs. No	0.15	0.08	0.05
vdiscal	vessel disease	Triple vs. non triple	-0.15	0.08	0.06
dominance	dominance	left vs. right	-0.13	0.11	0.23
		balanced vs. right	-0.15	0.11	0.17
SAMEP	procedure site same as diagnostic site	Yes vs. No	-0.22	0.07	0.00
rca	RCA 50% stenosis	Yes vs. No	-0.16	0.13	0.22
lad	LAD 50% stenosis	Yes vs. No	-0.11	0.12	0.35
lcx	LCx 50% stenosis	Yes vs. No	-0.16	0.13	0.21
rcaocl	RCA 100% stenosis	Yes vs. No	0.09	0.09	0.31
ladocl	LAD 100% stenosis	Yes vs. No	-0.10	0.09	0.26
lcxocl	LCx 100% stenosis	Yes vs. No	0.12	0.09	0.22
wave	enrollment time	wave 4 vs. wave 5	0.06	0.06	0.34
lptt	previously treated	Yes vs. No	-0.18	0.10	0.07
HEPP	heparin prior to procedure	Yes vs. No	0.27	0.14	0.05
EOT	evidence of thrombus	Yes vs. No	-0.11	0.12	0.33
CALC	calcified	Yes vs. No	-0.25	0.06	0.00
OLES	ostial lesion	Yes vs. No	-0.13	0.10	0.21
TORT	lesion tortuosity	Moderate/Severe vs. none	0.13	0.07	0.06
p_drug	local drug delivery	Yes vs. No	0.38	0.21	0.07
p_ra	rotational atherectomy	Yes vs. No	0.31	0.24	0.20
p_at	other atherectomy attempt	Yes vs. No	0.35	0.18	0.05
rrev2	cause of procedure	Unstable vs. other	-0.01	0.11	0.89
		Stable vs. other	0.06	0.11	0.57
		Asymptomacit CAD vs. other	0.20	0.12	0.10
Age	age	>40 vs. ≥80	0.44	0.41	0.28
		40-50 vs. ≥80	-0.27	0.18	0.13
		50-60 vs. ≥80	0.00	0.14	0.99
		60-70 vs. ≥80	-0.01	0.13	0.95
		70-80 vs. ≥80	-0.07	0.14	0.61
ov_elut_le	overall drug-eluting stents use	Yes vs. No	-0.14	0.09	0.12

Table 6.4 continued

acc4	C type lesion according to AHA	Yes vs. No	-0.25	0.07	0.00
number of stents	number of stents	1 vs ≥3	-0.02	0.11	0.86
		2 vs. ≥3	-0.32	0.12	0.01
pasp	aspirin prior to procedure	Yes vs. No	-0.18	0.11	0.10
ptic	clopidogrel or ticlopidine prior to procedure	Yes vs. No	0.36	0.37	0.33
DASP	aspirin at discharge	Yes vs. No	0.32	0.18	0.07
dclotic	clopidogrel or ticlopidine at discharge	Yes vs. No	0.24	0.19	0.20
DLAN	long acting nitrates at discharge	Yes vs. No	0.09	0.08	0.28
DACE	ACE inhibitors at discharge	Yes vs. No	-0.06	0.06	0.27
dcstcost	cholesterol modifying agents	Yes vs. No	0.13	0.08	0.14
DATHN	none luminal irregularities in major vessel	Yes vs. No	-0.20	0.09	0.02
DATHR	RCA minimal irregularities	Yes vs. No	-0.05	0.07	0.45
DATHC	LCx minimal irregularities	Yes vs. No	-0.14	0.07	0.04
norm	vessel diameter	>2.5 vs. ≥3.5	-0.10	0.18	0.60
		2.5-3.0 vs. ≥3.5	0.27	0.11	0.01
		3.0-3.5 vs. ≥3.5	-0.07	0.10	0.50
stvessel	stent diameter bigger than vessel diameter	big stent vs. smaller stent	0.45	0.07	<.0001
len	lesion length	0-10 vs. ≥20	0.03	0.21	0.87
		10-15 vs. ≥20	-0.22	0.19	0.24
		15-20 vs. ≥20	-0.57	0.20	0.00
PAY	insurance	Medicare vs. Private	0.53	0.16	0.00
		None/self-pay vs. Private	-0.75	0.38	0.05
		Other public vs. Private	0.13	0.17	0.46

se indicates standard error; P P value.

Table 6.5 Variables in logistic regression model to predict the conditional probability of receiving postdilation (among patients without AMI and had multiple lesions treated)

Variable	Variable label		β	se	P
SEX	gender	Male vs. Female	-0.05	0.10	0.61
RACE	race	Asian vs. White	1.34	0.55	0.01
		Black vs. White	-0.06	0.28	0.84
		Other vs. White	-0.91	0.43	0.03
PRIBY	prior PCI	Yes vs. No	-0.52	0.16	0.00
primi	history of MI	Yes vs. No	0.02	0.11	0.88
hxcp	history of chest pain	Yes vs. No	-0.07	0.10	0.51
cpain	chest pain at admission	Yes vs. No	-0.09	0.12	0.46
hxhyp	history of hypertension	Yes vs. No	-0.20	0.12	0.11
hxcho	history of hypercholesterol	Yes vs. No	0.10	0.12	0.37
hxcoa	known hypercoagulable state	Yes vs. No	0.69	0.37	0.07
smoke	smoking	current smoker vs. others	-0.21	0.14	0.12
		former smokers vs. others	-0.15	0.10	0.16
SAMEP	procedure site same as diagnostic site	Yes vs. No	0.22	0.10	0.03
domin	dominance	left vs. other	0.45	0.18	0.01
vdiscal3	vessel disease	triple vs. others	0.38	0.17	0.03
len2	any lesion length >25mm	longer than 25 mm vs. not	0.09	0.10	0.39
LPT2	any lesion previously treated	Yes vs. No	-0.01	0.25	0.98
EOT2	any lesion had evidence of thrombus	Yes vs. No	0.44	0.34	0.19
CALC2	any lesion calcified	Yes vs. No	0.06	0.10	0.55
ULC2	any lesion ulcerated	Yes vs. No	0.09	0.19	0.65
OLES2	any ostial lesion	Yes vs. No	0.11	0.18	0.54
C lesion	any C type lesion	Yes vs. No	0.19	0.11	0.08
Age	age	<50 vs. >70	0.17	0.20	0.41
		50-60 vs. >70	-0.11	0.16	0.48
		60-70 vs. >70	0.13	0.15	0.41
DATHN	no minimal irregularities in major vessel	Yes vs. No	0.47	0.14	0.00
DATHR	RCA minimal irregularities	Yes vs. No	0.26	0.12	0.02
DATHC	LCx minimal irregularities	Yes vs. No	0.26	0.12	0.03
AMPER	amenable with PCI	Yes vs. No	0.39	0.16	0.02
cnt	numer of lesion treated	2 vs. ≥4	-0.19	0.24	0.44
		3 vs. ≥4	0.14	0.27	0.61
RCA	RCA 50% stenosis	Yes vs. No	0.41	0.16	0.01
LAD	LAD 50% stenosis	Yes vs. No	0.57	0.16	0.00

Table 6.5 continued

LCX	LCx 50% stenosis	Yes vs. No	0.34	0.13	0.01
rca100	RCA 100% stenosis	Yes vs. No	-0.24	0.15	0.12
lad100	LAD 100% stenosis	Yes vs. No	0.31	0.16	0.05
unstable	unstable angina	Yes vs. No	0.21	0.22	0.34
stable	stable angina	Yes vs. No	0.20	0.22	0.36
asymcad	asymptomatic CAD	Yes vs. No	0.13	0.22	0.54
p_drug	local drug delivery	Yes vs. No	-0.41	0.29	0.16
p_ra	rotational atherectomy attempt	Yes vs. No	0.22	0.27	0.40
p_st	stent attempt	2 vs. ≥3	-0.35	0.21	0.10
DBB	beta blockers at discharge	Yes vs. No	-0.13	0.11	0.23
DCAL	calcium channel blockers at discharge	Yes vs. No	0.08	0.12	0.51
p_nd	new device attempted	2 vs. ≥3	0.33	0.20	0.10
MDRA	IIb/IIIa receptor antagonist	Yes vs. No	0.14	0.11	0.22
RENM	renal protective medicine	Yes vs. No	-0.30	0.16	0.06
phep	heparin prior to procedure	Yes vs. No	-0.16	0.10	0.10
pasp	aspirin prior to procedure	Yes vs. No	-0.08	0.15	0.59
norm	vessel diameter< 3mm	Yes vs. No	0.06	0.09	0.53

se indicates standard error; P P value.

Table 6.6 Variables in logistic regression model to predict the conditional probability of receiving postdilation (among patients with AMI and had only one lesion treated)

Variable	Variable label		β	se	P
SEX	gender	Male vs. Female	-0.04	0.10	0.67
HISPA	hispanic	Yes vs. No	-0.38	0.21	0.07
BMI	BMI	<25 vs. ≥39	-0.06	0.19	0.74
		25-30 vs. ≥39	-0.31	0.17	0.07
		30-35 vs. ≥39	0.06	0.19	0.75
		35-39 vs. ≥39	-0.16	0.27	0.56
PPROC	prior PCI	Yes vs. No	0.13	0.15	0.40
PRIBY	prior CABG	Yes vs. No	-0.22	0.22	0.33
primii	history of MI	Yes vs. No	-0.17	0.16	0.28
HXDB	history of diabetes	Yes vs. No	-0.17	0.11	0.11
hxchff	histroy of CHF	Yes vs. No	-0.52	0.21	0.01
hxhypp	history of hypertension	Yes vs. No	-0.20	0.11	0.07
HACHF	CHF at admission	Yes vs. No	0.50	0.18	0.01
hxchoo	history of hypercholesterolemia	Yes vs. No	0.21	0.10	0.04
dominance	dominance	left vs. right	-0.45	0.19	0.02
		balanced vs. right	-0.39	0.17	0.02
vdiscal2	vessel disease	Yes vs. No	-0.16	0.10	0.11
SAMEP	procedure site same as diagnostic site	Yes vs. No	-0.12	0.14	0.40
rca	RCA 50% stenosis	Yes vs. No	-0.54	0.30	0.07
lad	LAD 50% stenosis	Yes vs. No	-0.82	0.29	0.01
lcx	LCx 50% stenosis	Yes vs. No	-0.77	0.30	0.01
ladocl	LAD 100% stenosis	Yes vs. No	0.22	0.13	0.11
lcxocl	LCx 100% stenosis	Yes vs. No	0.31	0.15	0.04
AMPER	amenable with PCI	Yes vs. No	-0.33	0.17	0.05
wave	enrollment time	wave 4 vs. wave 5	0.16	0.10	0.08
HEPP	heparin prior to procedure	Yes vs. No	-0.17	0.11	0.13
RCOL	receive collaterals	Yes vs. No	-0.50	0.13	<.0001
OLES	ostial lesion	Yes vs. No	-0.39	0.20	0.05
TORT	lesion tortuosity	Moderate/Severe vs. none	0.10	0.11	0.39
p_drug	local drug delivery	Yes vs. No	0.26	0.19	0.16
p_at	othe atherectomy attempt	Yes vs. No	0.61	0.59	0.30
Age	age	>40 vs. ≥80	0.64	0.48	0.19
		40-50 vs. ≥80	-0.08	0.22	0.71
		50-60 vs. ≥80	-0.02	0.19	0.92
		60-70 vs. ≥80	0.00	0.20	0.99
		70-80 vs. ≥80	-0.27	0.21	0.21
SHOCK	shock	Yes vs. No	0.14	0.26	0.59

Table 6.6 continued

number of stents	number of stents	1 vs ≥3	0.25	0.18	0.17
		2 vs. ≥3	-0.19	0.20	0.34
len	lesion length	0-10 vs. ≥20	0.07	0.27	0.80
		10-15 vs. ≥20	0.32	0.24	0.18
		15-20 vs. ≥20	-0.34	0.24	0.15
stvessel	stent diameter bigger than vessle diameter	big stent vs. smaller stent	0.51	0.10	<.0001
pasp	aspirin prior to procedure	Yes vs. No	0.10	0.15	0.48
DLAN	long acting nitrate at discharge	Yes vs. No	0.25	0.21	0.22
DBB	beta blockers at discharge	Yes vs. No	0.22	0.15	0.14
dcstcost	cholesterol modifying agents	Yes vs. No	-0.06	0.15	0.70

se indicates standard error; P P value.

Table 6.7 Variables in logistic regression model to predict the conditional probability of receiving postdilation (among patients with AMI and had more than one lesion treated)

Variable	Variable label		β	se	P
SEX	gender	Male vs. Female	0.12	0.23	0.61
HISPA	hispanic	Yes vs. No	0.43	0.47	0.36
RACE	race	White vs. Non white	-0.26	0.26	0.32
primii	history of MI	Yes vs. No	0.67	0.25	0.01
codiss	severe non cardiac events	Yes vs. No	0.46	0.23	0.04
HXDB	history of diabetes	Yes vs. No	0.33	0.21	0.12
hachff	history of CHF	Yes vs. No	-0.34	0.36	0.35
hxchoo	history of hypercholesterolemia	Yes vs. No	-0.25	0.21	0.24
smoke2	smoking	Yes vs. No	0.35	0.21	0.09
SHOCK	shock	Yes vs. No	1.42	0.87	0.10
SAMEP	procedure site same as diagnostic site	Yes vs. No	0.26	0.28	0.37
domin	dominance	left vs. right	0.46	0.37	0.21
		balanced vs. right	0.57	0.35	0.11
vdis	vessel disease	double vs. other	-0.29	0.21	0.16
BMI	BMI	<25 vs. >=40	0.61	0.44	0.17
		25-30 vs. >=40	0.24	0.38	0.53
		30-35 vs. >=40	0.69	0.39	0.08
		35-40 vs. >=40	0.43	0.64	0.50
len2	any lesion length >25mm	Yes vs. No	0.32	0.23	0.16
LPT2	any lesion previously treated	Yes vs. No	0.96	0.82	0.24
CALC2	any lesion calcified	Yes vs. No	-0.18	0.23	0.43
OLES2	anly ostial lesion	Yes vs. No	0.82	0.40	0.04
Age	age	<50 vs. >70	0.24	0.40	0.55
		50-60 vs. >70	0.10	0.36	0.79
		60-70 vs. >70	-0.05	0.33	0.88
DATHC	LCx minimal irregularities	Yes vs. No	0.26	0.20	0.20
AMPER	amenable with PCI	Yes vs. No	-0.47	0.34	0.17
CABGR	rejected for CABG	Yes vs. No	-0.68	0.54	0.21
number of lesions	number of lesion	2 vs. ≥3	0.10	0.32	0.75
RCA	RCA 50% stenosis	Yes vs. No	0.22	0.26	0.39
LAD	LAD 50% stenosis	Yes vs. No	0.36	0.25	0.14
rca100	RCA 100% stenosis	Yes vs. No	-0.39	0.25	0.12
p_st	stent attempt	2 vs. ≥3	-1.22	0.52	0.02
DBB	beta blockers at discharge	Yes vs. No	0.56	0.32	0.08
p_nd	new device attemptd	2 vs. ≥3	0.82	0.52	0.12
MPRA	IIb/IIIa receptor antagonist	Yes vs. No	-0.80	0.25	0.00

Table 6.7 continued

RENM	renal protective medicine	Yes vs. No	0.56	0.28	0.04
RTHR	thrombolytic reperfusion	Yes vs. No	1.78	0.70	0.01
pasp	aspirin prior to procedure	Yes vs. No	-0.84	0.32	0.01
norm	vessel diameter <3 mm	Yes vs. No	0.38	0.21	0.07

se indicates standard error; P P value.

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