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Clopidogrel After Drug-Eluting Stent Implantation: Is Current Practice Sufficient?

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The DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) network is part of AHRQ's Effective Health Care program. It is a collaborative network of research centers that support the rapid development of new scientific information and analytic tools. The DEcIDE network assists health care providers, patients, and policymakers seeking unbiased information about the outcomes, clinical effectiveness, safety, and appropriateness of health care items and services, particularly prescription medications and medical devices.

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Abstract

Context. Recent studies of drug-eluting intracoronary stents suggest that current antiplatelet regimens may not be sufficient to prevent late stent thrombosis.

Objective. To assess the association between clopidogrel use and long-term clinical outcomes of patients receiving drug-eluting and bare metal stents for treatment of coronary artery disease.

Design. An observational study examining consecutive patients receiving intracoronary stents between January 1, 2000 and July 31, 2005, with follow-up contact at six, twelve and twenty four months through September 7, 2006.

Setting. Duke Heart Center, a tertiary care medical center in Durham, North Carolina.

Patients. The study population included 4666 patients undergoing initial percutaneous coronary intervention with a bare metal or drug-eluting stent.

Interventions. Landmark analyses were performed among patients who were event-free (no death, myocardial infarction, or revascularization) at six and twelve months follow-up. At these points patients were divided into four groups based upon stent type and self-reported clopidogrel use: drug-eluting stent with clopidogrel, drug-eluting stent without clopidogrel, bare metal stent with clopidogrel, and bare metal stent without clopidogrel.

Main Outcome Measures. Death, nonfatal myocardial infarction, and the composite of death or myocardial infarction at twenty four months follow-up.

Results. Among drug-eluting stent patients who were event-free at six months, clopidogrel use was a significant predictor of lower rates of death (2.0% with vs. 5.3% without, p=0.031) and death or myocardial infarction (3.1% with vs. 7.2% without, p=0.021) at 24 months; however, among bare metal stent patients there were no differences in death (3.7% with vs. 4.5% without, p=0.50) or death and myocardial infarction (5.5% with vs. 6.0% without, p=0.70). Among drug-eluting stent patients who were event-free at twelve months, clopidogrel use continued to predict lower rates of death (0.0% with vs. 3.5% without, p=0.004) and death or myocardial infarction rates (0.0% with vs. 4.5% without, p<0.001) at 24 months; however, among bare metal stent patients there continued to be no differences in death (3.3% with vs. 2.7% without, p=0.57) or death or myocardial infarction (4.7% with vs. 3.6% without, p=0.44).

Conclusion. The extended use of clopidogrel in drug-eluting stent patients may be associated with a reduced risk for death and death or myocardial infarction. However, the appropriate duration for clopidogrel administration can only be determined within the context of a large-scale randomized clinical trial.

Introduction

The incidence of early vessel closure after coronary stent implantation was markedly reduced by the adoption of thienopyridine antiplatelet therapy.[1] The widespread adoption of dual antiplatelet therapy (aspirin and thienopyridines) has further reduced the risk of subacute thrombosis after bare metal stent (BMS) implantation to 0.5% -1.9%.[1-3]

Instructions for the use of drug-eluting stents (DES) commercially available in the United States specify treatment with clopidogrel for at least 3 months (for sirolimus coated stents) or 6 months (for paclitaxel coated stents) after implantation. Premature discontinuation of this minimum antiplatelet therapy has been strongly associated with stent thrombosis.[4,5] However, reports of late thrombosis events among DES patients have cast doubt on whether the recommended regimens are sufficient.[6,7] An observational analysis from BASKET-LATE examined the incidence of clinical events after cessation of clopidogrel therapy.[8] This study identified 746 patients who were free of major adverse events 6 months after DES or BMS placement. All patients had stopped taking clopidogrel and were followed for an additional 12 months. At 18-months follow-up, there was no difference between DES and BMS patients in cumulative rates of death or myocardial infarction. However, after clopidogrel discontinuation patients receiving DES vs. BMS experienced higher rates of death and myocardial infarction (4.9% vs. 1.3%). These results have furthered uncertainty regarding the minimal necessary duration of antiplatelet therapy after DES implantation.

We sought to assess the association between clopidogrel use and long-term rates of death and death or myocardial infarction following initial percutaneous coronary intervention with drug-eluting or bare metal stents.

Methods

Study Population

The study population includes consecutive Duke Heart Center patients who had an initial percutaneous coronary intervention (PCI) with at least one bare metal stent from January 1, 2000 through July 31, 2005, and with at least one drug-eluting stent from April 01, 2003 through July 31, 2005. The follow-up period extended through September 07, 2006 to ensure that all patients had an opportunity for at least 12 months of follow-up information. Exclusion criteria included congenital heart disease, moderate/severe valvular heart disease, prior coronary artery bypass graft (CABG) surgery or PCI procedure, and significant ($\geq$ 75% stenosis) left main coronary artery disease. Patients also were excluded if interventions other than stent placement occurred during their PCI procedure, or if they were not contacted for follow-up medication use for each analysis period. All study information was stored in the Duke Databank for Cardiovascular Disease (DDCD).

Human Subjects Review

Duke University Medical Center Institutional Review Board approval was obtained on February 27, 2006 with a waiver of the requirement for written informed consent (Registry Number 8223-06-2R0ER).

Data Collection

Baseline Data

Baseline demographic, medical history, physical examination and initial cardiac catheterization results information were collected prospectively, as previously described.[9-11] Briefly, initial demographic data was received from Duke University Medical Center's administrative systems, clinical data was collected by the Duke Heart Center, and ZIP code data were obtained from the 2000 US Census Report.

Follow-Up Clinical Event and Medication Data

As part of our standard DDCD follow-up protocol, all patients were contacted at 6 months and 1 year after their initial procedure (BMS or DES), and annually thereafter. We analyzed follow-up information on occurrence of 2 events (death and non-fatal MI) and use of 2 medications (clopidogrel and aspirin). An independent mortality committee reviewed follow-up results to confirm deaths. Follow-up myocardial infarction was based on clinical diagnoses assigned by the patient's medical providers and was not centrally adjudicated. Follow-up was considered complete if the Mortality Committee confirmed the patient's death or if the patient was successfully contacted at the scheduled follow-up interval. Follow-up was 98% complete for all scheduled contacts as of September 7, 2006. Patients with incomplete follow-up were censored at the time of last contact.

During their follow-up contacts at 6 months, 1 year and 2 years, patients were asked to provide information regarding their current medications. We considered patients to be using clopidogrel at the time of follow-up when this medication was specifically listed. Patient aspirin use was determined from the same medication list and from responses to a question asking whether patients were regular aspirin users. No attempt was made to verify patient reported medication use.

Treatment Group Assignments

Stent Type

Patients who received both BMS and DES during the same procedure were assigned to DES, since subsequent antiplatelet therapy requirements would be based on the presence of this device.

Landmark Analyses Based on Clopidogrel Use

Landmark analysis is a form of survival analysis that classifies patients based on some intermediate (non-outcome) event that occurs during follow-up.[12] Prognosis is then evaluated from this "landmark" time point. In our analyses, we define landmark time and study outcomes in terms of their elapsed time from a patient's index procedure. Two

landmarks were used in this study: 6 month clopidogrel use (yes or no) and 12 month clopidogrel use (yes or no)(Figures 1A and 1B). Patients who were event-free (no death, MI, or revascularization) at 6 months and completed the 6-month follow-up contact, including questions regarding medication use, were assigned to one of 4 groups: DES with clopidogrel (DES+C), DES without clopidogrel (DES-C), BMS with clopidogrel (BMS+C) and BMS without clopidogrel (BMS-C). Outcomes for these groups were evaluated to 24 months after the initial PCI procedure. Similarly, patients who were event-free at 12 months and completed the 12-month follow-up contact, including medication use, were assigned in a second landmark analysis to four groups (by stent type and clopidogrel use) and their 24 month outcomes were evaluated. When classifying groups, a window of 90 days before and after the follow-up points was allowed because of potential time lags in the follow-up process. For the 12-month landmark analysis, patients with PCI procedures occurring after July 31, 2004 were excluded because they did not have the opportunity for follow-up at 24-months.

Data Analyses

Baseline characteristics and event rates were summarized for patient groups as numbers (percentages) for categorical variables and as medians with interquartile ranges (25th, 75th) for continuous variables. Tables of baseline and angiographic characteristics, and follow-up aspirin and clopidogrel use were categorized by treatment modality. Binary variables were compared across interventions using the Pearson Chi-square test. Continuous and ordinal categorical variables were compared using the Wilcoxon rank sum test. Statistical significance was determined at the 2-sided 0.05 level.

Unadjusted and adjusted cumulative incidence rates were calculated using inverse probability weighted estimators.[13-15] The inverse weighted estimators were based on partitioning the data into monthly intervals.[13] Unadjusted estimates were based on weights that are a function of Kaplan-Meier estimates for the treatment-specific censoring distributions. Inverse probability weighted adjusted estimates were based on estimated propensity scores and Cox proportional hazards estimates of the treatment-drug group specific censoring distributions.[16] SAS PROC GENMOD (Cary, N.C., U.S.A.) with robust standard errors was used to estimate treatment effects, 95% confidence intervals, and p-values.[17] Weighted Cox proportional hazards models and adjusted cumulative incidence curves were constructed using inverse probability weights.[18]

Four treatment-drug group propensity scores were estimated using logistic regression models. The following variables were used in our propensity score and Cox proportional hazard models: patient demographics (race, age, gender), CAD risk factors (smoking history, hypertension, diabetes), cardiovascular history and physical examination (body mass index, systolic blood pressure, carotid bruits, heart rate, history and severity of congestive heart failure, history of myocardial infarction, mild valvular heart disease, third heart sound, history of cerebrovascular disease, history of peripheral vascular disease), diagnostic catheterization findings (left ventricular ejection fraction, extent of coronary artery disease), comorbid conditions (Charlson Index, history of chronic obstructive pulmonary disease, connective tissue disease, renal disease, liver disease, metastatic cancer, solid tumor), stent characteristics (average stent diameter and total length of stents), socioeconomic status (ZIP code level median income per household and average house value), and patient-reported aspirin use.

Results

Study Population

Between January 1, 2000 and July 31, 2005, 4927 patients received an initial PCI procedure at the Duke Heart Center. We excluded 261 patients, 156 with balloon angioplasty without a stent device and 105 receiving a non-stent device (e.g., atherectomy, excimer laser, brachytherapy. Of the 4666 patients remaining, 3165 received a bare metal and 1501 a drug-eluting stent.

Landmark Analysis at 6 Months

Baseline Characteristics

Our population included 3609 patients who were event-free 6 months after their initial stent procedure. All four groups were similar with regard to age, African-American race, and gender (Table 1). However, fewer patients in the BMS–C group had a history of diabetes while more patients in the DES-C group had a history of CHF. While both DES groups had fewer patients with a history of MI than the BMS groups, they also had more patients with multi-vessel disease and their patients resided in ZIP codes with greater household incomes and house values. There also was significant variation across the groups in self-reported regular aspirin use. By 24 months, clopidogrel use had diminished among patients who reported using it at 6 months (Table 1). In the same time period, clopidogrel use increased among patients who did not report it at 6 months. Thus, by 24 months follow-up, there was a 40.7% difference in clopidogrel use between DES +C vs. DES-C ; and a 54.1% difference between BMS+C vs. BMS-C.

Unadjusted Results

In patients who were event-free at 6 months, unadjusted 2 year differences between the four groups revealed disparities in event rates. At 24 months, the DES+C group vs. the DES-C group had significantly lower rates of death, non-fatal MI, and death or MI (Table 2). However, there were no statistically significant differences between BMS+C and BMS-C patients with regard to these events. In comparisons with BMS patients, DES+C patients had significantly lower rates of death and death or MI than did BMS+C or BMS-C patients, but no difference in non-fatal MI.

Adjusted Results

DES+C patients had significantly lower rates of death and death or MI than did DES-C patients, but no difference in non-fatal MI (Table 2; Figures 2A and 2B). In the weighted Cox proportional hazard model, the adjusted hazard ratio for death of DES-C compared with DES+C was 2.43 (95%CI of 1.12, 5.26; p-value = 0.025). The adjusted hazard ratio for death or MI of DES-C compared with DES+C was 1.93 (95% CI of 1.05, 3.56; p-value = 0.035). There were no differences between BMS+C and BMS-C with regard to death, non-fatal MI, and death or MI. In this analysis, differences between DES+C and BMS+C were not statistically significant; however, differences between DES+C and BMS-C were statistically significant for death and death or MI.

Landmark Analysis at 12 Months

Baseline Characteristics

Our population included 2518 patients who were event-free at 12 months. Patients in all 4 groups were similar with regards to age, African-American race, gender, history of CHF, and socioeconomic status (Table 3); however, fewer patients in the BMS-C group had a history of diabetes. Both DES groups had fewer patients with a history of MI than the BMS groups, and the DES+C group had the highest percent of patients with multi-vessel disease. Most patients in all 4 groups were receiving aspirin at 6, 12 and 24 months; however, there appeared to be some crossover in patient-reported clopidogrel use between 6 and 12 months. By 24 months follow-up, there was a 61.7% difference in clopidogrel use between DES+C vs. DES-C and a 64.2% difference between BMS+C and BMS-C.

Unadjusted Results

Patients in the DES+C vs. DES-C group had significantly lower rates of death, non-fatal MI, and death or MI; whereas, there were no significant BMS+C vs. BMS-C differences for these events(Table 4). Compared to BMS patients (BMS+C and BMS-C), DES+C patients had significant reductions in the outcomes of death, non-fatal MI, and death or MI.

Adjusted Results

DES+C patients vs. DES-C patients had lower rates of death, non-fatal MI, and death or MI (Table 4; Figures 3A and 3B). Again, there were no differences between BMS+C vs. BMS-C patients for these events. With regard to DES+C vs. BMS+C, the DES+C group had significantly lower rates of death, and death or MI, but no statistically significant difference in non-fatal MI. Patients receiving DES+C vs. BMS-C had significantly lower rates of death, non-fatal MI, and death or MI.

Aspirin Subgroup Results

To assess whether aspirin use confounded the clopidogrel results, we analyzed the subset of patients who reported aspirin use at 6 months (Figures 4A and 4B). The adjusted cumulative mortality and death or MI figures in the aspirin cohort mimicked the results for adjusted outcomes in the 6 and 12 month landmark analyses, except that the event rates were lower. Compared to DES-C, patients with DES+C tended to have lower mortality (Figure 4A) and had lower rates of death or MI (Figure 4B). Thus, these results reinforce those observed in our overall analyses.

Comment

Our observational results suggest that patients who received long-term clopidogrel therapy following a percutaneous coronary intervention using at least one drug-eluting stent had a significantly improved prognosis compared with similar patients not receiving this therapy. Current FDA approved indications for clopidogrel following DES implantation call for 3 to 6 months of therapy, depending on the specific device used. Such regimens were shown to be safe and effective in the pivotal clinical trials for

the Cypher and Taxus stents when judged by one year outcomes.[19-21] Recently, several lines of evidence, including unpublished long-term follow-up from these same trials,[22] have suggested that DES use is associated with a late increased risk of catastrophic stent thrombosis at a rate significantly higher than with BMS. These data have led to speculation that DES may require protracted and possibly indefinite clopidogrel therapy. There are, however, no clinical trials that currently address the effectiveness of such a strategy or its required duration. Our study, therefore, provides new evidence that continued clopidogrel therapy conveys an important prognostic benefit after DES implantation. The absence of a similar benefit for BMS patients taking clopidogrel provides important reassurance that the differences observed in this study were not simply the effect of clopidogrel regimens extended in response to some unmeasured prognostic factors unrelated to type of stent. With 600,000 US hospitalized patients receiving stent devices each year,[23] the need for definitive evidence on this issue rises to the level of a public health crisis.

Our study results foster interesting hypotheses for future investigations. By simultaneously comparing patients in four treatment groups defined by stent type and clopidogrel use, we found that DES patients receiving clopidogrel six and twelve months after their initial procedure have significantly lower rates of death and death or MI than DES patients not receiving this medication. These results complement those from the PREMIER Registry[5] and, together with the CREDO trial,[24] suggest that all DES patients should continue to take clopidogrel for at least 12 months after PCI, and possibly indefinitely, while BMS may be a more appropriate stent choice for patients unable to take clopidogrel for an extended length of time. These possible benefits of clopidogrel appear to be maintained for at least 24 months; however, further research is required to determine the optimal duration of clopidogrel use in more clinically and angiographically complex patients than were enrolled in the pivotal DES clinical trials.

Limitations

There are two important caveats to this analysis. First, clopidogrel use was not randomly assigned. Thus, the decision to continue the drug beyond the periods recommended by the relevant clinical trials may have been correlated with unmeasured prognostic factors. However, in order for such confounding to create the appearance of better prognosis in the DES patients on clopidogrel, the bias in treatment selection would have to be towards use in lower risk patients, which is counterintuitive. Obvious biases, such as treatment of younger patients with less severe CAD or less major comorbidity were controlled for in this analysis. The second important caveat is that clopidogrel use in our analysis was identified by patient report at 2 discrete time points (6 and 12 months follow-up). Thus, these data are subject to recall bias. Further, the indications and rationale for long-term clopidogrel regimens and for its discontinuation were not collected. Because follow-up contacts did not necessarily occur at exactly 6 and 12 months, we used a 90 day window around the anniversary date to determine follow-up contact and medication use. Narrowing this window to 30 days produced outcomes with similar relationships.

The 24-month event rates of 0.0%for death, non-fatal MI, and death or MI for DES with clopidogrel in the 12 month landmark analysis underestimate the true event rates. However, 14 of the DES patients died or had a non-fatal MI and none of these 14 patients was in the DES+C group. We believe that our results along with those from BASKET-LATE serve to identify key parameters for subsequent research in this area.[25] Extended clopidogrel therapy has its own risks and our analysis does not evaluate the long-term non-fatal implications of its use. Other studies are required to assess relationships between long-term clopidogrel use and the risk for major bleeding events, the role for devices used to facilitate stent deployment in DES patients receiving long-term clopidogrel therapy, as well as relationships between target-vessel and non-target vessel stenosis in DES and BMS patients. If the use of DES is, "committing millions of patients to lifelong potent antithrombotic therapy,"[25] our society must consider how this therapy will be delivered to patients without adequate financial resources.

Conclusions

In a large consecutive cohort of contemporary patients receiving percutaneous coronary intervention, the long-term risk for death and major cardiac events was significantly increased among DES patients who had discontinued clopidogrel therapy at six or twelve months. Extended duration clopidogrel therapy following drug-eluting stent implantation was associated with a lower incidence of death or myocardial infarction, a finding that has immediate implications for clinical practice. We propose a three-arm clinical trial to further investigate these results. Patients in two arms would be randomized to discontinue clopidogrel therapy at 12- and 24-months after DES implantation; whereas, patients in the third arm would continue clopidogrel through three years of follow-up. A sample size of approximately 10,000 patients would be required to detect a 25% reduction in death or MI at three years.

Author Contributions

Dr. Eisenstein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Eric Eisenstein and Kevin Anstrom contributed equally to this work and share the lead authorship of this manuscript.

Study concept and design: Eisenstein, Anstrom, Kong, Shaw, Califf.

Acquisition of data: Anstrom, Shaw, Califf.

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Table 1. 6-month landmark view: baseline patient characteristics and longitudinal medication use

	DES* + Clopidogrel (n=637)	DES – Clopidogrel (n=579)	BMS† + Clopidogrel (n=417)	BMS – Clopidogrel (n=1976)	P-Value
No. (%) of Participants‡					
Age, years	61 (53, 71)	60 (53, 70)	61 (53, 70)	61 (52, 71)	0.73
Black race	121 (19.0)	137 (23.7)	82 (19.7)	395 (20.0)	0.18
Male	398 (62.5)	368 (63.6)	266 (63.8)	1233 (62.4)	0.93
History of diabetes	171 (26.8)	171 (29.5)	121 (29.0)	449 (22.7)	0.001
History of CHF§	60 (9.6)	82 (14.5)	38 (9.3)	208 (11.0)	0.026
History of MI**	247 (38.8)	221 (38.2)	213 (51.1)	913 (46.2)	<0.001
Number of diseased vessels					<0.001
1	370 (58.1)	356 (61.5)	275 (65.9)	1331 (67.4)	
2	186 (29.2)	178 (30.7)	109 (26.1)	531 (26.9)	
3	81 (12.7)	45 (7.8)	33 (7.9)	114 (5.8)	
Income per household ($1000)	36.5 (29.2, 41.7)	35.4 (29.3, 41.3)	35.1 (29.3, 40.6)	33.1 (29.3, 39.8)	<0.001
Average house value ($1000)	82.9 (59.5, 120.4)	82.6 (59.5, 105.7)	80.4 (61.5, 108.5)	75.7 (62.2, 96.0)	0.006
Aspirin use at:					
6 Months	600 (94.2)	430 (74.3)	360 (86.3)	1583 (80.1)	<0.001
12 Months	478 (91.2)	371 (86.3)	335 (84.0)	1569 (85.0)	0.003
24 Months	179 (93.2)	148 (85.6)	304 (82.2)	1541 (87.1)	0.003
Clopidogrel use at:					
6 Months	637 (100)	0 (0)	417 (100)	0 (0)	<0.001
12 Months	382 (72.9)	64 (14.9)	309 (77.4)	93 (5.0)	<0.001
24 Months	106 (55.2)	25 (14.5)	230 (62.2)	143 (8.1)	<0.001

*Drug eluting stent
†Bare metal stent
‡Categorical variables are presented as number (%) and continuous variables are presented as median (Q1, Q3)
§Congestive heart failure
**Myocardial infarction

Table 2. Unadjusted and adjusted 24-month outcomes based on 6-month patient-reported clopidogrel use

		Number of Events			
	# at risk at 6 months	Death	MI*	Death/ MI	# at risk at 24 months
DES+C†	637	7	5	11	290
DES-C‡	579	21	13	31	245
BMS+C§	417	16	5	21	387
BMS-C**	1976	88	28	115	1852

	Unadjusted Outcomes			Adjusted Outcomes		
	Death	MI	Death/ MI	Death	MI	Death/ MI
DES+C (%)	1.6	0.8	2.1	2.0	1.3	3.1
DES-C (%)	5.8	3.3	8.4	5.3	2.6	7.2
BMS+C (%)	3.9	1.2	5.1	3.7	1.7	5.5
BMS-C (%)	4.5	1.4	5.9	4.5	1.6	6.0
P-value (3df††)	0.002	0.088	<0.001	0.054	0.63	0.065
Interaction P-value‡‡ (1df)	0.043	0.054	0.007	0.18	0.31	0.12
DES+C – DES-C (%)	-4.2	-2.5	-6.3	-3.3	-1.3	-4.1
(95% Confidence Interval)	(-7.1, -1.4)	(-4.5, -0.5)	(-9.6, -3.1)	(-6.3, -0.3)	(-3.4, 0.8)	(-7.6, -0.6)
P-value (1df)	0.004	0.015	<0.001	0.031	0.24	0.021
BMS+C - BMS-C (%)	-0.6	-0.2	-0.7	-0.7	0.2	-0.5
(95% Confidence Interval)	(-2.7, 1.5)	(-1.4, 1.0)	(-3.1, 1.7)	(-2.9, 1.4)	(-1.6, 1.9)	(-3.2, 2.2)
P-value (1df)	0.60	0.74	0.55	0.50	0.86	0.70
DES+C - BMS+C (%)	-2.3	-0.4	-3.1	-1.7	-0.4	-2.4
(95% Confidence Interval)	(-4.6, -0.1)	(-1.7, 0.9)	(-5.6, -0.6)	(-4.2, 0.8)	(-2.6, 1.8)	(-5.6, 0.9)
P-value (1df)	0.044	0.52	0.017	0.18	0.72	0.16
DES-C - BMS-C (%)	1.3	1.9	2.5	0.8	1.0	1.2
(95% Confidence Interval)	(-1.4, 4.0)	(-0.1, 3.8)	(-0.7, 5.7)	(-1.8, 3.5)	(-0.6, 2.7)	(-1.8, 4.2)
P-value (1df)	0.34	0.061	0.12	0.55	0.22	0.44
DES+C - BMS-C (%)	-2.9	-0.6	-3.8	-2.5	-0.3	-2.9
(95% Confidence Interval)	(-4.4, -1.4)	(-1.5, 0.2)	(-5.4, -2.1)	(-4.4, -0.6)	(-1.8, 1.3)	(-5.3, -0.5)
P-value (1df)	<0.001	0.16	<0.001	0.011	0.76	0.017

*Non-fatal myocardial infarction
† Drug-eluting stent with clopidogrel use
‡Drug-eluting stent without clopidogrel use
§ Bare metal stent with clopidogrel use
** Bare metal stent without clopidogrel use
††Degrees of freedom
‡‡ Interaction between stent-type and clopidogrel use I

Table 3. 12-month landmark view: baseline patient characteristics and longitudinal medication use

	DES* + Clopidogrel (n=252)	DES – Clopidogrel (n=276)	BMS† + Clopidogrel (n=346)	BMS – Clopidogrel (n=1644)	P-Value
No. (%) of Participants‡					
Age, median (Q1,Q3)	61 (53, 70)	61 (53, 70)	62 (53, 72)	62 (53, 72)	0.76
Black race	36 (14.3)	62 (22.5)	69 (19.9)	310 (18.9)	0.12
Male	164 (65.1)	170 (61.6)	204 (59.0)	1031 (62.7)	0.45
History of diabetes	69 (27.4)	79 (28.6)	109 (31.5)	364 (22.1)	<0.001
History of CHF§	25 (10.0)	27 (10.0)	29 (8.5)	163 (10.0)	0.87
History of MI**	95 (37.7)	94 (34.1)	170 (49.1)	745 (45.3)	<0.001
Number of diseased vessels					
1	144 (57.1)	173 (62.7)	223 (64.5)	1130 (68.7)	<0.001
2	78 (31.0)	83 (30.1)	98 (28.3)	427 (26.0)	
3	30 (11.9)	20 (7.3)	25 (7.2)	87 (5.3)	
Income per household ($1000)	35.4 (29.3, 41.2)	36.0 (29.3, 41.2)	33.1 (29.3, 40.6)	33.1 (29.3, 39.8)	0.13
Average house value ($1000)	80.9 (59.5, 103.9)	82.9 (60.7, 105.9)	78.1 (60.6, 102.9)	75.7 (62.8, 95.5)	0.30
Aspirin usage at:					
6 Months	223 (88.5)	235 (85.1)	277 (80.1)	1373 (83.5)	0.045
12 Months	234 (92.9)	236 (85.5)	295 (85.3)	1398 (85.0)	0.011
24 Months	140 (94.0)	151 (86.8)	257 (81.1)	1360 (88.1)	<0.001
Clopidogrel use at:					
6 Months	218 (86.5)	68 (24.6)	271 (78.3)	74 (4.5)	<0.001
12 Months	252 (100)	0 (0)	346 (100)	0 (0)	<0.001
24 Months	104 (69.8)	14 (8.1)	221 (69.7)	85 (5.5)	<0.001

*Drug eluting stent
†Bare metal stent
‡Categorical variables are presented as number (%) and continuous variables are presented as median (Q1, Q3)
§Congestive heart failure
**Myocardial infarction

Table 4. Unadjusted and adjusted 24-month outcomes based on 12-month patient-reported clopidogrel use

	Number of Events				
	# at risk at 12 months	Death	MI*	Death/ MI	# at risk at 24 months
DES+C†	252	0	0	0	230
DES-C‡	276	10	4	14	244
BMS+C§	346	12	4	16	331
BMS-C**	1644	42	14	56	1596

	Unadjusted Outcomes			Adjusted Outcomes		
	Death	MI	Death/ MI	Death	MI	Death/ MI
DES+C (%)	0.0	0.0	0.0	0.0	0.0	0.0
DES-C (%)	3.8	1.6	5.4	3.5	1.0	4.5
BMS+C (%)	3.5	1.2	4.7	3.3	1.4	4.7
BMS-C (%)	2.6	0.9	3.4	2.7	0.9	3.6
P-value (3df††)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Interaction P-value ‡‡ (1df)	0.003	0.061	<0.001	0.012	0.13	0.003
DES+C - DES-C (%)	-3.8	-1.6	-5.4	-3.5	-1.0	-4.5
(95% Confidence Interval)	(-6.1, -1.5)	(-3.1, -0.0)	(-8.1, -2.6)	(-5.9, -1.1)	(-1.9, -0.1)	(-7.1, -1.9)
P-value (1df)	0.002	0.044	<0.001	0.004	0.047	<0.001
BMS+C - BMS-C (%)	0.9	0.3	1.2	0.6	0.4	1.0
(95% Confidence Interval)	(-1.2, 3.0)	(-0.9, 1.5)	(-1.2, 3.6)	(-1.5, 2.8)	(-1.1, 1.9)	(-1.6, 3.6)
P-value (1df)	0.39	0.63	0.32	0.57	0.60	0.44
DES+C - BMS+C (%)	-3.5	-1.2	-4.7	-3.3	-1.4	-4.7
(95% Confidence Interval)	(-5.4, -1.6)	(-2.3, -0.0)	(-6.9, -2.4)	(-5.3, -1.3)	(-2.8, 0.0)	(-7.1, -2.3)
P-value (1df)	<0.001	0.045	<0.001	0.002	0.056	<0.001
DES-C - BMS-C (%)	1.3	0.7	2.0	0.9	0.0	0.9
(95% Confidence Interval)	(-1.2, 3.7)	(-0.9, 2.3)	(-0.9, 4.9)	(-1.7, 3.4)	(-1.1, 1.1)	(-1.9, 3.6)
P-value (1df)	0.32	0.39	0.18	0.51	0.99	0.54
DES+C - BMS-C (%)	-2.6	-0.9	-3.4	-2.7	-1.0	-3.6
(95% Confidence Interval)	(-3.3, -1.8)	(-1.3, -0.4)	(-4.3, -2.5)	(-3.5, -1.9)	(-1.5, -0.5)	(-4.6, -2.7)
P-value (1df)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

*Non-fatal myocardial infarction
† Drug-eluting stent with clopidogrel use
‡Drug-eluting stent without clopidogrel use
§ Bare metal stent with clopidogrel use
** Bare metal stent without clopidogrel use
††Degrees of freedom
‡‡ Interaction between stent-type and clopidogrel use

Figure 1A. Diagram of 6-month landmark analysis

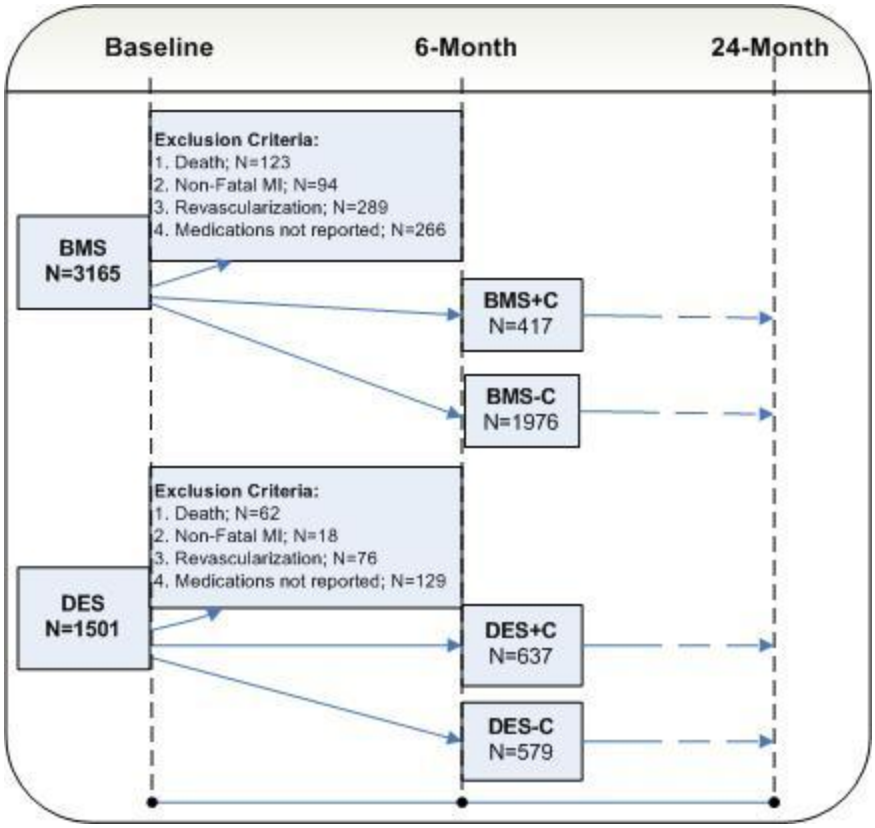


Figure 1B. Diagram of 12-month landmark analysis

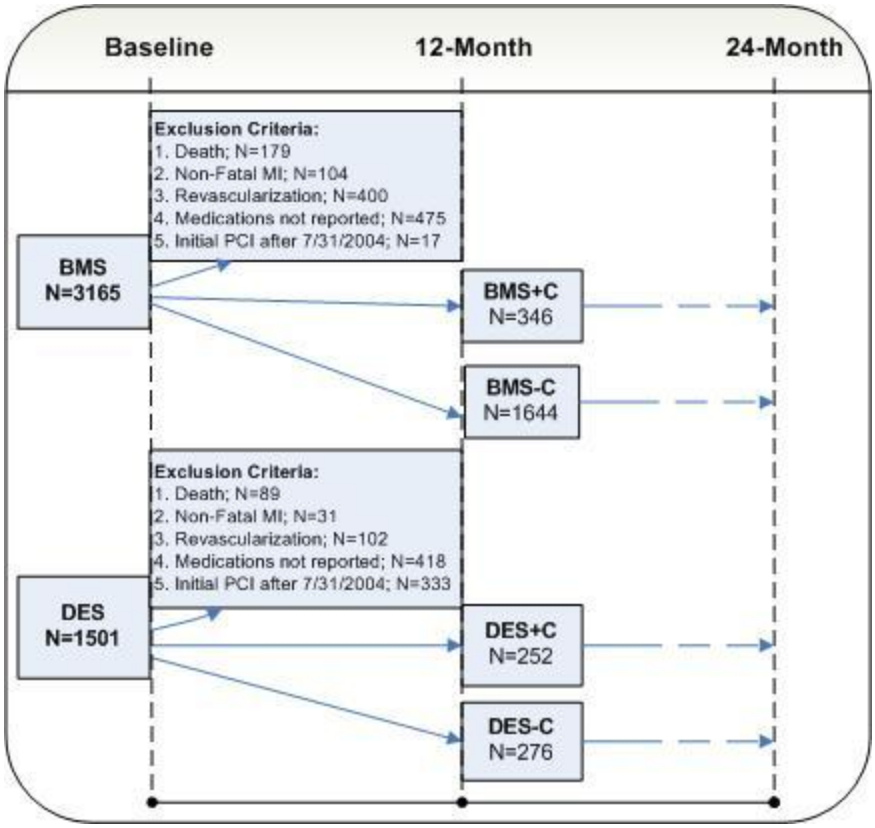
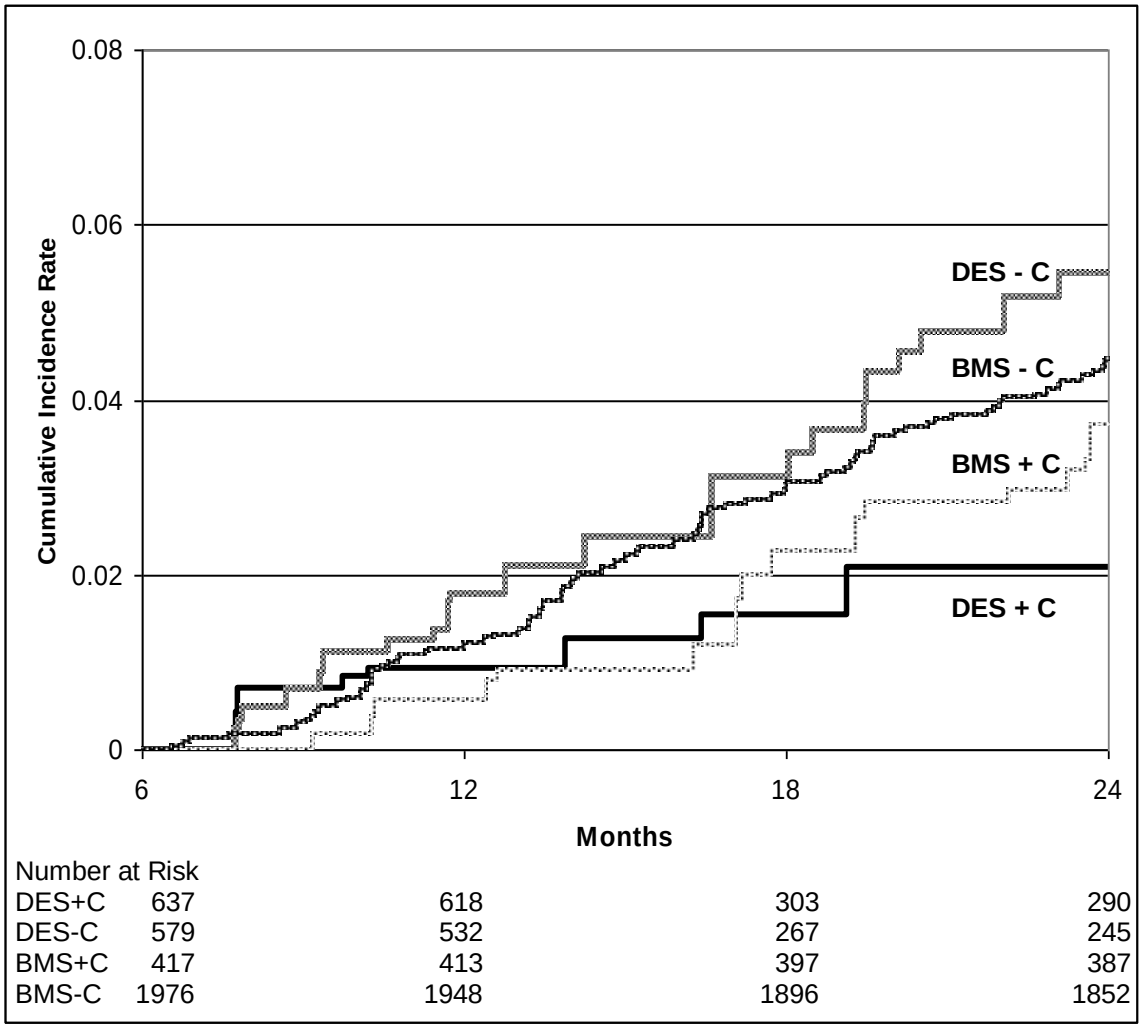
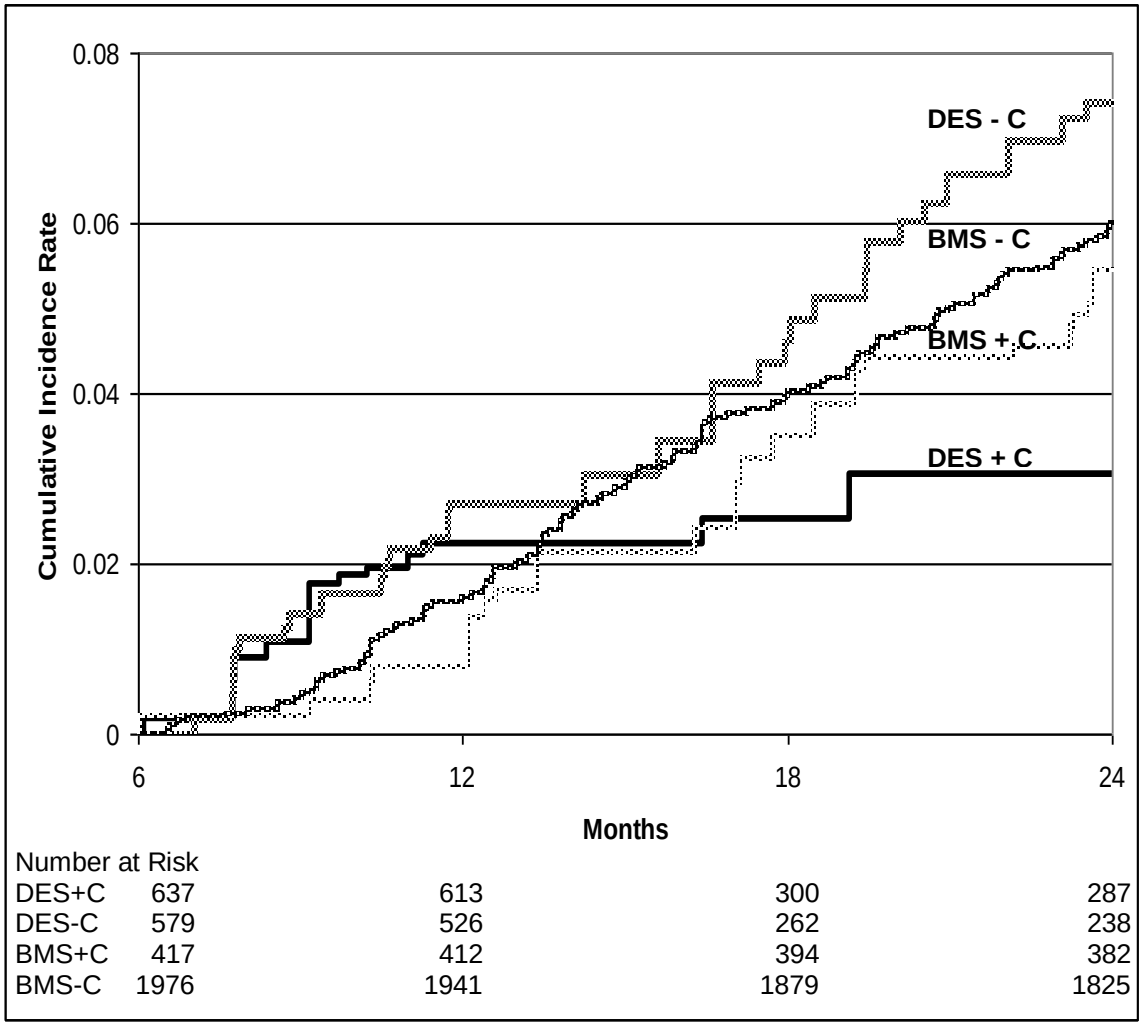


Figure 2A. Adjusted cumulative mortality rates using the 6-month landmark analysis



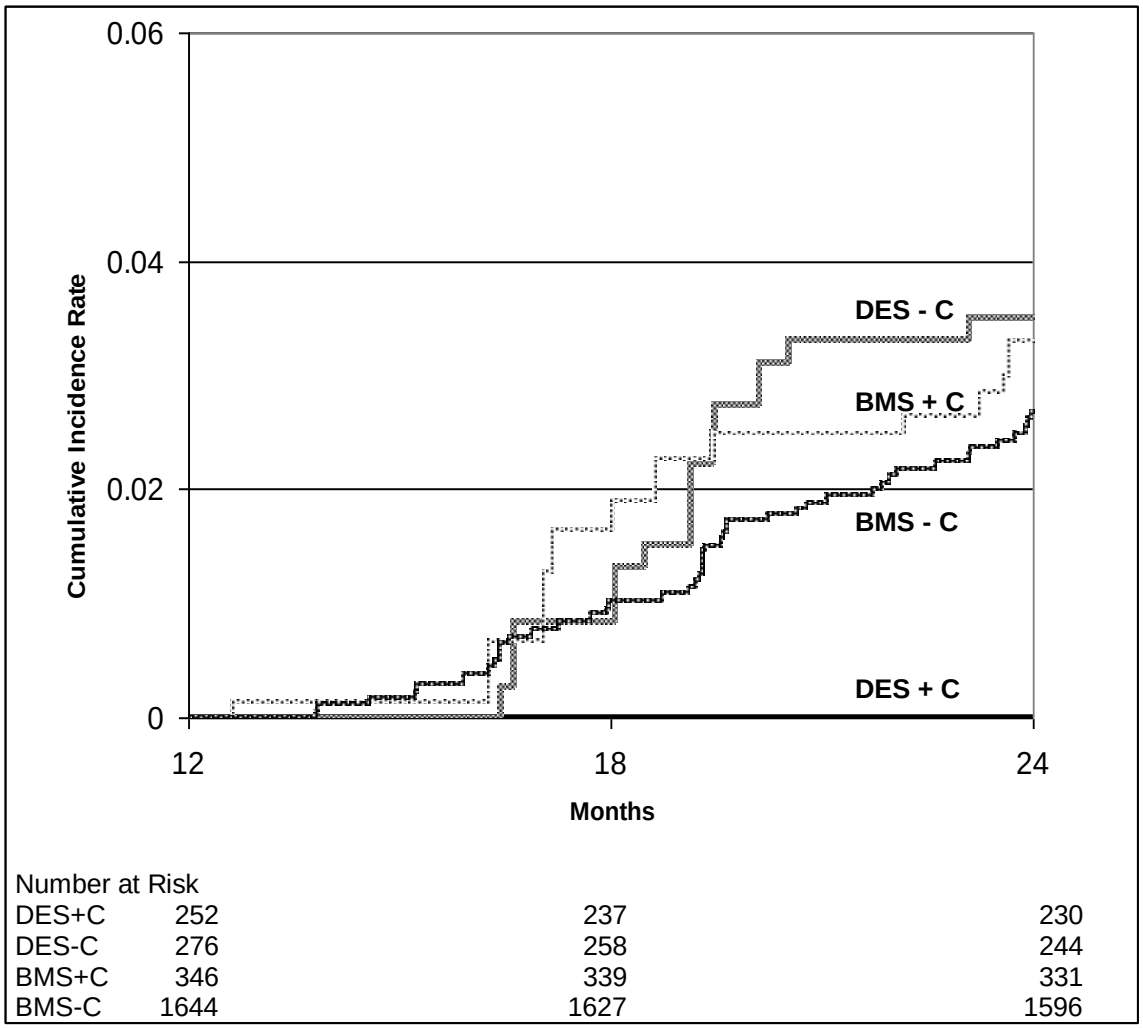
Number at Risk				
DES+C	637	618	303	290
DES-C	579	532	267	245
BMS+C	417	413	397	387
BMS-C	1976	1948	1896	1852

Figure 2B. Adjusted cumulative rates of composite death or myocardial infarction using the 6-month landmark analysis



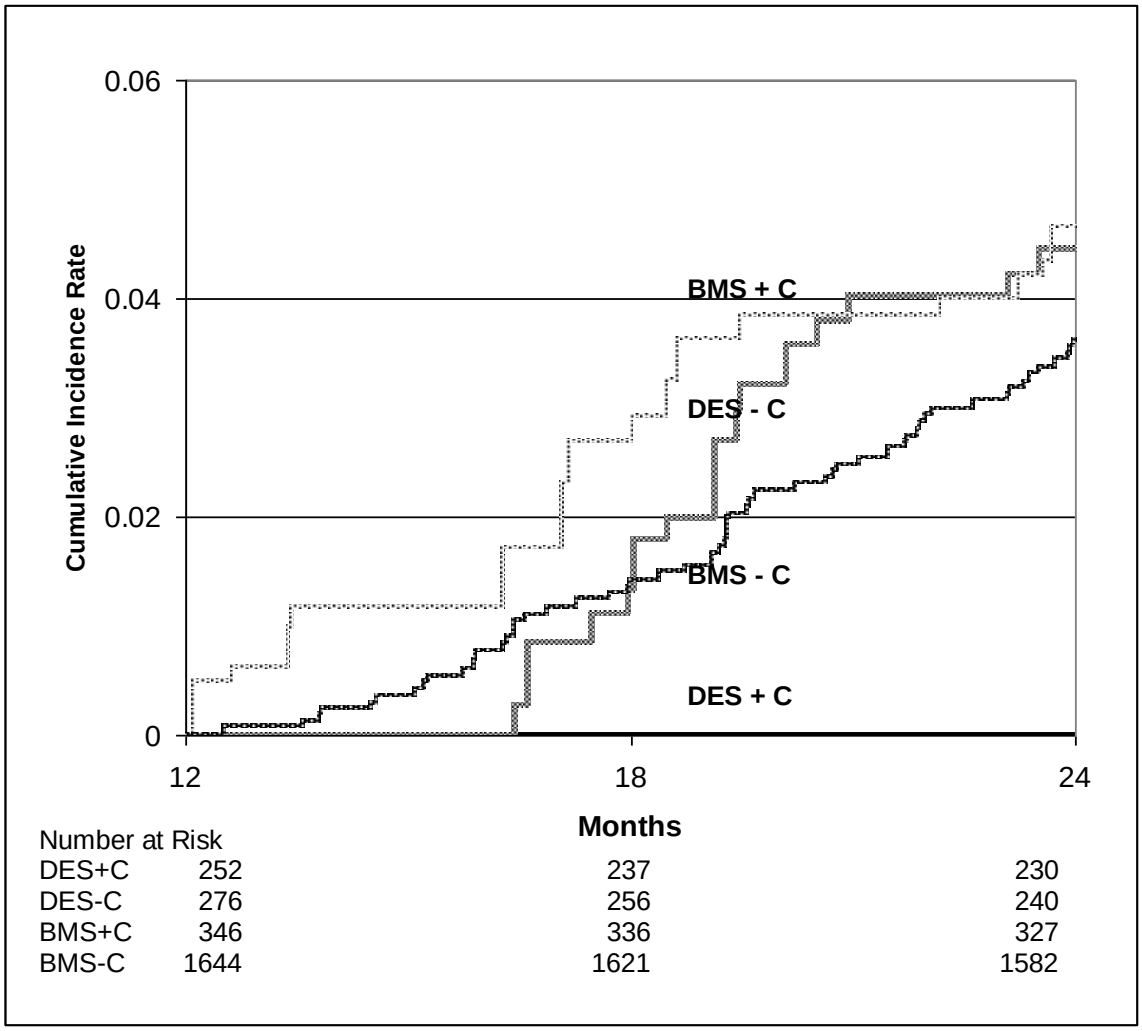
Number at Risk				
DES+C	637	613	300	287
DES-C	579	526	262	238
BMS+C	417	412	394	382
BMS-C	1976	1941	1879	1825

Figure 3A. Adjusted cumulative mortality rates using the 12-month landmark analysis



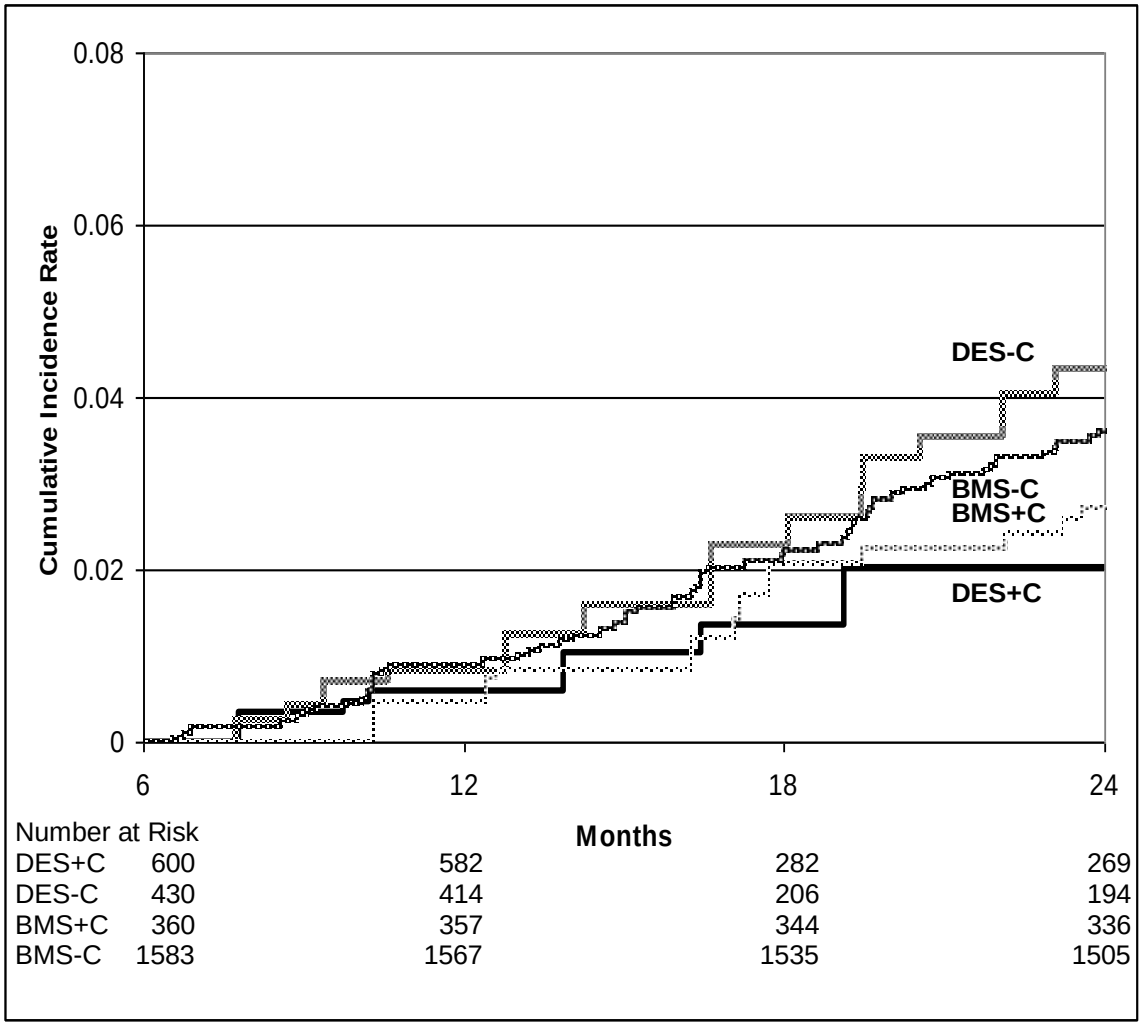
Number at Risk			
DES+C	252	237	230
DES-C	276	258	244
BMS+C	346	339	331
BMS-C	1644	1627	1596

Figure 3B. Adjusted cumulative rates of composite death or myocardial infarction using the 12-month landmark analysis



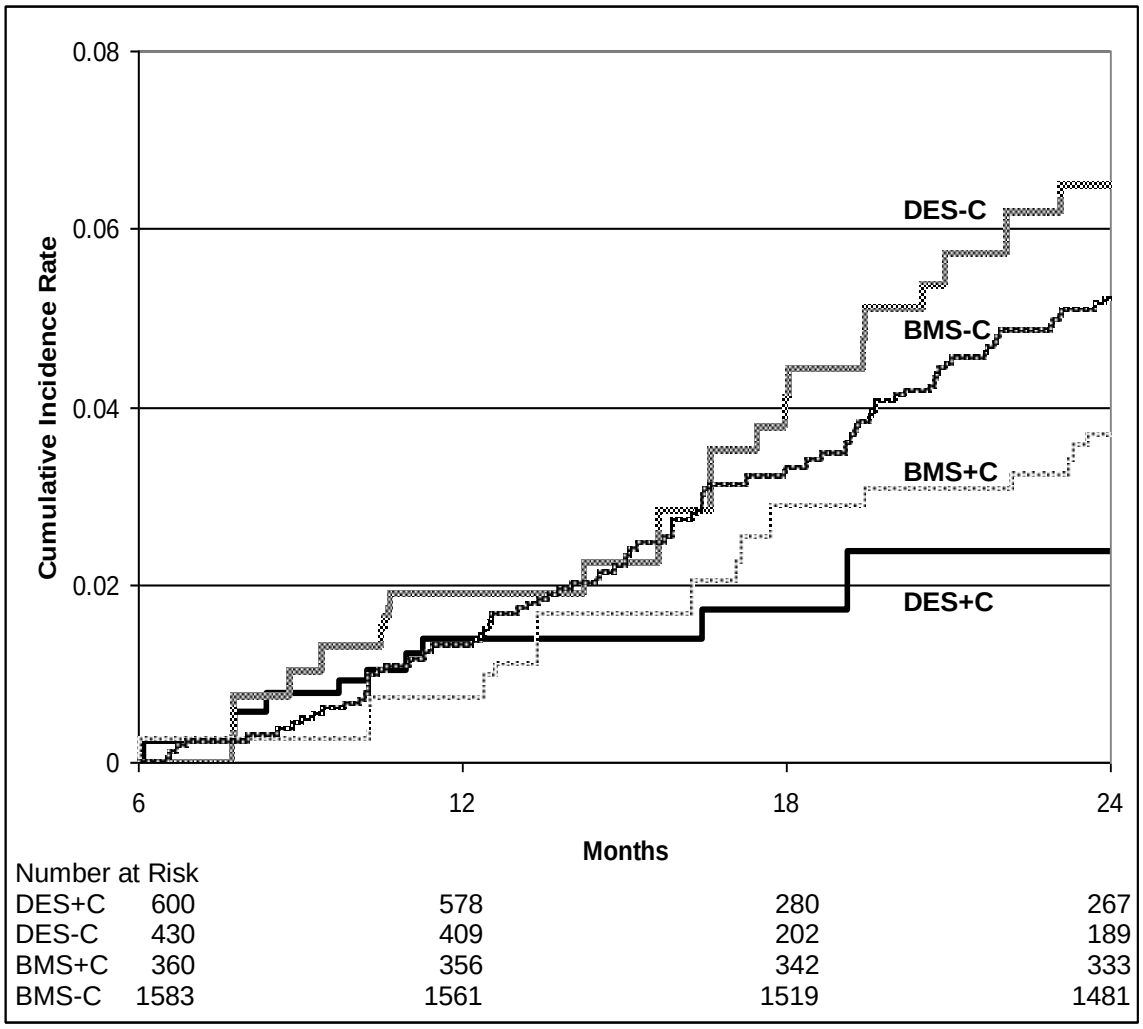
Number at Risk			
DES+C	252	237	230
DES-C	276	256	240
BMS+C	346	336	327
BMS-C	1644	1621	1582

Figure 4A. Aspirin subgroup: adjusted cumulative mortality rates using the 6-month landmark analysis



p-value for the DES+C vs. DES-C comparison is 0.099

Figure 4B. Aspirin subgroup: adjusted cumulative rates of composite death or myocardial infarction using the 6-month landmark analysis



Number at Risk				
DES+C	600	578	280	267
DES-C	430	409	202	189
BMS+C	360	356	342	333
BMS-C	1583	1561	1519	1481

p-value for the DES+C vs. DES-C comparison is 0.020