

Impact of Diabetes on Long-Term Outcome After Primary Angioplasty

Insights from the DESERT cooperation

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OBJECTIVE—Diabetes has been shown to be associated with worse survival and repeat target vessel revascularization (TVR) after primary angioplasty. The aim of the current study was to evaluate the impact of diabetes on long-term outcome in patients undergoing primary angioplasty treated with bare metal stents (BMS) and drug-eluting stents (DES).

RESEARCH DESIGN AND METHODS—Our population is represented by 6,298 ST-segment elevation myocardial infarction (STEMI) patients undergoing primary angioplasty included in the DESERT database from 11 randomized trials comparing DES with BMS.

RESULTS—Diabetes was observed in 972 patients (15.4%) who were older ($P < 0.001$), more likely to be female ($P < 0.001$), with higher prevalence of hypertension ($P < 0.001$), hypercholesterolemia ($P < 0.001$), and longer ischemia time ($P < 0.001$), and without any difference in angiographic and procedural characteristics. At long-term follow-up ($1,201 \pm 441$ days), diabetes was associated with higher rates of death (19.1% vs. 7.4%; $P < 0.0001$), reinfarction (10.4% vs. 7.5%; $P < 0.001$), stent thrombosis (7.6% vs. 4.8%; $P = 0.002$) with similar temporal distribution—acute, subacute, late, and very late—between diabetic and control patients, and TVR (18.6% vs. 15.1%; $P = 0.006$). These results were confirmed in patients receiving BMS or DES, except for TVR, there being no difference observed between diabetic and nondiabetic patients treated with DES. The impact of diabetes on outcome was confirmed after correction for baseline confounding factors (mortality, $P < 0.001$; repeat myocardial infarction, $P = 0.006$; stent thrombosis, $P = 0.007$; TVR, $P = 0.027$).

CONCLUSIONS—This study shows that among STEMI patients undergoing primary angioplasty, diabetes is associated with worse long-term mortality, reinfarction, and stent thrombosis in patients receiving DES and BMS. DES implantation, however, does mitigate the known deleterious effect of diabetes on TVR after BMS.

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Primary angioplasty currently represents the best reperfusion therapy for the treatment of ST-segment elevation myocardial infarction (STEMI) (1–2). Further improvement has been obtained by optimization of antithrombotic therapies and adjunctive mechanical devices (3–5). Special attention has been given in the last years to diabetes, because it has been associated with higher rates of impaired reperfusion, mortality, and target vessel revascularization (TVR) after primary angioplasty (6–8). In fact, even though bare metal stents implantation (BMS) has reduced the occurrence of restenosis as compared with balloon angioplasty in selected STEMI patients (9,10), the results seem to be worse in unselected populations (11,12), especially among diabetic patients (13–15). Drug-eluting stents (DES) have been shown in several randomized trials to reduce restenosis and TVR in both elective (16,17) or STEMI patients (18,19) compared with BMS. However, concerns have emerged on the potential higher risk of stent thrombosis and death with DES (20,21), which might be even more pronounced among STEMI patients (22,23). Few data have been reported on the impact of diabetes on long-term outcome with both BMS and DES in STEMI; therefore, that was the aim of the current study.

RESEARCH DESIGN AND METHODS

Our population is represented by STEMI patients included in the DESERT cooperation. Detailed data have been previously described (19). Briefly, we collected data from 11 randomized trials on DES in STEMI, including baseline characteristics (age, gender, diabetes, hypertension, hypercholesterolemia, smoking, previous revascularization, infarct location, ischemia time) and major angiographic variables (preprocedural thrombolysis in myocardial infarction [TIMI] flow, infarct-related artery, postprocedural TIMI flow, use of Gp IIb/IIIa inhibitors), and complete follow-up data, such as mortality, reinfarction, TVR, and stent thrombosis (defined according to Academic Research Consortium definite or

probable definition). A temporal analysis was performed for stent thrombosis events that were divided into four groups: acute (within 24 h); subacute (between 24 h and 30 days); late (between 1 and 12 months); and very late (later than 12 months of follow-up).

Statistical analysis

Statistical analysis was performed with the SPSS 15.0 statistical package. Continuous data were expressed as mean \pm SD and categorical data as percentage. The ANOVA was appropriately used for continuous variables. The χ^2 test or the Fisher exact test was used for categorical variables. The differences in event rates between groups during the follow-up period were assessed by the Kaplan-Meier method using the log-rank test. Cox proportional hazards method analysis was used to calculate relative risks adjusted for differences in baseline clinical and

angiographic characteristics that were all entered in block.

RESULTS

Patient population

Our population is represented by 6,298 STEMI patients. Diabetes was observed in 972 (15.4%) patients. As shown in Table 1, patients with diabetes were older (63 ± 11.4 vs. 60.2 ± 12 years; $P < 0.001$), more likely to be female (71.6% vs. 77.6%; $P < 0.001$), and more likely to have hypertension (61% vs. 40.5%; $P < 0.001$), hypercholesterolemia (53.6% vs. 34.6%; $P < 0.001$), and longer ischemia time (358 ± 258 vs. 264 ± 199 min; $P < 0.001$). No difference was observed in terms of angiographic and procedural characteristics. Almost 50% of patients underwent PCI of left anterior descending artery. Glycoprotein IIb-IIIa inhibitors were equally administered in both

groups (71.9% vs. 69.9%), as much as statin therapy at discharge (96.5% vs. 95.1%). As reported in Table 1, diabetic patients were less often using clopidogrel at follow-up.

Diabetes and long-term outcome

Follow-up data were available at a mean of $1,201 \pm 441$ days. At long-term follow-up, diabetes was associated with a significantly higher rate of death (19.1% vs. 7.4%; hazard ratio [HR] 2.38 [95% CI 1.97–2.93]; $P < 0.0001$) (Fig. 1) and reinfarction (10.4% vs. 7.5%; HR 1.58 [1.23–2.04]; $P < 0.001$) (Fig. 1), stent thrombosis (7.6% vs. 4.8%; 1.573 [1.17–2.11]; $P = 0.002$) (Fig. 2), with similar temporal distribution (acute, subacute, late, and very late) between diabetic and control patients (Fig. 3) and TVR (18.6% vs. 15.1%; 1.28 [1.07–1.52]; $P = 0.006$) (Fig. 2). These results were confirmed in patients receiving BMS or DES, except for TVR, in which no difference was observed between diabetic and nondiabetic patients treated with DES (Fig. 2).

The impact of diabetes on outcome was confirmed after correction for baseline confounding factors (age, gender, hypertension, hypercholesterolemia, ischemia time) (mortality: HR 1.76 [95% CI 1.35–2.29]; $P < 0.001$; reinfarction: 1.48 [1.12–1.97]; $P = 0.006$; stent thrombosis: 1.5 [1.12–2.02]; $P = 0.007$; TVR: 1.22 [1.02–1.46]; $P = 0.027$).

CONCLUSIONS—The main finding of the current study was that diabetes was associated with a significantly higher mortality, reinfarction, TVR, and stent thrombosis. These results were similarly observed among patients treated with BMS or DES, except for TVR, in which no difference was observed among patients treated with DES.

Several studies have demonstrated that hyperglycemia at admission, even independently from the presence of diabetes (stress hyperglycemia), is associated with larger infarct size and higher mortality in patients with STEMI (24–28). In fact, several in vitro and in vivo experiments have shown that hyperglycemia may be involved in the reperfusion injury (29–34). Acute hyperglycemia increases intercellular adhesion molecule-1 levels (29), which could augment plugging of leukocytes in the capillaries (30). Hyperglycemia also may augment thrombus formation. Blood glucose has been demonstrated to be an independent predictor of platelet-dependent thrombosis,

Table 1—Patient characteristics according to diabetes

Variables	Diabetes (n = 972)	Control (n = 5,326)	P
Age (years) mean \pm SD	63 \pm 11.4	60.2 \pm 12	<0.001
Sex (%)	71.6	77.6	<0.001
Hypertension (%)	61	40.5	<0.001
Hypercholesterolemia (%)	53.6	34.6	<0.001
Symptom onset to balloon time (min), mean \pm SD	358 \pm 258	264 \pm 199	<0.001
Preprocedural TIMI flow (%)			
0–1	63.6	66.8	0.11
2	15.2	14.6	
3	21.2	18.6	
Postprocedural TIMI 3 flow (%)	89.4	90.7	0.22
DES (%)	63.4	63.2	0.9
Type of DES (%)			
Cypher	28.3	26.4	0.2
Taxus	70.7	72.5	
Endeavor	1.0	1.1	
Glycoprotein IIb-IIIa inhibitors (%)	71.9	69.9	0.24
Infarct-related artery (%)			
LM	0.1	0.2	0.31
LAD	46.4	42.9	
AL	0.1	0.1	
LCX	12.5	13.4	
RCA	38.9	42.4	
Graft	0.1	0.1	
Statins at discharge (%)	96.5	95.1	0.13
DAT at follow-up (%)			
6 months	91	92.6	0.092
12 months	58.5	64.5	0.001
24 months	20.4	16.1	0.002
36 months	15.4	12.1	0.007

DAT, dual antiplatelet therapy; Dg, diagonal branch; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; RCA, right coronary artery.

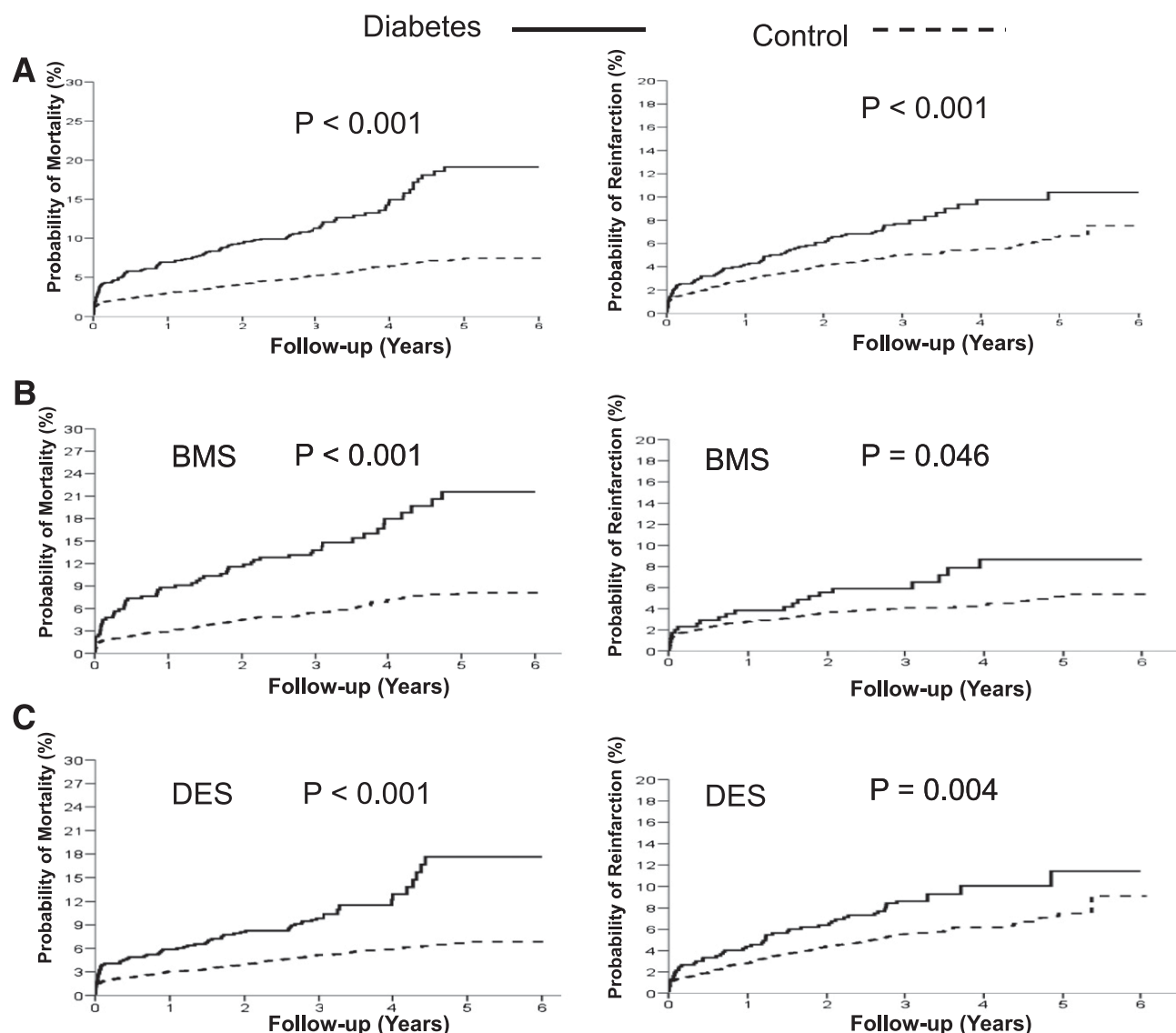


Figure 1—Kaplan-Meier survival curves show the impact of diabetes on survival (left graphs) and reinfarction (right graphs) in the overall population (A), in patients with BMS (B), and in patients with DES (C).

even in the normal range (31). A recent study suggested that a microthrombus in the capillaries play a crucial role in the no-reflow phenomenon after STEMI (32).

In a recent report, De Luca et al. (7) found that among patients treated with glycoprotein IIb/IIIa inhibitors, diabetes was associated with higher occurrences of distal embolization and impaired myocardial reperfusion and higher mortality.

However, diabetes is associated with a significantly higher rates of restenosis (13,14). In a previous report, De Luca et al. (35) found that BMS did not provide significant benefits in outcome as compared with balloon angioplasty in unselected diabetic patients undergoing primary angioplasty. The recent introduction

of DES certainly has reduced the risk of restenosis, which may be counterbalanced by a higher rate of late in-stent thrombosis, especially among STEMI. Few data have been reported regarding diabetic patients with STEMI in the era of DES. A recent individual patient data meta-analysis showed that among STEMI diabetic patients undergoing primary angioplasty, the use of DES was safe and associated with a significant reduction in TVR at 1-year follow-up. However, a late catch-up phenomenon in terms of restenosis has been described with a potential risk of late in-stent thrombosis. A subanalysis of the PASEO trial showed that at 5-year follow-up, diabetes was associated with a significantly worse outcome with both DES and BMS (36,37).

However, diabetes did not affect the long-term occurrence of TVR among patients treated with DES.

This is first large report on the impact of diabetes on long-term outcome of STEMI patients undergoing primary angioplasty with BMS or DES. We found that diabetes was associated with significantly higher mortality, reinfarction, and in-stent thrombosis, irrespective of DES or BMS. However, although diabetes was associated with a significantly higher rate of TVR among patients treated with DES, it did increase TVR among patients treated with DES. A similar temporal distribution was observed in terms of stent thrombosis between diabetic and control patients with both BMS and DES.

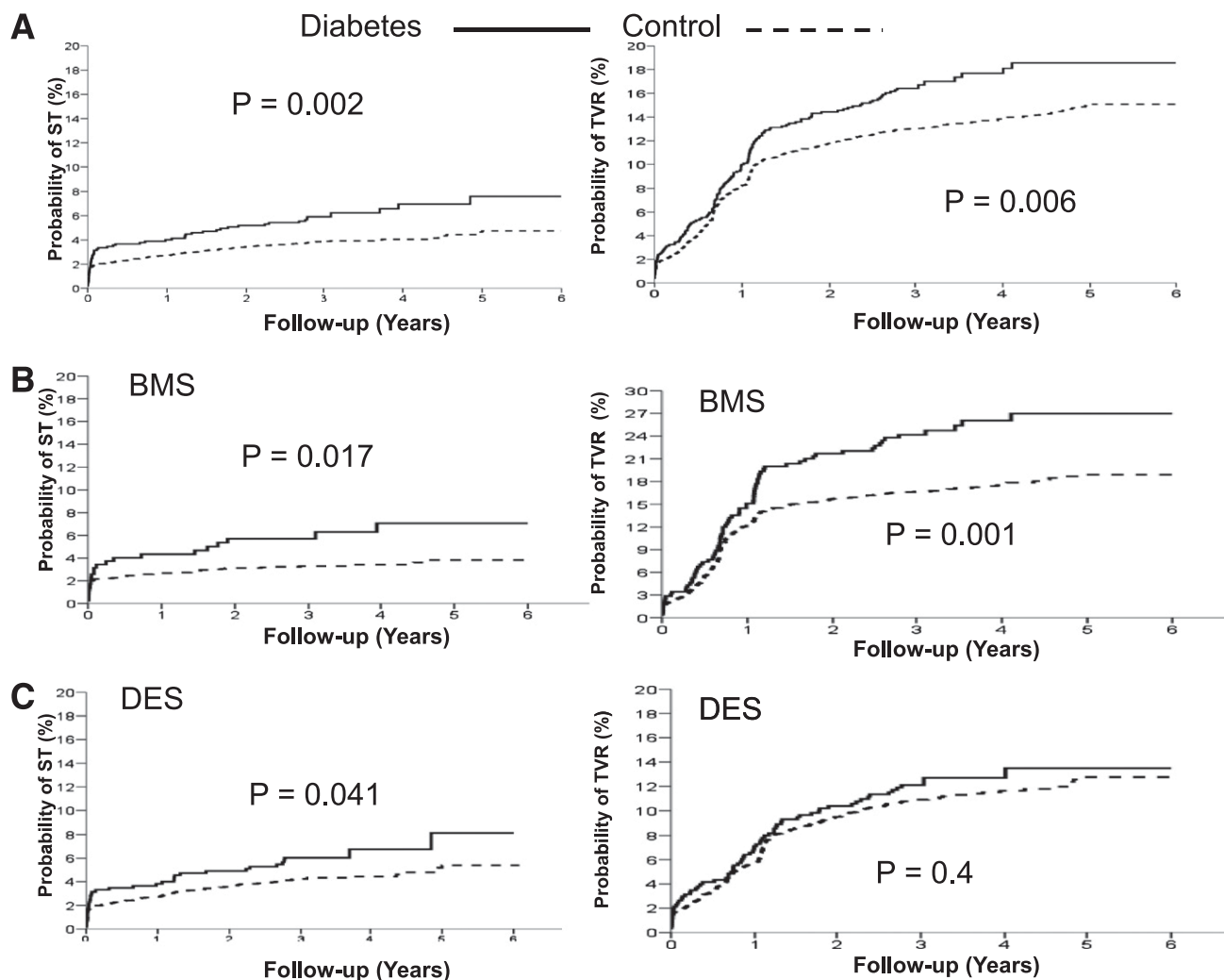


Figure 2—Kaplan-Meier survival curves show the impact of diabetes on event-free survival from stent thrombosis (ST; left graphs) and TVR (right graphs) in the overall population (A), in patients with BMS (B), and in patients with DES (C).

Limitations

Our patients were enrolled in randomized trials, and few patients had cardiogenic shock. Thus, the conclusion of this meta-analysis cannot be extended to all patients undergoing primary PCI for STEMI. The results of the current analysis apply only to sirolimus-eluting stent and paclitaxel-eluting stent because substantial randomized studies in STEMI have not yet been performed with newer DES. Admission glucose and HbA1c levels that have been shown as major determinants of outcome in STEMI patients were not routinely collected. Data regarding the duration of diabetes and the therapeutic regimen were not available, and the type of diabetes was not uniformly defined among studies (IDDM/NIDDM in some or any insulin-requiring diabetes in some others). Therefore, the prognostic impact of such variables could not be analyzed.

Finally, the levels of LDL, triglyceride, and BMI were not collected in our database. Their availability certainly would have improved our results.

Conclusion

This study shows that among STEMI patients undergoing primary angioplasty, diabetes is associated with worse long-term mortality, reinfarction, and in-stent thrombosis, even with DES implantation, which was able to overcome the known deleterious effect of diabetes on TVR. Diabetes did not impact on the temporal distribution of stent thrombosis events with BMS and DES.

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G.D.L. and G.W.S. conceived and designed the study. G.D.L. performed statistical analysis and drafted the manuscript. G.D.L., M.T.D., C.S., H.K., M.S., L.T., B.v.d.H., M.A.V., C.K., C.M., T.C., G.S., L.S.D.d.I.L., V.P., E.D.L., R.V., H.S., and G.W.S. interpreted data. M.T.D., C.S., H.K., M.S., L.T., B.v.d.H., M.A.V., C.K., C.M., T.C., G.S., L.S.D.d.I.L., V.P., E.D.L., R.V., H.S., and G.W.S. performed critical revision of the manuscript for important intellectual content of the article. G.D.L. had full access to the data and takes full responsibility for this work as a whole, including the study design and the decision to submit and publish the manuscript.

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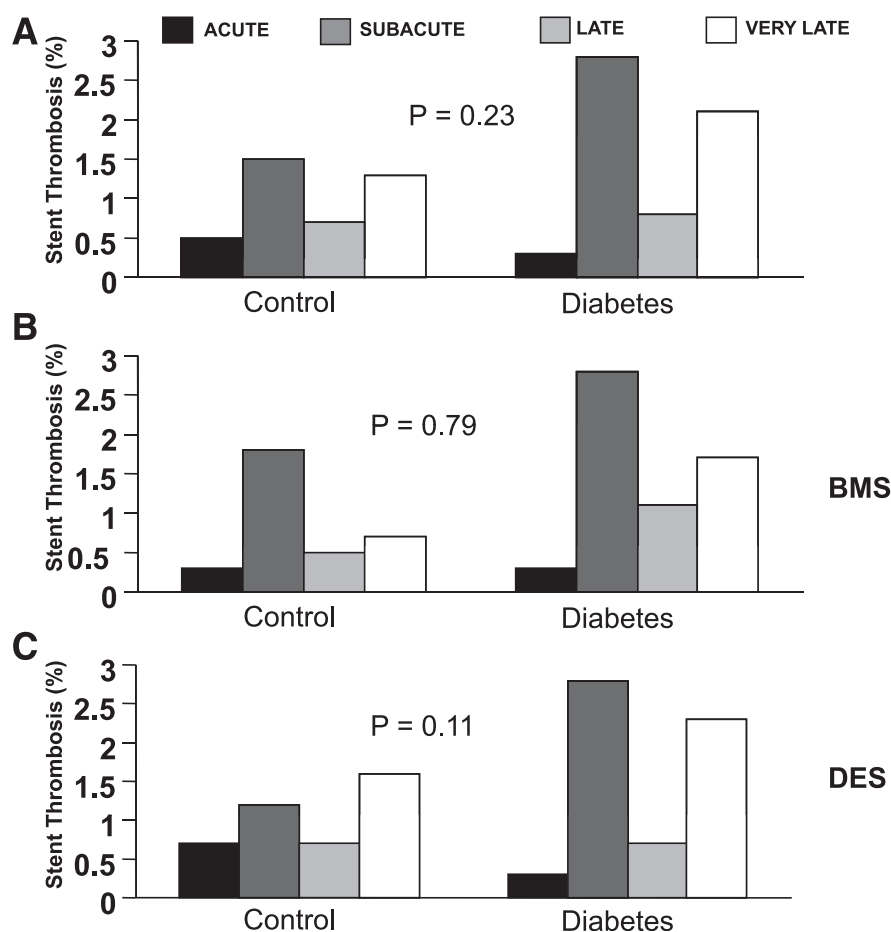


Figure 3—Bar graphs show time distribution of stent thrombosis in overall population. BMS Kaplan-Meier survival curves show the impact of diabetes on event-free survival from stent thrombosis in overall population (A), in patients with BMS (B), and in patients with DES (C).

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