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Incidence of Thrombotic Occlusion and Major Adverse Cardiac Events Between Two and Four Weeks After Coronary Stent Placement: Analysis of 5,678 Patients With a Four-Week Ticlopidine Regimen

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OBJECTIVES We attempted to make a comprehensive assessment of the risk of stent failure (death, myocardial infarction or angiographically documented occlusion), differentiating early (first and second weeks) and late (third and fourth weeks) events.

BACKGROUND The risk of stent failure decreases rapidly within the first week. It has been suggested that the risk rate for late events is close to 0% and that the thienopyridine regimen (ticlopidine or clopidogrel) could be safely reduced from four to two weeks, minimizing the risk of hematological complications.

METHODS We analyzed 5,678 patients with successful coronary stent placement and a four-week ticlopidine regimen.

RESULTS The rate of stent failure was 2.5% at four weeks, with 112 early (2.0%) and 30 late events (0.5%). Multivariate analysis identified different risk factors for early versus late events. While variables on stenosis severity and procedural results that can be influenced by the operator were identified as independent risk factors for early events (percent stenosis before and after the procedure, residual dissection, length of stented segment), more clinical variables were associated with late events (age, reduced left ventricular function, systemic hypertension as a protective factor). The late-event rate was <0.1% in the absence of these factors, but it was 2.5% with all three risk factors present.

CONCLUSIONS The risk of late stent failure is low with a four-week ticlopidine regimen. However, high-risk subgroups have a risk of 2.5%. As this rate is presumably higher if thienopyridines are discontinued after two weeks, these data suggest that a risk stratification to a two- or four-week regimen is preferable to a general reduction. (J Am Coll Cardiol 2001;37: 2066–73) © 2001 by the American College of Cardiology

The frequency of thrombotic stent occlusion and associated major adverse cardiac events has been dramatically reduced by the introduction of a combined antiplatelet regimen with aspirin and ticlopidine (1–4). In the four pivotal randomized trials proving efficacy, ticlopidine was given for at least four weeks, in parallel with the previous standard antithrombotic regimen of anticoagulation with aspirin plus warfarin. In general, the risk of stent occlusion is particularly high during the first four days (5), with a substantial decrease afterwards. In view of this decreasing risk, the necessary length of therapy has been disputed, and a two-week regimen has been suggested (6,7). The predominant concern is the frequent side effects of ticlopidine. Diarrhea, nausea, vomiting and skin rashes are fairly frequent. The most serious side effects, however, are neutropenia, which probably occurs in approximately 1% of patients who have had a four-week therapy (1,3,8–10) and, less frequently, thrombocytopenia and thrombotic thrombocytopenic purpura (11). Recently, ticlopidine has widely been replaced by clopidogrel, a newer thienopyridine derivative, after several studies have revealed a more favorable safety profile than ticlopidine (10,12–14). Then again, serious safety issues about clopidogrel therapy have been raised recently (15,16), although the risk appears to be much lower than it is with ticlopidine. The interest in limiting the length of thieniopyridine therapy in general was further promoted by the results of several nonrandomized trials. These indicated that the discontinuation of either ticlopidine (6,7) or clopidogrel (17) after only two weeks of therapy was associated with a very low frequency of stent thrombosis and associated adverse cardiac events.

However, several issues arise with all these modifications, initially pursued to lower the approximately 1% rate of severe hematologic side effects with a four-week ticlopidine regimen. The requirement for thienopyridine therapy during the first two weeks appears to be undisputed, by contrast with the second two weeks of therapy. During this period, the risk of stent occlusion appears to be low, perhaps close to zero. However, the precise incidence of late stent failure has not been determined in a large population receiving thienopyridine therapy, and a comprehensive analysis of risk factors for late events is lacking. Such data might allow

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Abbreviations and Acronyms

ATLAST	= Antiplatelet Therapy versus Antiplatelet Therapy Alone in Patients at Increased Risk of Stent Thrombosis trial
CART	= classification and regression tree
FANTASTIC	= Full Anticoagulation Versus Aspirin and Ticlopidine study
ISAR	= Intracoronary Stenting and Antithrombotic Regimen trial
LV	= left ventricle or left ventricular
MATTIS	= Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting
MI	= myocardial infarction

differentiation between groups of patients with higher or lower risks, leading to a differential approach and stratification. Furthermore, the risk-benefit calculation for a four-week versus a two-week regimen might lead to different results for clopidogrel, considering its more favorable side-effect profile and its presumably comparable cardiac efficacy.

We performed this retrospective study to determine the risk of stent failure with a focus on late events during the second two weeks and the identification of independent risk factors for late stent failure. In this analysis, we included all patients who were treated at our institutions and received a four-week ticlopidine regimen.

METHODS

Patient population. This study analyzed 5,678 successful stent-placement procedures having post-procedural combined antiplatelet regimens of aspirin and ticlopidine for four weeks' duration. This analysis comprised all procedures performed at our institutions from the beginning of 1994 to the end of 1999, excluding only patients with coumadin treatment and patients in cardiogenic shock before the procedure. These were excluded from the analysis because their clinical course is multifactorial. Procedural success was defined by a residual stenosis <30% and distal Thrombolysis in Myocardial Infarction (TIMI) grade flow ≥2. A residual dissection did not constitute failure if flow remained stable at TIMI grade 3. Procedures with final TIMI flow grade 2 were judged to be successful only if there was no visible residual dissection and pre-procedural flow had been TIMI grade 0 to 1.

Stent placement and post-procedural management. No additional alternative technique was used before (i.e., rotablator, laser or other debulking devices) or after stenting (i.e., intracoronary radiation therapy). During the intervention, patients received heparin (12,000 to 15,000 IE intraarterially) and aspirin (500 mg intravenously). Stent implantation of either a slotted-tube or multicellular type was performed either as loose stents firmly hand-crimped onto conventional angioplasty balloon catheters (n = 4,080) or pre-mounted on their commercially available delivery systems (n = 1,598). Various stent types were used: Multi-Link stent (n = 1,428; ACS-Guidant, Temecula, California), Inflow stent (n = 1,334; Inflow Dynamics, Munich, Germany), Palmaz-Schatz stent (n = 1,051; Johnson & Johnson Interventional Systems, Warren, New Jersey), Jostent (n = 735; JOMED, Rangendingen, Germany), Pura-A (n = 451; Devon Medical, Hamburg, Germany), NIR stent (n = 308; Scimed-Boston Scientific, Maple Grove, Minnesota) and several other types in <60 procedures (total n = 371). Procedural results were assessed by angiography only; no intravascular ultrasound studies were utilized. All patients were given ticlopidine (250 mg twice a day, Tiklyd, Sanofi-Winthrop, Munich, Germany) for four weeks in addition to aspirin (100 mg twice a day, indefinitely). Most patients received a loading regimen for ticlopidine with three doses of 500 mg, started as early as possible before or immediately after the intervention (<30 min after the procedure). The study period comprises the introduction of glycoprotein IIb/IIIa inhibitors. Overall, abciximab was administered in 1,943 procedures (34.2%); it increased from 7.4% in the first year to 64.8% in the last year to become routine for patients with acute coronary syndromes, with visible intracoronary thrombi, or with flow-limiting dissections or occlusion during the procedure.

A complete 30-day follow-up is available for all procedures; all patients were seen as outpatients one month after discharge or contacted by telephone.

Definitions. "Stent failure" was defined as either death, myocardial infarction (MI) (episode of typical chest pain, new pathological Q waves or creatine kinase rise >3 times the upper limit of normal [>240 U/l] with concomitant increase of the MB isoenzyme) or angiographically documented stent vessel occlusion. These events were differentiated as "early" if they occurred within the first 14 days and "late" for events during days 15 to 30. A "reduced left ventricle (LV) function" was defined as an ejection fraction <50%. The "length of stented segment" was the sum of the length of all stents implanted in the coronary segment. A "residual dissection" was noted by the operator at the end of the procedure in the presence of a dissection >5 mm in the stented or adjacent segment. In this setting, the procedure was considered successful only if flow was TIMI grade 3.

Data analysis and statistics. Quantitative angiographic analysis was performed off-line on a commercially available system with edge detection algorithms (CMS, Medis Medical Imaging Systems, Nuenen, The Netherlands) by trained technicians not involved in the procedures. Data were continuously assessed and entered into a relational database. Clinical data were recorded to define procedures; angiographic data were assessed for individual lesions treated during a procedure.

Analyses were performed with S-Plus software (MathSoft, Seattle, Washington), expanded by a function library by Harrell (18). Statistical significance was assumed at $p < 0.05$. The risk of stent failure was analyzed per logistic regression analysis; all factors with p value <0.10 by univariate comparison were entered into this analysis. Rel-

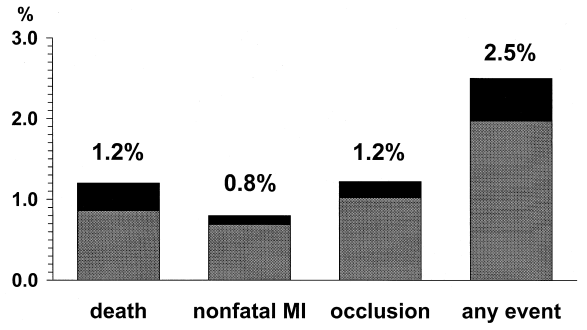

Figure 1. Cumulative event rates during the first 30 days after the procedure. **Hatched box** = early events (days 1 to 14); **black box** = late events (days 15 to 30). MI = myocardial infarction.

ative risks were computed for significant correlates; for continuous variables, these were calculated for the first versus the third quartile. For interventions in more than one lesion, angiographic variables of one randomly assigned lesion were entered into the analysis. Detailed subgroup analysis and stratification in different risk subsets were made using the classification and regression tree (CART) (19), which was based only on independent factors by logistic regression analysis to reduce the possibility of an interplay of the risk factors.

RESULTS

During the follow-up of 30 days, 142 events of stent failure were observed (2.5%): 112 during the first two weeks (early events; 2.0%) and 30 in the second half (days 15 to 30; late events; 0.5%). The cumulative event rates of death, nonfatal MI and angiographically documented stent occlusion are differentiated in Figure 1. The rate for stent failure calculated per calendar year was very stable during the study period from 1994 to 1999: 2.2% in the first year and 2.6% in the last year (range, 2.2% to 2.9%). The relative number of late events (overall, 21% of all events) was also stable: 18% in the first year and 25% in the last year (range 17% to 26%).

The temporal distribution of all events during the 30-day observation period is shown in Figure 2. This illustrates that the majority of events occurred on the day of the procedure (n = 38) and the second day (n = 23); together, 43% of all events. Beyond this accumulation, events of stent failure were noted on almost every day during the 30-day follow-up. All deaths during the observation period were of cardiac or procedure-related origin. All included events of MI were related to the treated vessel; in nine patients they were due to side-branch occlusion with a patent stent.

Baseline characteristics of patients without events, with early events or with late events are listed separately for these three groups in Table 1. For most of these baseline characteristics, there were significant differences by univariate analysis among the three groups. Likewise, Table 2 lists the procedural data for the three groups, revealing several significant differences. Therefore, we analyzed all factors with $p < 0.10$ (by univariate analysis) in a logistic regression model for stent failure during the first 30 days. This analysis identified ten clinical, angiographic and procedural factors as independent risk factors, which are illustrated in Figure 3, by their relative risk. To differentiate the risk for early and for late events, all factors were entered into two respective, separate multivariate analyses. Their results are illustrated in Figure 4. There is a striking difference between the two analyses: while angiographic factors of stenosis severity before the procedure and qualitative and quantitative factors

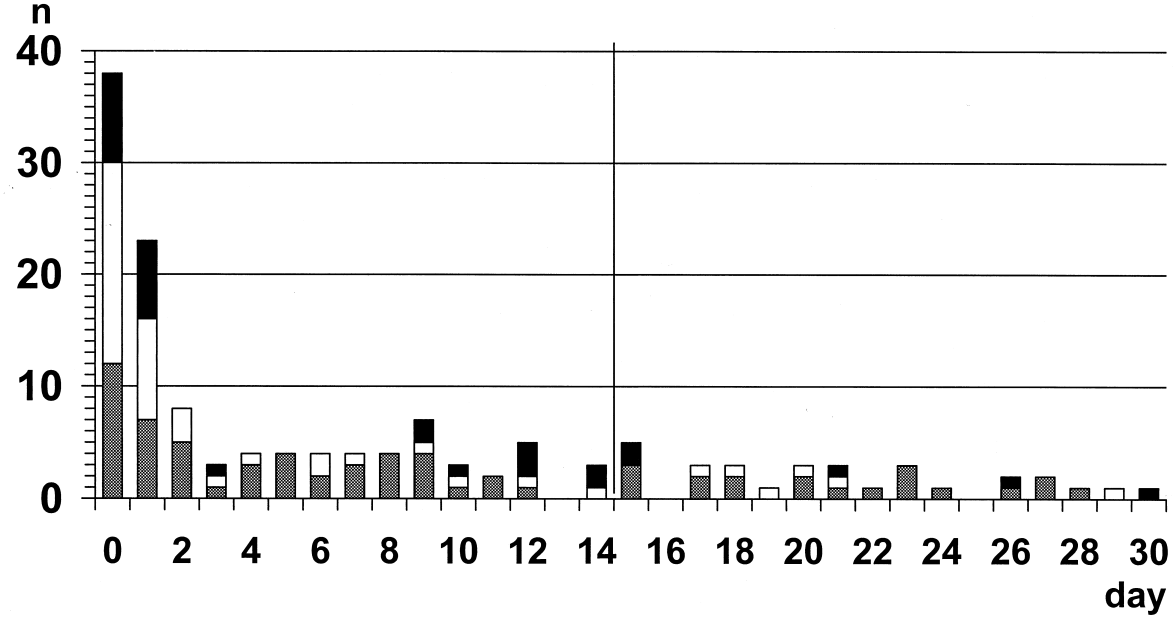

Figure 2. Temporal distribution of all events. There were 112 events (2.0%) that occurred during the first 14 days and 30 events during days 15 to 30 (0.5%). Events per day are illustrated in a hierarchial order: **hatched box** = death; **white box** = nonfatal myocardial infarction; **black box** = occlusion.

Table 1. Baseline Clinical and Angiographic Characteristics

		Stent Failure		
	No Event	Early	Late	p Value
Number of procedures	5,536	112	30	—
Women (%)	23.2	29.5	36.7	0.067
Age (yr)	64.2 ± 11.1	66.6 ± 11.6	70.4 ± 11.3	< 0.001
Cardiovascular risk factors (%)				
Arterial hypertension	71.4	65.2	53.3	0.034
Hypercholesterolemia	54.4	53.6	40.0	0.29
Diabetes mellitus	20.7	29.5	30.0	0.035
Smoker	42.7	33.0	33.3	0.075
Acute MI (%)	18.8	33.9	20.0	< 0.001
Multivessel disease (%)	72.5	81.3	83.3	0.051
Reduced LV function (%)	35.4	54.5	60.0	< 0.001
Restenotic lesion (%)	16.8	7.1	10.0	0.015

p values as calculated by univariate analysis.
LV = left ventricular; MI = myocardial infarction.

of the obtained final result are independent risk factors for early events, only general clinical (age, hypertension) or angiographic (LV function) variables are risk factors for late events.

These independent risk factors for late events were used to identify groups of patients having specific high or low risks. The respective results from a CART analysis of these factors are illustrated in Figure 5. Starting from a rate of 0.5% for stent failure in the total population (circle on top in Fig. 5), the event rate rises to 0.9% if the patient is >65 years old (49.9% of study population). If these older patients do not have arterial hypertension (11.6% of the total study population), the rate increases to 1.6% and peaks at 2.5% for patients who, in addition, have a reduced LV function (5.0% of study population). On the other extreme, patients <65 years old and without reduced LV function (33.3% of study population) have an event rate of 0.1%.

DISCUSSION

Major findings. This study analyzes the risk of stent failure (defined as death, MI or angiographically documented stent occlusion) in an unselected study population with a contemporary four-week antithrombotic regimen after coronary stent placement (aspirin and thienopyridines). Focussing on the incidence of late events, that is, those occurring during the second two weeks after the procedure, the study revealed three major findings: 1) the risk of stent failure decreases rapidly during the first few days and is very rare in the third and fourth weeks, with a cumulative rate of 0.5%. 2) The

Table 2. Procedural Data

		Stent Failure		
	No Event	Early	Late	p Value
ACC/AHA type B2/C (%)	75.6	89.3	93.3	< 0.001
Target lesion (%)				0.42
LAD	41.5	43.8	43.4	
CX	19.8	15.2	20.0	
Left main	1.8	2.7	3.3	
RCA	31.0	27.7	23.3	
Venous bypass graft	5.9	10.7	10.0	
Vessel size (mm)	3.02 ± 0.53	3.02 ± 0.58	3.00 ± 0.47	0.97
% stenosis before PTCA	77.6 ± 16.5	84.4 ± 15.4	75.2 ± 19.9	< 0.001
Lesion length (mm)	12.6 ± 7.3	13.9 ± 7.6	13.3 ± 9.0	0.23
Number of stents placed	1.7 ± 1.2	2.1 ± 1.3	1.8 ± 0.84	< 0.001
Length of stented segment (mm)	20.9 ± 13.2	27.6 ± 17.1	25.3 ± 15.6	< 0.001
Premounted stents used (%)	28.1	31.3	33.3	0.62
Max balloon pressure (atm)	13.7 ± 3.0	13.1 ± 3.2	13.1 ± 4.6	0.053
Balloon/vessel ratio	1.09 ± 0.12	1.08 ± 0.10	1.09 ± 0.11	0.50
% stenosis after stenting	5.2 ± 9.1	9.7 ± 20.0	4.0 ± 8.9	< 0.001
Residual dissection (%)	1.1	10.7	3.3	<0.001
Final flow grade TIMI 2 (%)	1.4	7.1	6.7	< 0.001
Abciximab therapy (%)	33.8	54.5	43.3	< 0.001

p values as calculated by univariate analysis.
ACC = American College of Cardiology; AHA = American Heart Association; CX = circumflex artery; LAD = left anterior descending coronary artery; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

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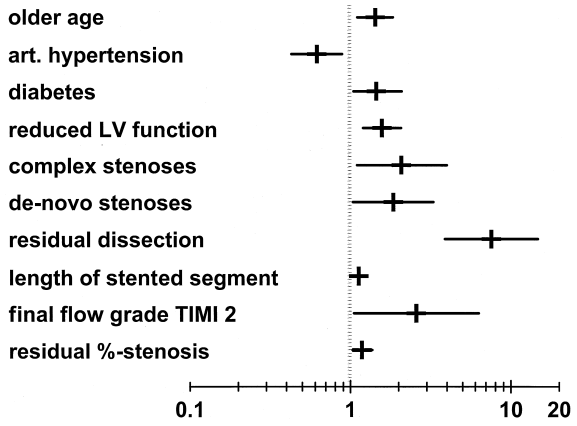

Figure 3. Significant and independent factors for stent failure within the first 30 days, displayed with their relative risk and 95% confidence interval (for continuous variables these were calculated for the first vs. the third quartile: age, 57.0 vs. 72.2 years; length of stented segment, 15 vs. 25 mm; residual stenosis, 5.5 vs. 10.5%). LV = left ventricular; TIMI = Thrombolysis In Myocardial Infarction.

risk of late events is determined by procedure- and operator-independent clinical factors (age, LV function, arterial hypertension). This is in contradistinction to the risk of early events which is predominantly determined by angiographic and procedural factors. These, at least partially, reflect the success of the procedure and, therefore, can be influenced by the operator and his/her experience. 3) The identification of risk factors for late events makes it possible to define subgroups of patients having specific high or low risks; in the presence of all risk factors the late event rate is as high as 2.5%.

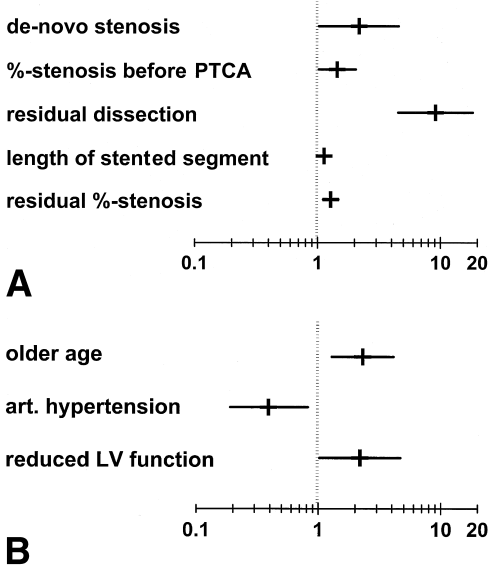

Figure 4. Significant and independent factors for stent failure differentiating the early period (i.e., the first 14 days) **(A)** from the late period (i.e., days 15 to 30) **(B)**. Factors are displayed with their relative risk and 95% confidence interval (for continuous variables these were calculated for the first vs. the third quartile) (Fig. 3). LV = left ventricular; PTCA = percutaneous transluminal coronary angioplasty.

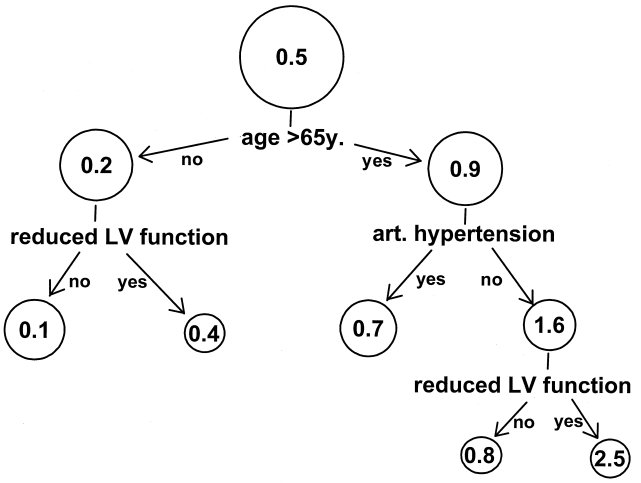

Figure 5. Risk rates for late stent failure and their relation to significant risk factors (Fig. 4B). The **numbers inside circles** represent the rate of stent failure in this subgroup; the **area of a circle** represents the size of the subgroup (in relation to the **circle on top**, which comprises all analyzed procedures; n = 5,611). LV = left ventricular.

Incidence of late events in previous studies with ticlopidine. The necessary length of a post-procedural thienopyridine therapy has not been thoroughly established. The four pivotal randomized trials proving the efficacy of a combined antiplatelet regimen with aspirin and ticlopidine after coronary stent placement had utilized ticlopidine regimens of at least four weeks (1–4). Late events, that is, those occurring in the second two weeks were very rare; in the Intracoronary Stenting and Antithrombotic Regimen (ISAR) (1), Stent Anticoagulation Restenosis Study (STARS) (4) and Full ANTicoagulation versus ASpirin and TIClopidine (FANTASTIC) trials (2), no adverse cardiac event was observed in the ticlopidine group during the third and fourth weeks. In the Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting (MATTIS) (3), a study with a specifically high-risk population, one of a total of 10 observed cardiac events occurred after 27 days. In a previous retrospective analysis in an unselected patient cohort, the majority of stent failures occurred within the first four days (5), with a rapid decline afterwards. This early risk was paralleled by the statistically detectable delayed onset of action of ticlopidine. In this previous analysis, the significant protective effect of ticlopidine was relatively low during the first three days, with a peak at the eighth day; it is noteworthy that a statistically significant effect could still be identified for the later period between the eighth and 30th days. In this time period, one third of all events had occurred (5).

Comparison of clopidogrel and ticlopidine. In general, clopidogrel is assumed to have a similar cardiac efficacy as ticlopidine. Both published randomized trials comparing ticlopidine and clopidogrel report higher cardiac event rates with clopidogrel that were not statistically significant (10,14), but, due to their design, neither had the statistical power to prove an equivalence or a difference in cardiac

efficacy. Considering these data together with more favorable results from nonrandomized trials (12,13,17,20), only a modest level of evidence for the cardiac equivalency of clopidogrel can be assumed (21,22). Published data on the late events of stent failure with clopidogrel are limited because most studies report only cumulative 30-day event rates (10,12–14); Jauhar et al. (20) had observed a 0.8% rate of late stent occlusion.

Necessary length of thienopyridine therapy. From all these data, with the use of ticlopidine and clopidogrel, there is an evident paucity of late stent failure, which challenges the principle of a four-week regimen of thienopyridines, especially for ticlopidine. Therefore, regimens shortened to two weeks were investigated. In a selected patient population, Berger et al. (6) found no adverse cardiac event after the discontinuation of ticlopidine or clopidogrel (17) after two weeks. Preliminary data from the Antiplatelet Therapy Versus Antiplatelet Therapy Alone in Patients at Increased Risk of Stent Thrombosis (ATLAST) trial indicate that, in this higher-risk study population, the rate of stent thrombosis was 0.3% after two weeks (7); overall, approximately one fourth of all cardiac events observed in this trial occurred in this late period. However, all these studies with thienopyridines were not large enough to distinguish an incidence of late stent thrombosis between 0% and 0.5% or even 1%.

Therefore, the current report provides, for the first time, a reliable figure for the rate of late stent failure with thienopyridine therapy. The documented rate of late stent failure of 0.5% is too low to justify a four-week thienopyridine regimen in all patients but too high to endorse a two-week regimen for all. It is, therefore, crucial to stratify patients, to identify risk factors and to adjust the length of therapy accordingly. In this study, we performed logistic regression analysis to identify independent risk factors for late stent failure. In patients with all three significant risk factors, the rate of late stent failure was 2.5%. Hence, a four-week thienopyridine regimen seems advisable for these high-risk patients. On the other hand, this risk stratification will also make possible the identification of a much larger group of patients with a lower risk in whom a two-week regimen might suffice. Their lower cardiac risk must be weighted against the increasing risk for noncardiac side effects. Because this risk is lower with clopidogrel than it is with ticlopidine, the group of patients optimally stratified to a two-week clopidogrel regimen is presumably smaller than it would be if ticlopidine is used. Therefore, these data refine our knowledge of the feasibility of a two-week thienopyridine regimen, as suggested by Berger et al. (6,17).

Risk factors for early versus late stent failure. This is the first study to differentiate risk factors for early versus late events; previous analyses studied all adverse cardiac events of the first four weeks together. Because the majority of events occur during the first few days, these analyses predominantly reflect the risk for early stent failure. Our analysis of the risk during all four weeks together (Fig. 3) is in keeping with the results from these previous analyses (5,23,24). These had identified the predominant influence of angiographic and procedural risk factors for early outcome, along with age, LV function, unstable coronary syndromes and diabetes. Our data differentiating the risk of early versus late stent failure (Fig. 4, A and B) illustrate a particular distinction: early risk is largely dependent on procedural factors that (at least partially) can be influenced by the operator's stent placement technique and skills, but late risk is predominantly determined by unalterable factors such as age, LV function and systemic hypertension.

Risk factors for late stent failure. Age and impaired LV function are known risk factors for adverse outcome after stent placement (5,23,24), as well as after percutaneous coronary interventions in general (25). In addition, our analysis identified the presence or history of arterial hypertension as a protective factor. Previous reports have been inconsistent on the role of systemic hypertension: although it has been described as a predictive factor for acute closure after standard percutaneous transluminal coronary angioplasty (26), such a relation was not confirmed in recent analyses for stent placement (5,23,24). An opposing, that is, protective, effect of arterial hypertension has been described for patients with primary angioplasty in acute MI; higher systolic pressure was associated with a lower incidence of death and repeat MI during early follow-up (27). Such a relation might have affected our analysis, considering that approximately 20% of patients presented with acute MI. However, these data are qualified by the difficulty in establishing arterial hypertension as a definite cardiovascular risk factor in an individual patient presenting with high systemic pressure at baseline catheterization but no previous history. Therefore, further studies are needed to sufficiently describe the role of arterial hypertension for early outcome after stent placement.

Abciximab use and incidence of stent failure. In our study, patients with stent failure had received abciximab significantly more frequently, particularly patients with early events (54.5% vs. 33.5% in patients without events). These data have to be interpreted with caution in view of the actual indication for treatment. Approximately 20% of patients included in our analysis had presented with acute MI, today an established indication for glycoprotein IIb/IIIa inhibitors (28,29). Beyond this indication, abciximab was administered in patients with complicated procedures and suboptimal angiographic results, reflecting a risk stratification based on our previous analyses (5,30). Therefore, our data reflect the selective use of this drug rather than a negative effect of abciximab administration. Furthermore, we assume that the administration of glycoprotein IIb/IIIa inhibitors in selected patients deriving particular benefit from such therapy (29) somewhat diluted our results and reduced the sensitivity to detect risk factors, especially for early events.

Study limitations. The available data for this study are not sufficient to analyze the risk for hematologic side effects of thienopyridine therapy, because routine blood counts were

not performed after discharge from the hospital. During the hospital stay (typically three days), we did not observe any severe ticlopidine-induced neutropenia or thrombocytopenia. However, these limited data do not permit the establishment of a reliable figure for the rate of severe hematologic complications.

Our definition of stent failure comprised death, MI and angiographically documented stent vessel occlusion in order to summarize stent thrombosis together with all clinically relevant cardiac events. This figure truly reflects the clinical success of an interventional procedure but is not identical to the actual incidence of stent thrombosis. For example, clinically silent occlusions may have been missed because repeat angiography was not routinely performed after 30 days but, typically, performed for recurrent symptoms suggestive of ischemia. Furthermore, stent vessel occlusion was not securely established in all cases of death, although all were of cardiac or procedure-related origin.

There are specific differences in methodology between our patient cohort and those of previous reports that might qualify as a direct comparison. We did not use intravascular ultrasound to confirm the final procedural result. Previous studies have suggested that intravascular ultrasound guidance may improve the short-term and long-term results (31,32) and may lower rates of stent thrombosis (33). We included a small number of patients with final TIMI-2 flow, but only if there was no visible dissection and the vessel had been totally occluded before the procedure. This factor was an independent risk factor for stent failure during the 30-day follow-up. Finally, the study period comprises the introduction of IIb/IIIa inhibitors. For any comparison, it should be considered that the overall use of these compounds was relatively low (34.2%). Additional studies are needed to further clarify these differences and their specific impact.

This analysis included only patients who had received a four-week ticlopidine regimen. Therefore, definite conclusions should be limited to such patients and should not be extrapolated to patients with a two-week regimen or to patients receiving clopidogrel. Although late events are presumably more frequent if thienopyridines are discontinued after two weeks, adequately sized randomized trials are essential to address the necessary length of thienopyridine therapy. In view of the substantially lower rate of severe hematologic side effects with clopidogrel, dissimilar conclusions concerning risks and benefits of two-week therapy of the two drugs are likely. Until such studies have been done, recommendations for a general reduction of the thienopyridine regimen to two weeks are not advisable.

Conclusions. In this study in a large, unselected population of 5,678 patients with a four-week ticlopidine regimen, late stent failure is a rare event (0.5%). Risk factors for these rare complications are older age and poor LV function, with arterial hypertension as a protective factor. In contradistinction to late events, early events are determined by angiographic factors and procedural success, which are at least partially operator-dependent.

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