Intracoronary Doppler– and Quantitative Coronary Angiography–Derived Predictors of Major Adverse Cardiac Events After Stent Implantation

Michael Haude, MD; Dietrich Baumgart, MD; Edoardo Verna, MD; Jan J. Piek, MD; Chris Vrints, MD; Peter Probst, MD; Raimund Erbel, MD

Background—Distal coronary flow velocity reserve (CVR) is significantly improved after a successful balloon angioplasty (PTCA). Furthermore, a postinterventional CVR >2.5 and a percent diameter stenosis (%DS) ≤35% are predictive for a low incidence of major adverse cardiac events (MACE) at 6 months of 16%. Similar results are lacking for coronary stenting.

Methods and Results—In 150 patients, baseline and hyperemic coronary flow velocities were recorded with a Doppler guidewire distal to the target lesion and in an unobstructed reference artery before and after PTCA, after stenting, and at 6 months. Distal CVR and relative CVR (CVRrel) were calculated. Logistic regression and receiver operating characteristic analyses were applied to determine prognostic cutoff values of CVR, CVRrel, %DS, and minimal lumen diameter separately and in combination to predict MACE at 6 months. After stenting, CVR (2.96 ± 0.87 versus 2.40 ± 0.7; P = 0.001), CVRrel (1.02 ± 0.24 versus 0.81 ± 0.24; P = 0.001), and minimal lumen diameter (2.98 ± 0.56 versus 2.11 ± 0.74 mm; P = 0.001) were significantly higher than after PTCA. Thirty-three patients developed MACE. A postinterventional CVRrel >0.88 was the best single predictor of MACE, with an incidence of 6.8%, whereas the combination of a CVRrel >0.88 and a %DS ≤11.2% predicted an incidence of MACE of 1.5%.

Conclusions—Measurement of CVRrel and %DS after stent implantation are best suitable to predict MACE at 6 months.

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Key Words: stents ■ blood flow ■ restenosis ■ angioplasty ■ prognosis

Recently, Doppler flow wires became available to measure coronary blood flow velocity reserve (CVR) during human cardiac catheterization and to calculate CVR as a physiological measure of stenosis severity.1,2 Using this device, the Doppler Endpoint Balloon Angioplasty Trial Europe (DEBATE) documented a significant increase in CVR distal to the target lesion to 2.5 after a successful balloon angioplasty (PTCA).3 Clinically even more relevant, a subgroup of patients with a postprocedural CVR of >2.5 and a residual diameter stenosis (%DS) of ≤35% presented an incidence of major adverse cardiac events (MACE) of only 16% at 6 months. Nevertheless, the DEBATE trial left some unanswered questions. Is this CVR value of 2.5 the best that can be achieved postinterventionally in the presence of residual stenosis, because it is common after PTCA? If residual stenosis can be minimized and distal CVR optimized, do these patients present MACE less frequently?

Stents minimize residual stenosis and create a rounder arterial conduit with a smoothened surface.4,5 Thereby, improved local blood flow conditions can be expected.6–10 The purpose of this observational trial was to identify the short-term and long-term impact of the stent on absolute and relative CVR and on patients’ clinical outcome by coronary blood flow velocity measurements.

Methods

Patients

Table 1 summarizes baseline characteristics of 150 patients with elective stent implantation who were enrolled in the study. They had to be symptomatic and/or to present objective ischemia in a stress test. Lesion length was limited to 15 mm to allow coverage with a single stent. All patients gave informed consent for the initial procedure, including stent placement and blood flow velocity measurements, and for a 6-month invasive control.

Subacute myocardial infarction (MI), chronic total occlusion of the target lesion, 3-vessel disease, or contraindications against stenting were exclusion criteria.

Interventional Procedure, Including Flow Velocity Measurements

Premarkedication included acetylsalicylic acid 100 to 300 mg/d. Before intervention, 5000 to 10 000 IU heparin IV was administered, but no
glycoprotein IIb/IIIa inhibitors. Coronary angiography was performed according to local practice. After the diagnostic part, a 6F or 8F guiding catheter was inserted, and a 0.014-in Doppler guidewire (Flo Wire, Endosonics) was passed through the target lesion with the tip positioned ≥2 cm to the stenosis. Then distal blood flow velocity recordings were obtained under basal and during hyperemic conditions induced by intracoronary injection of 12 μg adenosine to the right or 18 μg to the left coronary artery. During flow velocity measurements, the guiding catheter should be withdrawn from the ostium to provide maximum flow. Good-quality recordings were necessary to continue with the study. PTCA was performed according to local practice with a balloon-to-artery ratio of ≥1 to 1. In 72 patients (48%), the Flo Wire was used as the interventional guidewire, and in the remaining patients, an additional “working” wire was positioned. Control angiography was performed in ≥2 planes identical to the preinterventional coronary angiography. At least 5 minutes after the final balloon deflation and 3 minutes after the preceding contrast injection, blood flow velocity measurements were repeated at baseline and during hyperemia. Then stents were implanted according to local practice, with the same balloon size as for PTCA, with an implantation pressure of ≥12 atm. Stents were dilated in 68 patients (45%) with pressures ≥14 atm. When control coronary angiography documented a good angiographic result, blood flow velocity measurements at baseline and during hyperemia were repeated. Finally, wires were withdrawn from the target artery, and the Doppler guidewire was positioned in the mid part of an unobstructed reference vessel (left anterior descending artery in 62 patients [41%], left circumflex artery [LCx] in 64 [43%], and right coronary artery in 24 [16%]) to perform blood flow velocity recordings at baseline and during hyperemia.

Follow-Up Procedures

After 5.9±0.4 months, all patients underwent reevaluation of their clinical status, a stress test, and repeat cardiac catheterization. Coronary angiography was performed in identical views as during the initial procedure. Blood flow velocity recordings were repeated at baseline and during hyperemia distal to the previously treated vessel site and in the nonstenotic reference artery. Angiographic restenosis was defined as a >50% DS at the previously treated vessel site.

Definition of MACE

Death, MI, and restenosis requiring target lesion revascularization (TLR) were selected as MACE. Q-wave MI was defined as any postprocedural increase of creatinine phosphokinase (CPK) to >3 times the local threshold value with ≥8% CPK-MB fraction and the development of new Q waves, whereas non-Q-wave MI was based solely on enzyme increase. TLR was intended when symptomatic patients with or without pathological stress test presented a >50% DS independent of the results of the blood flow velocity recordings.

Coronary Blood Flow Velocity Measurements

Doppler flow velocity spectra were recorded continuously on videotape with the FloMap or FloMod system (Endosonics), which automatically detect maximum blood flow velocity and calculate absolute CVR as the ratio of average peak velocity (APV) during maximum hyperemia divided by baseline APV.11 In addition, relative CVR (CVR_rel) was calculated as the ratio of absolute CVR distal to the target lesion divided by absolute CVR in the unobstructed reference artery.12–14 Blood flow velocity recordings and coronary angiograms were analyzed offline in a core laboratory at the University of Essen.

Quantitative Coronary Angiography

After intracoronary injection of 0.2 mg nitroglycerin or 1 to 3 mg isosorbide dinitrate, coronary angiograms for quantitative analysis were performed before and after PTCA, after stenting, and at 6 months. We used the edge-detection system developed by Reiber et al (CMS, Medis).15 The mean variation for this system in determining the absolute diameter is ≤0.13 mm. For calibration, the non–contrast-filled guiding catheter was used. From 2 orthogonal views, minimal lumen diameter (MLD), interpolated reference diameter, and %DS were calculated as a mean.

Statistical Analysis

Continuous variables are expressed as mean±SD. Differences within these variables were evaluated by ANOVA and paired or unpaired Student’s t test when appropriate. Qualitative variables were analyzed by χ² or Fisher’s exact test.

According to the statistical approach in the DEBATE trial, both univariate and multivariate logistic regression analyses were performed to study the diagnostic value of quantitative coronary angiography (QCA) and Doppler parameters to predict MACE at 6

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**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Age, y</th>
<th>B/A indicates balloon to artery; lesion type is AHA/ACC classification. Results are mean±SD or absolute numbers with percentages in parentheses.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±11</td>
<td></td>
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<tr>
<td>Men</td>
<td>135 (90)</td>
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<tr>
<td>Risk factors</td>
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<td>Diabetes mellitus</td>
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<td>Hypertension</td>
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<tr>
<td>Hyperlipidemia</td>
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<tr>
<td>Smoking</td>
<td>16 (11)</td>
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<tr>
<td>Clinical features</td>
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<tr>
<td>Unstable angina pectoris</td>
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<tr>
<td>Previous MI</td>
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<tr>
<td>Previous bypass surgery</td>
<td>0 (0)</td>
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<tr>
<td>Previous PTCA of nontarget vessel</td>
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<td>Vessel involvement</td>
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<td>Single-vessel disease</td>
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<tr>
<td>Multivessel disease</td>
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<td>Target vessel</td>
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<td>Left anterior descending artery</td>
<td>105 (70)</td>
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<tr>
<td>Left circumflex artery</td>
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<td>Lesion type</td>
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<tr>
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<tr>
<td>Type B2</td>
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<tr>
<td>Type C</td>
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<td>Calcification</td>
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<td>Eccentricity</td>
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<td>Palmaz-Schatz</td>
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<tr>
<td>Jostent</td>
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<td>NIR</td>
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<td>Multilink</td>
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<td>Procedure details</td>
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<td>Maximum balloon diameter, mm, PTCA</td>
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<td></td>
</tr>
<tr>
<td>Maximum balloon diameter, mm, stent</td>
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<tr>
<td>Maximum B/A ratio PTCA</td>
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<tr>
<td>Maximum B/A ratio stent</td>
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<tr>
<td>Maximum inflation pressure, atm, PTCA</td>
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<tr>
<td>Maximum inflation pressure, atm, stent</td>
<td>14.5±2.2</td>
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</table>
months. No additional clinical variables were introduced into the model, because the specific aim of the study was to identify Doppler and QCA indices predictive of MACE after stenting. Each observed value of the significant predictive variables was considered a possible “prognostic threshold.” Sensitivity and specificity were calculated at each threshold. Receiver operating characteristic (ROC) curves were constructed, and the areas under the ROC curve are reported with 95% confidence limits.16

Finally, the “best” threshold of a significant predictive variable was defined as the cutoff point where sensitivity equals specificity.17 On the basis of this threshold, the patient population was divided into 2 categories. The frequency of events in both categories was determined, and differences were evaluated by \( \chi^2 \) analysis with the report of relative risks. Two-sided probability values are reported for all appropriate tests, with statistical significance taken at the 0.05 probability level.

Results
In all 150 patients, sequential Doppler recordings and coronary angiograms were of sufficient quality to perform quantitative analysis. No patient was lost to clinical and angiographic follow-up.

Major Adverse Cardiac Events
Thirty-three patients developed MACE. No patient died. Five patients (3%) developed non–Q-wave MIs (maximum CPK rise of 418±108 IU/L and CPK-MB rise of 55±12 IU/L) 1 to 5 days after the intervention. In these patients, residual %DS was significantly larger (27±11% versus 12±13%, \( P=0.001 \)) and \( CVR_{\text{rel}} \) significantly lower (0.79±0.18 versus 1.03±0.25, \( P=0.001 \)). All patients with non–Q-wave MI were treated medically. Angiographic restenosis requiring TLR was documented in 28 patients (19%).

Doppler Flow Velocity Measurements
Figure 1 illustrates a representative case example. There was no significant shift (=15%) in baseline APV distal to the target lesion and in the reference artery during measurements (Figure 2). In contrast, a stepwise significant increase in hyperemic distal APV was measured after PTCA and stenting, which decreased nonsignificantly at follow-up because of 28 patients with restenosis (Figure 2). Distal CVR increased significantly after PTCA and again after stenting and thereby reached the level of the reference CVR with no significant change at follow-up (Figure 2). \( CVR_{\text{rel}} \) also increased significantly after PTCA and stenting but decreased nonsignificantly at follow-up because of 28 patients with restenosis (Figure 3). \( CVR_{\text{rel}} \) at follow-up in patients without restenosis was similar to that after stenting (1.02±0.24 versus 1.05±0.22; \( P=0.224 \)). Reference CVRs during the initial procedure and at follow-up were not significantly different (2.94±0.74 versus 3.09±0.78; \( P=0.167 \)).

In 18 (12%) of 150 patients, \( CVR \) in the unobstructed coronary artery was \( \leq 2.0 \), reflecting microvascular disease. After stenting, \( CVR_{\text{rel}} \) was 1.01±0.16 in these patients versus 1.02±0.23 in the remaining patients. Furthermore, the MACE rate was similar, occurring in 4 (22.2%) of 18 patients versus 29 (21.9%) of 132 patients.

No physiologically relevant changes in blood pressure (systolic blood pressure 135±25 mm Hg before PTCA, 133±23 mm Hg after PTCA, 131±26 mm Hg after stent implantation,
6 months, MLDs (2.17±0.70 mm; P=0.001) were smaller and %DS (33±17%; P=0.001) larger. Angiographic restenosis was documented in 28 patients (19%).

**Doppler- and QCA-Derived Predictive Values for MACE**

Table 2 summarizes Doppler and QCA parameters as independent risk factors for MACE. A postinterventional DS of >11.2% was a better predictor than an MLD of ≤2.77 mm. The difference of ROC areas was 11.7% (95% CI 1.4% to 22.1%; P=0.026). A CVR of ≤0.88 after stenting was a better functional predictor of MACE than a distal CVR of ≤2.86. The difference of ROC areas was 13.2% (95% CI 3.3% to 23.1%; P=0.009). Distal CVR and CVRrel after stent implantation were significantly lower and %DS significantly higher in patients with MACE, whereas postinterventional MLD was not statistically different in patients with or without MACE (Table 3).

**Subgroup Analysis**

Best results on MACE were obtained in patients with a postinterventional CVRrel of >0.88 who presented an incidence of 6.8% (Figure 4a). If morphometric and functional cutoff criteria are combined, patients with a poststent CVRrel >0.88 and a residual DS of ≤11.2% presented a MACE rate of only 1.5% (Figure 4b). Patients not fulfilling the morphometric cutoff criteria had a 2.84- to 3.13-fold higher relative risk for MACE (Figure 5), whereas patients who did not fulfill the functional cutoff criteria presented a 3.26- to 7.78-fold higher relative risk. Patients who did not fulfill the combined morphometric and functional criteria presented a 4.18- to 26.54-fold higher relative risk for MACE.

**Discussion**

Our study documents that distal CVR and CVRrel are significantly improved after successful stent implantation com-
pared with PTCA alone, apart from the well-known enlargement of luminal dimensions. This supports previous reports using intracoronary Doppler or densitometric evaluations of CVR.6 –9,18

Furthermore, intracoronary Doppler– and QCA-derived parameters could be identified that were predictive for MACE at 6 months. A %DS was the best single independent morphometric parameter derived from QCA to predict MACE with a cutoff value of 11.2%, which was substantially lower than the value of 35% after PTCA in the DEBATE trial.3 CVR rel was found to be the overall best independent parameter and clearly topped distal CVR as a functional parameter to predict MACE. Because CVR rel was not calculated in the DEBATE trial, only distal CVR values after PTCA can be compared. These were almost identical, documenting that underdilatation in our study is unlikely.

One advantage of CVR rel over CVR is the unequivocal normal value of 1, whereas there is an ongoing debate concerning the cutoff value for a normal CVR, which is reported to range between 1.8 and 3.0.19 –21 Especially in the presence of additional microvascular disease,22 –24 CVR after a successful stent implantation with minimization of the residual stenosis can remain low. This particular aspect may be neglected if CVR rel is applied. Patients with a postinterventional CVR rel of >0.88 showed an incidence of MACE of 6.5% at 6 months, which improved to 1.5% if these patients were additionally screened for a postinterventional DS of ≤11.2%. By use of these new cutoff criteria, a more favorable outcome can be predicted after stenting compared with the results of the DEBATE trial for PTCA.

Because TLR was the main contributor to MACE, the combined Doppler- and QCA-derived parameters may also predict the extent of the restenosis process. Stents inhibit elastic recoil and thereby create a larger postinterventional lumen than PTCA, which better compensates for vessel shrinkage and neointima proliferation causing restenosis. Nevertheless, it is surprising that flow parameters, especially CVR rel predict restenosis and TLR better than any morphometric QCA parameter. An immediate and almost complete recovery of the microvascular response may predict a less aggressive neointimal response.

More recently, intracoronary pressure measurements after PTCA and stent implantation with the calculation of fractional flow reserve presented results similar to those documented here.26 This is not surprising, because a previous report showed a close correlation between CVR rel and fractional flow reserve, which was not documented for distal CVR.

Limitations of the Present Study
To answer the above-listed questions, Doppler flow velocity and QCA measurements were performed in carefully selected patients scheduled for stent implantation. Most patients had single-vessel coronary artery disease to allow Doppler measurements in a nonobstructed reference vessel. The study results cannot automatically be transferred to patients with lesions in the right coronary artery, although no data are available to support different results on CVR or CVR rel compared with the left anterior descending or left circumflex artery.

Furthermore, CVR rel cannot be calculated in patients with 3-vessel coronary artery disease. Patients with MIs were excluded because microvascular recovery of the infarcted vascular bed after restoration of the supplying epicardial vessel by stent implantation is unpredictable.21 Translesion pressure measurements with calculation of fractional flow reserve seem to be superior in this setting.

We accepted only predefined changes in blood pressure, heart rate, and baseline APV throughout the individual measurement sequence to avoid side effects on derived blood flow parameters.22 In particular, a significant shift of baseline APV has a substantial impact on CVR and CVR rel.23 To compensate for such a shift, our group recently reported an
algorithm to calculate a corrected baseline APV before calculating CVR and CVR_{norm}.

Because investigators were not blinded to the Doppler flow velocity and QCA results at follow-up, the incidence of TLR could be driven by these measurements. Nevertheless, the indication for TLR was predefined on the basis of the patient’s angina status and/or the objective documentation of ischemia during a stress test.

We applied the same statistical approach to define cutoff values as was chosen in the DEBATE trial, which is more objective than predefined sensitivity or specificity values.

This study should evaluate the predictive value of Doppler- and QCA-derived parameters alone, instead of combining them with other demographic or procedural parameters predictive of restenosis. It can be speculated that any reasonable combination of well-known risk factors for restenosis together with the derived Doppler and QCA parameters could provide different results.

Furthermore, it is questionable whether stent-like post-PTCA results with a residual stenosis <11.2% provide a beneficial long-term outcome similar to that for stented patients presented here. The aspect of provisional stenting based on Doppler-derived flow velocity parameters is covered in part by 2 large prospective multicenter randomized trials (DEBATE 2 and DESTINI), which are completed and await publication.

**Clinical Implications**

Study results document that patients with stent implantation can be stratified for their long-term prognosis on the basis of Doppler- and QCA-derived parameters measured immediately after intervention. Because the improvement of CVR and CVR_{norm} after stenting is driven by lumen enlargement and by the immediate recovery of microvascular capacity, operators should first try to minimize DS to ≤11.2% and to gain an MLD of >2.77 mm controlled by QCA, which sometimes requires stent dilation with higher pressure or larger balloons. Nevertheless, the subsequent individual impact on Doppler parameters remains unpredictable. In our patients, 45% fulfilled the optimal criteria to prevent MACE without additional stent dilatation.

**References**


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