Evaluation of Colestipol/Niacin Therapy With Computer-Derived Coronary End Point Measures

A Comparison of Different Measures of Treatment Effect

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Background. The Cholesterol Lowering Atherosclerosis Study has demonstrated beneficial effect of colestipol/niacin on coronary atherosclerosis using a panel-determined global coronary change score. We now report treatment group comparisons using quantitative coronary angiographic (QCA) measures from all processable segments in 85 of 162 randomly selected baseline/2-year film pairs.

Methods and Results. Treatment benefit was established for percent stenosis for either continuous or categorical analyses with regression established regardless of the per-patient scoring procedure. In addition, treatment benefit favoring regression was established in some cases for roughness and for percent involvement, a longitudinal estimate of the percent of coronary surface involved by raised lesions. Benefit on minimum diameter was directly related to whether the segment was proximal to a graft insertion and hemodynamically related to the bypass graft. QCA correlates of panel-determined progression were increases in percent stenosis and numbers of occluded lesions in native arteries and the number of progressing lesions in bypass grafts.

Conclusions. These results demonstrate that a variety of computer measures can be used as end points in coronary angiographic therapy trials, but change in percent stenosis correlates best with visual panel assessments and best reflects the treatment benefit; when treatment effect sizes are moderate to large, the required sample size of coronary angiographic trials can be reduced when QCA is used. (Circulation 1992;86:1701-1709)

KEY WORDS • atherosclerosis • clinical trials • quantitative coronary angiography • regression

Controled clinical trials testing risk factor reduction with angiographic end points provide a central mechanistic link in the evidence that coronary atherosclerosis is reversible. Observations in human angiograms bridge a gap between therapy trials demonstrating reduced coronary heart disease mortality and morbidity rates1 and treatment effects in animal models.2,3 Five angiographic trials (FATS, POSCH, UCSF SCOR, the Lifestyle Heart Trial, and STARS)4-8 have recently confirmed and extended the 1987 findings of coronary regression reported by the Cholesterol Lowering Atherosclerosis Study (CLAS)9 using related...
CLAS was a randomized, placebo-controlled clinical trial testing combined colestipol plus niacin therapy in femoral, coronary, and carotid arteries of high-risk, post-coronary bypass patients.\(^1\) Trial size and length were set for a femoral artery end point, and coronary angiograms were evaluated by human panel readers as a safety measure. Two- and 4-year CLAS coronary results derived from human panel reading showing a strong and consistent therapy effect have been published.\(^9,15\) We have reported on the reliability of the CLAS coronary panel process for film evaluation,\(^16\) on the precision of the CLAS QCA procedure,\(^17\) and on the agreement between these two methods in assessment of the conventional coronary end point measure, percent stenosis.\(^18\)

In this study, we present a complete analysis evaluating the effect of colestipol/niacin therapy on QCA-derived coronary end point measures in all processable coronary artery segments from a randomly selected 50% sample of CLAS patients. We explore the effect of treatment on changes in new QCA coronary measures and the established measure, percent stenosis. We also combine segmental QCA changes into a per-patient score using varying strictness of rules for categorizing patients. We then relate QCA changes to segment location in order to estimate relative effect sizes of treatment. Finally, we correlate QCA measures with the panel-based global coronary change score in order to determine which QCA measures are associated with human-determined coronary status.

**Methods**

**CLAS Design, Angiography, and Results**

CLAS study design and conduct have been described in detail elsewhere.\(^14\) Randomization to one of two treatment groups (colestipol/niacin plus dietary intervention, placebo plus less stringent dietary intervention) occurred for 188 nonsmoking men between 40 and 59 years of age who had undergone previous coronary bypass surgery. Major additional entry criteria required cholesterol levels between 4.79 and 9.07 mmol/l (185 and 350 mg/dl) and confirmed lipid-lowering response to the study medications before randomization.

Simultaneous 90° biplane angiographic examinations were performed by a single angiographer using the percutaneous femoral technique. If a subject developed angina during a procedure, sublingual nitroglycerin (usually 0.4 mg) was administered, and the time and dose were recorded. The repeat angiography replicated this dose and timing of nitroglycerin. Additional details of the angiographic procedure have been described elsewhere.\(^18\) A total of 162 men completed baseline and 2-year angiograms in CLAS, and 103 men completed 4-year angiograms in CLAS-II. The first end point used to determine treatment effect was the global coronary change score, a summary score of change in coronary disease status determined by panels of human readers upon visual inspection of angiographic changes in individual lesions in native arteries and bypass grafts.\(^9,15\)

**Global Coronary Change Score**

Methods for determining the global coronary change score have been previously described.\(^9,16\) In brief, a panel consisted of a moderator and two readers who evaluated two paired coronary films. Each reader (masked to treatment assignment and to the true temporal order of films) independently identified and estimated lesion size (percent stenosis) of all lesions. In addition, each reader independently recorded a global evaluation of the paired films using a four-point summary score that combined changes in both native artery and bypass graft lesions: 0, no demonstrable change; 1, definitely discernible change; 2, intermediate change; and 3, extreme change. Direction of change was assigned by panelists according to the mounting of films on projectors, and a consensus opinion was reached on the summary score. After all films had been evaluated, the blind for temporal order of the films was broken. The resulting decoded summary score, the global coronary change score, was the panel-based end point of change in coronary status.

**Quantitative Coronary Angiography**

Details of the methods for QCA have been previously described.\(^17,18\) In brief, QCA uses dual projectors for view matching, digitization, and computer analysis of paired films. The angiographic view of each segment in 90° biplane views on both films was matched by a technician (masked to treatment assignment but not temporal order) for orientation and degree of contrast filling. Film quality and lesion visualization were superior in the right anterior oblique (RAO) view (antero-posteral image train). This projection was chosen as the preferential view for QCA analysis. Ninety-three percent of all segments were processed in this view: RAO-30 (49%), RAO-15 (15%), and RAO-45 (34%). For seven percent of segments, the left anterior oblique (LAO) projection (lateral image train) was used provided that the segment under consideration was positioned in the center of the field where distortion is minimal.

Three sequential frames exposed during end diastole were digitized unless unobstructed, matched end-diastolic frames could not be found; in that case, three sequential frames from other phases of the cardiac cycle were used.\(^17,18\) For each film, all processable segments (defined from branch to branch) were tracked and evaluated. In the case of a stenosis residing at a branch point, the automated edge tracking algorithm handles this lesion as two different segmental lesions.

To find the edges of a vessel, the computer operator first identified the approximate vessel midline with a cursor. The computer algorithm then searched perpendicular to this midline to find points of maximum intensity gradient that were identified as vessel “edges.” After the edges were located, a new midline was defined as the smoothed midpoints of the edges, and the tracking process was repeated. This two-pass tracking was used to minimize the effect of the selection of the original midline by the technician. The search was restricted to a window of pixel values centered on the previously detected edge point.

Portions of a segment with localized ectasia were manually eliminated by the computer operator, and the normal diameter was computed from the noneptastic portion of the segment. If a segment showed diffuse ectasia, the normal diameter was defined as “missing,” and any measure requiring a normal diameter (e.g., percent stenosis) was not computed.
Because absolute measures of lumen geometry (for example, average and minimum diameter) were made in addition to percent stenosis and roughness, edge coordinates were corrected for pincushion distortion measured from the image of a 1-cm anteroposterior grid filmed at the beginning of each angiogram. All segmental measures were averaged over the three sequential digitized frames; diameters were converted to millimeters by a scaling factor using the known diameter of the catheter and corrections from the radiographic grid. The coefficient of variation of average and minimum diameter of the segment for the three frames was calculated and used to monitor image and edge tracking quality. When the coefficient of variation of the average diameter exceeded 5% or that of the minimum diameter exceeded 13%, the operator reviewed the edge tracking of the frames in question and corrected detectable errors (e.g., overlooked crossing vessel shadows). If the edge tracking problems were not correctable (e.g., if the segment was not uniformly opacified, the segment was too small, or the image quality was poor), the operator eliminated the segment from the data base. Lumen geometry measurements for acceptable sequential frames were then averaged.

**QCA Data Base**

Eighty-five (of 162) pairs of panel-read angiograms were randomly selected for analysis by QCA. The average (±SD) global coronary change score for this set of angiograms was 0.5±1.0 compared with 0.6±0.8 for the set of angiograms not analyzed in this study (NS). Similarly, no significant differences in average global coronary change scores were found between these sets of angiograms within each treatment group.

In total, 731 native arterial segments were tracked and evaluated by QCA with a median of 326 measurable diameters per segment and a median length of 25 mm. In addition, 352 bypass graft segments were tracked and evaluated by QCA with a median of 517 measurable diameters per segment and a median length of 39 mm. The QCA-evaluable segments represented 50% of those identified by the panel; the majority of nonevaluable segments were those with large stenoses (≥80%). Each segment was characterized by 1) segment type (native artery or bypass graft), 2) native artery vessel location (left main, left anterior descending, circumflex, diagonal, marginal, right coronary, right coronary posterior descending, or other unnamed vessels), and 3) graft status of the native artery (proximal to a graft insertion and hemodynamically related, proximal to a graft insertion and hemodynamically unrelated, distal to a graft insertion and hemodynamically related, some combination of the previous, or ungrafted).

A native coronary artery segment was classified as proximal to a graft insertion and hemodynamically related if it transmitted blood that mixed with blood traversing the graft. A native artery segment was classified as proximal to a graft insertion and hemodynamically unrelated if it did not transmit blood that mixed with blood traversing the graft. A native coronary artery segment was classified as distal to a graft insertion and hemodynamically related if some of the blood passing through the segment was transmitted by the graft.

The QCA data base consisted of 13 measures for matched segments at baseline and at 2 years after therapy. We report on four QCA measures that are representative of all 13 measures: 1) the minimum lumen diameter (millimeters) defined as the third percentile of the distribution of diameters within the segment, 2) percent diameter stenosis within the segment (of the most severe narrowing if more than one lesion was present) defined as 100 (1−minimum diameter/normal diameter); the “normal” diameter was taken to be the 90th percentile of the distribution of diameters within the segment, 3) roughness (millimeters) defined to be the root mean square of the difference between the measured diameter and a fitted lumen diameter obtained by fitting a least-squares line to the diameters, and 4) percent involvement defined as the ratio of the length of the segment with diameters less than 80% of all diameters in the segment to the total length of the segment.

The third and 90th percentile of segment diameters were chosen to represent the minimum and normal lumen diameters, respectively, in order to minimize the effects of image noise of the edge tracking process (i.e., to eliminate the possibility that poorly measured edge points might produce a large error in stenosis measurement). The 90th percentile estimate for the normal diameter was previously used in processing femoral angiograms.14 The third percentile was selected for the minimum diameter estimate because of the proportionally smaller number of edges that typically contribute to the most narrow portion of the vessel. Small lesions might remain undetected if a larger percentile value was used.

**Statistical Analyses**

Both continuous and categorical methods of analysis were used to arrive at per-patient estimates of the effect of treatment. The significance level was set at 0.05; tests of hypotheses were two sided.

**End Points Analyzed as Continuous Variables**

Continuous analyses were performed separately for segments in the native arteries and for segments in the bypass grafts in order to arrive at per-patient estimates of the effect of treatment. The average change (2-year minus baseline) in each QCA measure was tested against zero within each treatment group and tested for equality between treatment groups, both tests using a method by Rosner.19 In this method, the unit of analysis is the segment. The test procedure adjusts for the intraclass correlation among the segments within any given patient to permit testing for means on a per-patient basis. In addition, we included as a covariate the baseline value of the QCA measure for each segment because baseline levels were found to be a significant correlate of QCA-measured change.

**End Points Analyzed as Categorical Variables**

For the categorical analysis, we used an adaptation of the National Heart, Lung, and Blood Institute scoring procedure to first classify segments and then to classify patients on the basis of measured changes in both the native artery and bypass graft segments.13 For each QCA measure, we classified segments as progressing, regressing, or not changing on the basis of the size of the change in that measure. For percent stenosis, we classified a segment as regressing when the decrease was
greater than +10% and as progressing when the increase was greater than +10%; when the change was in the range −10% to +10%, we classified the segment as unchanged. The choice of a 10% difference was regarded as visually convincing of change in a side-by-side comparison of arteriograms by Brown and coworkers and was found to be appropriate for CLAS data as well. For other QCA measures, the cutoff for characterizing a segment as regressing, nonchanging, or progressing was taken to be the mean plus 1 standard deviation of the distribution of change in the placebo group. Cutoffs for the native arteries were for minimum diameter, 0.29 mm; roughness, 0.07 mm; and percent involvement, 16.1%. Cutoffs for the bypass grafts were for minimum diameter, 0.40 mm; roughness, 0.12 mm; and percent involvement, 16.7%. These cutoffs for all four QCA measures for the native arteries are approximately equal to two times the standard deviation of short-term repeat determinations (e.g., measurement error) using our QCA algorithm.

For each QCA measure, we then classified patients using the following rule, which incorporated changes in both native arteries and bypass grafts (Rule 1): a progressor was defined as a patient with progression in at least one segment (i.e., an increase in one segment > +10%), with no change in the others (i.e., all other segmental changes in the range −10% to +10%). A regressor was defined as a patient with regression in at least one segment (i.e., a decrease in one segment > +10%), with no change in the others. A patient was regarded as having demonstrated no change if all segments exhibited no change. Patients who had at least one segment that regressed while at least one segment progressed (with all other segments unchanged) were classified on the basis of the modal segmental response. If equal numbers of segments regressed and progressed (while all other segments were unchanged), the patient was classified as not having changed.

In addition, we contrasted this rule with three stricter rules. (The effect of increasing strictness results in moving more patients into the unchanged category.) Rule 2 required regression (or progression) in at least two segments in order to classify a patient. For this rule, patients with only one regressing (or progressing) segment were classified as unchanged. Rule 3 (like Rule 1) required regression (or progression) in at least one segment. However, patients with mixed segmental responses (i.e., both regressing and progressing segments) were classified as unchanged. Rule 4 (like Rule 2) required regression (or progression) in at least two segments. However, patients with mixed segmental responses were classified as unchanged.

As examples, a patient with three regressing and two progressing segments (and all other segments unchanged) would be classified by Rules 1 and 2 as a regressor and as unchanged by Rules 3 and 4. A patient with only one regressing segment (and all other segments unchanged) would be classified by Rules 1 and 3 as a regressor but would be classified as a nonchanger by Rules 2 and 4. A patient with two regressing and one progressing segments (and all other segments unchanged) would be classified as a regressor by Rules 1 and 2 and as unchanged by Rules 3 and 4.

For each of the rules and criteria, analysis of the association of treatment with patient status (regression versus progression/no change) was performed using either χ² or Fisher’s exact test.

**Treatment Effect Sizes by Segment Characteristics**

A multivariate analysis was carried out for each QCA measure in order to identify segment characteristics (e.g., segment type, vessel location of segment, and graft status of segment) associated with the 2-year outcome regardless of treatment assignment. These analyses also used the approach by Rosner and also included baseline values of each QCA measure as covariates.

For each significant segment characteristic, we then calculated the treatment effect size. The effect size contrasted on a per-patient basis the mean change in a QCA measure (for example, percent stenosis) for drug-treated patients with that for placebo-treated patients relative to the variance of the change in the QCA measure. Mean changes were computed for segments with the significant characteristic (for example, segments proximal to the graft insertion and hemodynamically related), whereas variance was computed for all native arterial segments. In symbols, then, the effect size is defined as

\[
\text{Effect size} = \bar{x}_D - \bar{x}_P/[V(x_D) + V(x_P)]^{1/2}
\]

where \(\bar{x}_D\) and \(\bar{x}_P\) are the simple mean changes (not adjusted) in a QCA measure for the drug and placebo patients using the segments with the characteristic, and \(V(x_D) + V(x_P)\) is the pooled variance of the change in QCA computed for segments in the native arteries. For comparison across the various characteristics (e.g., segment type, vessel location of segment, and graft status of segment), the pooled variance remains constant in calculating the effect sizes.

**Relation of QCA Measures to Panel-Based Global Coronary Score**

To determine which QCA measures were associated with coronary outcome, we chose the panel-based global coronary change score as a coronary outcome measure external to the QCA process. Univariate and stepwise multiple linear regression analyses were performed with the dependent variable \(Y\) equal to the global coronary change score. Independent variables, which used QCA measures, were computed separately for native arterial segments and bypass graft segments. However, the regression model included both native arterial segments and bypass graft segments because the panel-based global coronary change score summarized changes in both types of lesions. In addition, baseline QCA values were included as covariates in each regression model.

The independent variables were \(X_j\)=change in percent stenosis; \(X_1\)=change in minimum diameter; \(X_2\)=change in roughness; \(X_3\)=change in percent involvement; \(X_4\)=the number of regressing segments; \(X_5\)=the number of progressing segments; \(X_6\)=the change in the number of totally occluded segments; and \(X_j\)=the number of diseased segments that could not be measured by QCA; \(j=1\) (native arterial segments) and 2 (bypass graft segments). For the first two independent variables, we averaged the changes over all segments within a patient; for \(X_5\), we computed the change in total roughness (summed over all segments within a
TABLE 1. Continuous Analysis of Quantitative Coronary Angiography Measurements

<table>
<thead>
<tr>
<th>QCA measurement</th>
<th>Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>n*</td>
</tr>
<tr>
<td>Native arteries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum diameter (mm)</td>
<td>1.76</td>
<td>364/44</td>
</tr>
<tr>
<td></td>
<td>(0.76)</td>
<td>(0.82)</td>
</tr>
<tr>
<td>Percent stenosis</td>
<td>34.50</td>
<td>347/44</td>
</tr>
<tr>
<td>Roughness ( \times 10 ) (mm)</td>
<td>2.34</td>
<td>364/44</td>
</tr>
<tr>
<td></td>
<td>(1.33)</td>
<td>(1.27)</td>
</tr>
<tr>
<td>Percent involvement</td>
<td>39.95</td>
<td>343/44</td>
</tr>
<tr>
<td></td>
<td>(19.68)</td>
<td>(20.83)</td>
</tr>
<tr>
<td>Bypass grafts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum diameter (mm)</td>
<td>3.32</td>
<td>168/42</td>
</tr>
<tr>
<td></td>
<td>(0.92)</td>
<td>(0.92)</td>
</tr>
<tr>
<td>Percent stenosis</td>
<td>24.46</td>
<td>149/41</td>
</tr>
<tr>
<td></td>
<td>(10.93)</td>
<td>(12.89)</td>
</tr>
<tr>
<td>Roughness ( \times 10 ) (mm)</td>
<td>2.90</td>
<td>168/42</td>
</tr>
<tr>
<td></td>
<td>(1.64)</td>
<td>(1.75)</td>
</tr>
<tr>
<td>Percent involvement</td>
<td>26.03</td>
<td>149/41</td>
</tr>
<tr>
<td></td>
<td>(22.15)</td>
<td>(22.71)</td>
</tr>
</tbody>
</table>

QCA, quantitative coronary angiography. Values are mean; standard deviations in parentheses.

*Segments/patients.

patient; for \( X_4 \), we computed the change in the total length of the diseased segments (summed over all segments within a patient) divided by the total length of all evaluable segments within a patient; \( X_4 \) was included in the analysis because a significant percentage (76%) of severely narrowed lesions (i.e., lesions \( \geq 80\% \)) could not be measured by QCA.18

Results

End Points Analyzed as Categorical Variables

Table 2 summarizes per-patient coronary status according to each of the four classification rules based on segmental changes in each QCA measure. Regarding percent stenosis, there was significant regression (versus progression/no change) caused by drug therapy regardless of the choice of classification rules for determining patient status \((p<0.01)\). In addition, significant regression caused by drug therapy was found for roughness for rules requiring changes in at least two segments (Rules 2 and 4, \( p<0.05 \)) and for percent involvement for the strictest rule (Rule 4, \( p<0.05 \)). No treatment effect on minimum lumen diameter was found.

Treatment Effect Sizes by Segment Characteristics

Multivariate analyses exploring the correlation of segment type, vessel location, and graft status on changes in QCA measures revealed two significant characteristics of arterial segments. These were 1) native coronary artery segments proximal to a graft insertion and hemodynamically related, and 2) native coronary arterial segments distal to a graft insertion and hemodynamically related. The location of the native artery vessel (left main, left anterior descending, circumflex, diagonal, marginal, right coronary, right coronary posterior descending, or other unnamed vessels) was not found to be related to changes in QCA measures.

Figure 1 shows for each QCA measure the effect sizes for these two segmental characteristics and contrasts them with effect sizes computed for all native arterial segments and for all bypass graft segments. For percent diameter stenosis, the effect size caused by drug therapy in all native arterial segments was moderate (30%, which corresponds to a treatment differential, i.e., drug change minus placebo change of \(-3.39\%\)). The effect size became large (53%), which corresponds to a treatment differential of \(-9.36\%) when analyses were restricted to native arterial segments.
proximal to a graft insertion and hemodynamically related. On the other hand, the effect size in segments in the bypass grafts was small (9%, which corresponds to a treatment differential of −0.82%). Drug treatment also had a moderate effect (23%) on changes in roughness in the native arteries. Although the treatment effect in all native arterial segments on minimum diameter was small (13%), there was a large effect (40%) on this QCA measure when restricting analyses to native arterial segments proximal to a graft insertion and hemodynamically related.

Relation of QCA to Panel-Based Global Coronary Score

Table 3 summarizes the results of the regression analyses relating QCA measures with the panel-based global coronary change score. The sign of the correlation coefficient indicates the direction of the association. In the native arteries, the significant univariate correlates with panel-based progression were 1) increased percent stenosis ($p<0.001$), 2) decreased minimum diameter ($p=0.009$), 3) increased numbers of progressing segments ($p=0.004$), and 4) increased numbers of occluded segments ($p=0.008$). In the bypass grafts, the significant univariate correlates were 1) increased percent stenosis ($p=0.02$), 2) increased progressing segments ($p=0.0002$), and 3) increased numbers of occluded segments ($p=0.03$).

When evaluated multivariately using stepwise multiple regression methods, the three independent and significant correlates of panel-based coronary change score were 1) increased percent stenosis in the native arteries;

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**Table 2. Categorical Analysis of Quantitative Coronary Angiography Measurements**

<table>
<thead>
<tr>
<th>QCA measurements</th>
<th>Rule 1</th>
<th>Rule 2</th>
<th>Rule 3</th>
<th>Rule 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug</td>
<td>Placebo</td>
<td>Drug</td>
<td>Placebo</td>
</tr>
<tr>
<td>Minimum diameter (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regressors</td>
<td>48%</td>
<td>51%</td>
<td>NS</td>
<td>34%</td>
</tr>
<tr>
<td>Percent stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regressors</td>
<td>45%</td>
<td>12%</td>
<td>0.001</td>
<td>25%</td>
</tr>
<tr>
<td>Roughness ×10 (mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regressors</td>
<td>34%</td>
<td>22%</td>
<td>NS</td>
<td>30%</td>
</tr>
<tr>
<td>Percent involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regressors</td>
<td>52%</td>
<td>37%</td>
<td>NS</td>
<td>39%</td>
</tr>
</tbody>
</table>

Rule 1: One lesion must change, mixed response uses modal tie-breaking; Rule 2: two lesions must change, mixed response uses modal tie-breaking; Rule 3: one lesion must change, mixed response considered no change; Rule 4: two lesions must change, mixed response considered no change.

*χ² on 1 degree of freedom comparing coronary status (regressors, all others) vs. treatment (drug, placebo).
TABLE 3. Significant Univariate and Multivariate Quantitative Coronary Angiographic Predictors of Panel-Based Global Coronary Change Score

<table>
<thead>
<tr>
<th>Univariate QCA predictors</th>
<th>Correlation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in percent stenosis (%)</td>
<td>0.34</td>
<td>0.001</td>
</tr>
<tr>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BG</td>
<td>0.26</td>
<td>0.02</td>
</tr>
<tr>
<td>Change in minimum diameter (mm)</td>
<td>-0.28</td>
<td>0.009</td>
</tr>
<tr>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressing segments* (No.)</td>
<td>0.31</td>
<td>0.004</td>
</tr>
<tr>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BG</td>
<td>0.39</td>
<td>0.0002</td>
</tr>
<tr>
<td>Change in occluded segments (No.)</td>
<td>0.28</td>
<td>0.008</td>
</tr>
<tr>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BG</td>
<td>0.23</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariate QCA predictors</th>
<th>R²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in percent stenosis (%)</td>
<td>0.36</td>
<td>0.0001</td>
</tr>
<tr>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressing segments (No.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BG</td>
<td></td>
<td></td>
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<tr>
<td>Change in occluded segments (No.)</td>
<td></td>
<td></td>
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<tr>
<td>NA</td>
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</table>

QCA, quantitative coronary angiography; NA, native arteries; BG, bypass grafts.
*Progression defined as >10% increase in percent stenosis.

Discussion

Treatment Effects

These results demonstrate that the required sample size of human coronary angiographic trials can be significantly reduced if computerized quantitative film evaluation is used to augment human film reading. Significant therapy effects were found by analysis of a randomly selected 52% (85 of 162) of all randomized patients despite the fact that image processing was applicable to arterial segments containing less than half (49%) of all visible lesions. Treatment benefit was established for percent stenosis regardless of whether a continuous (native arteries only, upper half of Table 1) or a categorical analysis (native arteries and bypass grafts, Table 2) was performed, and, in the case of the categorical analyses, regression was established regardless of the strictness of the scoring procedure (Table 2, Rules 1–4). No treatment differences were noted for bypass grafts when the data were analyzed continuously, although there was a tendency for deterioration in the placebo group (lower half of Table 1). In addition, when the data were analyzed categorically, based on changes in both native arteries and bypass grafts, the drug group showed a significantly greater proportion of regressors using coronary measures of roughness (Table 2, Rules 2 and 4) and percent involvement (Table 2, Rule 4).

In contrast to these findings, an analysis of the panel-derived global coronary change score at midtrial in CLAS (performed for safety monitoring by an unblinded external advisory committee) did not reveal a significant therapy effect. The highly significant effect we report from a 52% random sample of CLAS patients using QCA measures may be attributed at least in part to greater precision in image processing. On the other hand, because image processing was applied to a 49% subset of lesions that were, on average, less severe than the larger population visible to panelists,18 these segment-based results may be influenced by lesion-selection bias leading to increased treatment response.

Percent Stenosis as an End Point Measure

The use of percent stenosis, the classical coronary lesion severity measure, is strongly supported in our data. Percent stenosis is widely used in current clinical trials for establishing disease improvement or deterioration regardless of film evaluation procedure.4–13,16 Comparison of treatment effect sizes (Figure 1) indicates that percent stenosis is the single best measure for discriminating drug treatment from placebo in all native arterial segments (effect size, 30%). However, when the analysis was restricted to low or alternating flow areas, (i.e., hemodynamically related segments proximal to a graft insertion), the effect size increased to 53%, comparable to that reported in FATS4 for the lovastatin/colestipol–treated patients (effect size for nine proximal segments in ungrafted arteries, 61%; for all segments, 53%) but less than that reported for colestipol/niacin–treated patients (effect size for nine proximal segments in ungrafted arteries, 85%; for all segments, 84%).

Roughness as an Alternative End Point

Although the presence or absence of unstable angina and myocardial infarction have been shown to be associated with angiographic measures of native coronary artery vessel edge roughness,20,21 QCA estimates of coronary vessel edge roughness have not been reported in controlled clinical trials. In pilot studies of computerized image processing of femoral arteries, we found femoral artery edge roughness to be significantly correlated with atherosclerosis and cholesterol content of the vessel wall.22 In addition, we have reported that femoral artery edge roughness measurements demonstrated significant beneficial effects from colestipol/niacín therapy in CLAS patients.23 In this study, roughness in coronary native artery segments was significantly reduced in colestipol/niacín–treated patients (Table 1), with no significant change in placebo patients or significant between-group differences. Furthermore, when roughness was analyzed categorically, significant regression was found for drug-treated patients compared with placebo-treated patients for the rules based on classifying two or more segments (Rules 2 and 4, Table 2).

Minimum Diameter as an Alternative End Point

Minimum diameter within a coronary segment, a secondary end point in FATS,4 was found to increase significantly with colestipol/niacín when compared with conventional therapy. In CLAS films, the minimum diameter was not found to be a significant measure (effect size, 13%). However, when the analysis was restricted to low or alternating flow areas (i.e., hemodynamically related segments proximal to a graft insertion), the effect size increased to 40%, as good as that
reported in FATS for the lovastatin/colestipol–treated patients (effect size for nine proximal segments in ungrafted arteries, 40%; for all segments, 34%) but less than that reported for colestipol/niacin–treated patients (effect size for nine proximal segments in ungrafted arteries, 63%; for all segments, 69%).

**Percent Involvement as an Alternative End Point**

Percent involvement is of interest because of its similarity to an estimation of coronary atherosclerosis used for surveying populations in the International Atherosclerosis Project and the World Health Organization. In the International Atherosclerosis Project, the percent of intimal surface covered by raised lesions in coronary arteries that had been opened by longitudinal incision was shown to be a major determinant of risk of death from ischemic heart disease. Our QCA measure, percent involvement, which is also a longitudinal estimate of the percent of coronary surface involved by raised lesions, showed significant treatment effects with the classification rule that operationally was most strict in defining regression (Table 2, Rule 4).

**Differential Treatment Effect Sizes Above and Below Bypass Insertion Site**

Treatment effects on percent stenosis were directly related to whether the segment was proximal to a graft insertion and hemodynamically related to the bypass graft. The influence of bypass grafting on the progression of proximal disease has been previously noted. Other studies have shown that hemodynamic factors influencing coronary arterial flow after bypass grafting include initial extent of proximal obstruction, relative distensibility of graft and artery (these influence the occurrence of pulsatile bidirectional flow), and the angle of the anastomosis that influences jetting and recirculation from the bypass. It is known that the insertion of a bypass graft distal to severe stenoses leads to reduced proximal flow in the native arteries, whereas flow downstream is increased. Flow stagnation above the graft insertion leads to increased atherogenesis, and increased flow and shear stress below the graft insertion may result in less propensity to atherosclerosis. Beneficial effect of colestipol/niacin therapy was most consistently seen with different QCA measures in segments in which low flow and flow stagnation are more common.

**Relation of QCA Measures to Panel-Based Global Coronary Score**

Human panel readers can provide both percent stenosis severity estimates and global change score, an overall assessment of change in varied pathology of the native coronary arteries and bypass grafts. Global change score has the advantage of reflecting the accumulated clinical wisdom of experienced angiographers but suffers the disadvantage of lacking precise description. To determine which QCA descriptors were independently associated with coronary outcome, we chose the panel-based global coronary change score as a coronary outcome measure external to the QCA process.

Change in percent stenosis was the fundamental lesion severity measure used by human film panelists to determine the global coronary changes scores in CLAS films. QCA measures of percent stenosis, analyzed both as continuous and categorical variables, confirmed significant treatment effects reported by panelists. Long and coworkers have developed an expert system predicting human panel–derived global change scores using the sum of visual estimates of change in percent stenosis. We have extended these findings and have determined that computer-derived measures are significantly correlated with the global coronary change score. In CLAS films, significant QCA correlates of panel-based progression in both the native arteries and bypass grafts were increased percent stenosis, increased numbers of progressing segments, and increased numbers of occluded segments. In addition, decreased minimum diameter in the native arteries was found to be a significant correlate of panel-based progression. When evaluated multivariately, panel-based progression was found to be correlated with increased percent stenosis in the native arteries, increased number of occluded lesions in the native arteries, and increased number of progressing lesions in the bypass grafts.

Thirty-six percent of the variability in the global coronary change score was explained by the QCA measures. It is possible that a larger percentage of the variability could have been explained if more lesions ≥80% could have been measured by QCA. Lack of an appropriate segment of uninvolved vessel and the difficulty of the maximum gradient algorithm in tracking vessels more than 80% occluded were the most common reasons why our automated method of QCA could not be applied to advanced lesions. Computer procedures that measure percent stenosis require uninvolved reference segments (used to determine normal vessel contours) immediately distal or proximal to a target lesion. When nearby vessel segments are not usable, human readers estimated vessel contours from a distant vessel segment or from other views of the same segment.

**Study Limitations**

In CLAS, as in other human coronary angiographic trials, it is not technically or ethically possible to establish the validity of the angiographic change measures by comparison with "true" anatomy or histopathology. We have adopted the criterion of discrimination between colestipol/niacin–treated and placebo-treated subjects for evaluating QCA measures as indicators of atherosclerosis change. Our rationale is that monotherapy with the bile acid binding resin cholestyramine (activity similar to colestipol) and monotherapy with niacin have each been shown to reduce ischemic heart disease mortality rates. Furthermore, colestipol plus niacin treatment has been shown to beneficially reduce cardiac event rates and has been shown to influence coronary anatomy in three independent studies.

An additional approach to the evaluation of individual QCA measures is suggested by the recent finding that human panel–derived global coronary change scores from baseline to 3 years were significantly predictive of ischemic heart disease events over 7 years of follow-up in POSCH. These results indicate that selection of a gold standard for computerized coronary angiographic measures used in clinical trials could be based on an ability to predict coronary event rates. The predictive ability of combined human scores and computer-derived measures could also be evaluated.
Conclusions

These results demonstrate that 1) a variety of computer measures can be used as end points in coronary angiographic therapy trials, but change in QCA-measured percent stenosis correlates best with visual panel assessments and best reflects the treatment benefit and 2) when treatment effect sizes are moderate to large, the required sample size of coronary angiographic trials can be reduced when QCA is used.

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