Comparison of Computer- and Human-Derived Coronary Angiographic End-Point Measures for Controlled Therapy Trials

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The Cholesterol Lowering Atherosclerosis Study, a randomized angiographic clinical trial, demonstrated the beneficial effect of niacin/colestipol plus diet therapy on coronary atherosclerosis. Outcome was determined by panel-based estimates (viewed in both still and cine modes) of percent stenosis severity and change in native artery and bypass graft lesions. Computer-based quantitative coronary angiography (QCA) was also used to measure lesion and bypass graft stenosis severity and change in individual frames closely matched in orientation, opacification, and cardiac phase. Both methods jointly evaluated 350 nonoccluded lesions. The correlation between QCA and panel estimates of lesion size was 0.70 (p<0.0001) and for change in lesion size was 0.28 (p=0.002). Agreement between the two methods in classifying lesion changes (i.e., regression, unchanged, or progression) occurred for 60% (210 of 350) of the lesions (κ±SEM=0.20±0.05, p<0.001). The panel identified 442 nonoccluded lesions for which QCA stenosis measurements could not be obtained. Lesions not measurable by QCA included those with stenosis >85% that could not be reliably edge tracked, segments with diffuse or ectatic disease that had no reliable reference diameter, and segments for which matched frames could not be located. Seventy-nine lesions, the majority between 21% and 40% stenosis, were identified and measured by QCA but were not identified by the panel. This comparison study demonstrates the need to consider available angiographic measurement methods in relation to the goals of their use. (Arteriosclerosis and Thrombosis 1992;12:348-356)

KEY WORDS: angiography • atherosclerosis • clinical trials • lesion estimation • quantitative coronary angiography

Three methods of film evaluation are used in clinical trials that test treatments for coronary atherosclerosis. Among eight recent trials, three employed human readers who visually inspected matched film pairs, one hand traced and digitized vessel edges for computerized lesion measurement, and four used computerized vessel edge finding and lesion measurement. We refer to this third method as quantitative coronary angiography (QCA). Published comparisons of these methods indicate that both QCA and hand-digitized measurements are more reproducible than those determined visually by human readers. The majority of studies evaluating human performance have tested heterogeneous film readers who viewed films under reading conditions that are no longer used in clinical trials. Changes introduced into clinical film-reading procedures to increase their utility for clinical trials include the use of 1) high-quality films in which coronary views are matched and recorded in identical order, 2) expert angiographic readers, 3) an optimal reading environment to minimize distractions and reader fatigue, and 4) prepared sketches that individually characterize the anatomy of each patient. Further, it is known that existing QCA methods do not evaluate all coronary lesions (e.g., lesions occurring at branch junctions), and published reports do not indicate what fraction of lesions are measurable in typical study subjects. Finally, comparative studies have typically been confined to sets of "well-visualized" lesions in selected coronary angiograms; no comparisons have used all identified lesions in representative trial subjects. Major factors that limit the scope of current computer procedures to locate vessel edges for automated severity measurement are 1) insufficient image contrast in vessels narrowed to less than 0.4-0.5 mm, 2) difficulty of tracking through overlapping shadows and at the origin of branches, 3) a requirement that some nearby segments of the vessel present normal outlines in the same radiographic view, and 4) the need for complete mixing of contrast medium in the target segment. The Cholesterol Lowering Atherosclerosis Study (CLAS) was a randomized, controlled clinical trial that tested niacin/colestipol plus diet therapy in nonsmoking men with previous coronary bypass surgery. Target
vessels were chosen to provide as complete a survey of atherosclerosis as possible that was consistent with patient safety. Femoral, coronary, and cervical vessel beds were visualized in 162 patients at baseline and after 2 treatment years (CLAS-I) and in a subset of 103 patients after 4 years (CLAS-II). A pilot study of computerized estimates of femoral atherosclerosis was used in 1975 to plan the sample size for CLAS. A coronary end-point determination by a panel of human readers, used for safety monitoring during the conduct of CLAS-I, was the first end point reported. Two-year femoral vessel results with computer measurements and 4-year coronary vessel results with panels of human readers have also been reported. We have determined in a random sample of 20 CLAS baseline films that sampling and averaging three sequential frames at end diastole yielded a cycle-to-cycle variability in QCA-determined percent stenosis of 8.2%. Also, we have demonstrated in all 162 pairs of baseline/2-year angiograms that human panel readers independently agreed on the size of the lesion or the change in lesion (percent stenosis ± 10%) 80% of the time.

In this article, we report a limited comparison of human panel reading and QCA in a 50% random sample of baseline/2-year coronary film pairs evaluated by both methods. We first compare the two methods of film evaluation with regard to lesion identification. However, because the angiographic views used in CLAS were not optimized for QCA analysis, the primary objective of this article is to contrast the estimation of lesion size and lesion change and the classification of lesions (e.g., unchanged, regressing, or progressing) for those lesions identified by both methods.

Methods

Study Population

CLAS-I study design and conduct have been described in detail elsewhere. Randomization to one of two treatment groups (drug plus dietary intervention or placebo plus 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/1 (185 and 350 mg/dl) and a confirmed lipid-lowering response to the study medication before randomization. A total of 162 men completed baseline and 2-year angiograms in CLAS-I, 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 as determined by panels of human readers on visual inspection of the changes in individual lesions in native arteries and bypass grafts.

The Panel Reading Method

The CLAS panel reading method has been previously described. In brief, a panel consisted of a moderator and two readers who evaluated two paired coronary films (film A mounted on the left projector and film B mounted on the right projector, as set by predetermined randomization). 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 on film A. Because it was believed that a reader could not reliably evaluate lesions smaller than 20%, any visible lesion believed to be <20% was recorded as 20%. Readers independently agreed on identified lesions 82% of the time and independently agreed on estimated percent stenosis (within 10%) 76% of the time. Next, a consensus diagram of film A was created after open discussion by the two readers with the moderator. Using the film A consensus diagram as a guide, the readers then independently viewed film B to evaluate changes in lesion size as well as to identify and estimate additional lesions, if any, that were not apparent on film A. Again, the smallest recorded percent stenosis was 20%. Readers independently agreed on a change in lesion 51% of the time and independently agreed on the size of lesion change (percent stenosis within 10%) 81% of the time. Another open discussion took place, and a consensus diagram of changes observed in film B was created. All lesions were uniquely labeled on this diagram for subsequent analyses with QCA. The interpanel variability in identifying lesions or lesion severity was less than 15%. However, more variability was seen in interpanel identification of lesion change (53%) and amount of change (20%).

Quantitative Coronary Angiography: Frame Selection

Details of the methods for QCA have been previously described. QCA employs dual projectors for view matching and simultaneous digitization of paired films. For QCA, film pairs were processed in tandem, and frames were selected for analysis only if the angiographic view of each segment was closely matched for segment orientation, degree of uniformity of contrast filling, cardiac phase, and film exposure. Arterial segments were defined from branch to branch. 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. For each film, all processable segments were tracked and evaluated.

Quantitative Coronary Angiography: Vessel Edge Tracking

To find the edges of a vessel, the computer operator first identified the approximate vessel midline with a cursor. The computer algorithm then searched perpendicularly to this midline to find the points of maximum intensity gradient, which were identified as vessel edges. A new midline was defined as the smoothed midpoints of the edge, and the tracking process was repeated. The search was restricted to a window of pixel values centered on the previously detected edge point.

Because absolute measures of lumen geometry (e.g., minimum and average diameter) were made in addition to lesion stenosis, edge coordinates were corrected for pin cushion distortion with a 1-cm grid filmed in the anterior position at the beginning of each angiogram. The correction transformed the image coordinates separately for each of the 100 squares on the grid. Because the film quality and lesion visualization were superior in the right anterior oblique (RAO) view, this projection was chosen as the preferential view for QCA analysis.
Ninety-three percent of all segments were processed in this view: RAO30° (49%), RAO15° (15%), and RAO45° (34%). In situations where a lesion was not accessible in this view, the left anterior oblique (LAO) projection was substituted, provided that the segment under consideration was positioned in the center of the field, where distortion is minimal.

To avoid overestimation of narrow points within arterial sections, the number of pixels used to calculate intensity gradients was adjusted from five to 13 according to the average width of the previous five vessel diameters. Computed intensity gradients for edge location were smoothed across three to seven pixels, depending on the size of the moving window. To reduce the effect of multiple gradient maxima/minima in a single scan line (typically due to branches or nearby vessels), an exponential weighting function, centered at a distance from the midline corresponding to the prior edge location, was applied to the smoothed gradient values. The coordinates of the maximum weighted gradient were selected as the edge point. To reduce technician-associated variability in selecting the initial midline, each edge search was repeated using a new computer-generated midline derived from initially detected edges. All diameters were converted to millimeters by a scaling factor, using the known diameter of the catheter and the corrections from the radiographic grid.

**Quantitative Coronary Angiography: Measurement Acceptance Criteria**

Twenty-five descriptors of lumen geometry, predominantly derived from diameter measurements, were obtained for each segment in each of three sequential digitized frames. The coefficient of variation of average and minimum diameters of the segment for the three frames was calculated and was 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, if the segment was too small, or if the image quality was poor), the operator eliminated the segment from the database. Lumen geometry measurements for acceptable sequential frames were then averaged.

**Quantitative Coronary Angiography: Lesion Measures**

For the comparison study, a panel/QCA database was generated, consisting of information from both methods of film evaluation of individual lesions. Eighty-five of 162 pairs of panel-read angiograms had been randomly selected for analysis by QCA. In total, 731 native arterial segments were tracked and evaluated, with an average of 326 measurable diameters per segment and a median length of 25 mm. The 731 segments included 429 (59%) segments with measurable lesion stenosis and 302 (41%) segments assessed with other lumen descriptors.

The panel/QCA lesion database was generated as follows. The QCA technician matched the computer-located lumen narrowing in processable segments with the panel-identified lesions. Lesion size (percent stenosis) was calculated as 100 (1 – LMD/D90), where LMD (the lesion minimal diameter) represented an average across five diameters centered around the computer-identified minimum within the area of the lesion, and D90 (the 90th percentile of the segmental diameter profile) was taken as an estimate of the "normal" or predisease size of the lumen. If D90 was judged to misrepresent normal vessel diameter because of advanced diffuse disease or vessel ectasia, percent stenosis was not calculated.

Percent stenosis was also calculated for areas of luminal narrowing identified by the QCA technician in computer-generated vessel edges but not labeled as a lesion by the panel. Separate labels were assigned to these lesions.

**Statistical Analysis**

The two methods of film evaluation were compared with regard to lesion identification, lesion size, lesion change, and lesion classification (unchanged, regressed, or progression). With regard to lesion identification, distributions were generated for lesions identified by both the panel and QCA, those identified by the panel but not evaluated by QCA, and those identified by QCA but not identified by the panel. Differences in distributions of lesion size and location were assessed using χ² procedures.

For the lesions evaluated by both methods on the baseline film, the absolute difference (|panel−QCA|) in lesion size was calculated and correlated (using stepwise regression methods) with 1) panel-based lesion size (0% or 20%, 21–40%, 41–60%, 61–80%, >80%); 2) status of the coronary segment (grafted or ungrafted); 3) segment location (left main, left anterior descending, circumflex, diagonal, marginal, right coronary, right coronary branches, and "all other"); 4) interpanelist agreement on the presence of a lesion (both or only one identified the lesion); and 5) interpanelist agreement on lesion size (≤10% or >10%).

In addition, the lesion change from baseline to 2 years was calculated for each method. The absolute difference (|panel−QCA|) in lesion change was correlated (using stepwise regression methods) with 1) panel-based lesion size; 2) coronary segment status; 3) segment location; 4) interpanelist agreement on the presence of change (both or only one indicated change); and 5) interpanelist agreement on the amount of change (≤10%, 11–20%, >20%). Each panel-identified lesion was classified as unchanged, progressing, or regressing (after decoding the temporal order of films A and B). For QCA, a lesion was classified as unchanged if the 2-year minus baseline change in percent stenosis was within 10%. A progressing lesion was one with a positive change in percent stenosis >10%, whereas a regressing lesion was one with a negative change >10%. A cutoff of 10% was adopted by Brown et al in a recent clinical trial because it represented three times the standard deviation of repeated measurement variances with computer-assisted QCA. Intermethod agreement in lesion change was assessed using the κ statistic.

**Results**

**Lesion Identification**

As shown in Figure 1, among the 1,022 identified lesions, 79 nonocclusive lesions (8% of total) were
evaluated only by QCA; 350 nonocclusive lesions (34%) were identified and evaluated jointly by the panel and QCA; 151 occlusive lesions (15%) were evaluated only by the panel but could also have been identified by the computer operator; and 442 nonocclusive lesions (43%) were identified and evaluated only by the panel. Although direct comparison of the two procedures was possible in 350 lesions, it was potentially possible in 501 (350+151) lesions (49%). Table 1 presents the distribution of all lesions stratified by lesion size.

The upper panel of Figure 2 demonstrates that as panel-based lesion estimates increased in size, fewer lesions could be evaluated by QCA. The location of lesions also influenced whether QCA could be applied (Figure 2, lower panel). Of the 442 nonocclusive lesions that QCA was not able to evaluate, 46 (10%) were in segments that could be tracked but that lacked a reliable D90 measurement, and 396 (90%) were in segments that could not be tracked. In addition, 151 segments were identified as total occlusions in both films (the lumen did not appear on the film and therefore could not be tracked). Other reasons that segments were not processed included 1) incomplete or nonhomogeneous vessel opacification; 2) insufficient image contrast due to "tissue blush" (residual dye in the background); 3) image "burnout," especially in distal segments of the left anterior descending artery; 4) overlapping vessels, sternal wires, and graft marking clips that interfered with edge tracking; and 5) matched views not available for a specific segment.

The 79 lesions evaluated by QCA but not recognized by the panel were significantly different from lesions evaluated by both QCA and the panel with regard to size (p<0.001) and location (p<0.001). Lesions located by QCA but not by the panel were smaller (77% QCA-identified versus 53% panel-identified lesions were <40% stenosis) and were more prevalent in branches of the right coronary artery (8% QCA versus 2% panel) and in unnamed branches (10% QCA versus 2% panel).

### Lesion Size

Table 2 presents the distribution of the absolute difference in estimated lesion size between the panel and QCA for all lesions and the distributions of the absolute difference in estimated lesion change for lesions that (according to the panel) changed and those that did not. Analysis of all lesions (data at the top of Table 2) is discussed first. The correlation (Spearman) between the panel and QCA measurements of lesion size was 0.70 (p<0.0001). The median absolute difference between the panel and QCA measurements of lesion size was 0.70 (p<0.0001). The median absolute difference between the panel and QCA measurements of lesion size was 10% (5th–95th percentile, 1–33%). (An example of an absolute difference of 10% is a panel estimate of 60% percent stenosis and a QCA estimate of 50%).

Stepwise regression analysis revealed that panel-based lesion size was the single best predictor of the absolute difference between the panel and QCA mea-

### Table 1. Lesions Identified by Panel and by Quantitative Coronary Angiography

<table>
<thead>
<tr>
<th>Lesion size*</th>
<th>Total</th>
<th>Both QCA and panel</th>
<th>Panel only†</th>
<th>QCA only</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–20%</td>
<td>175</td>
<td>90</td>
<td>77</td>
<td>8</td>
</tr>
<tr>
<td>21–40%</td>
<td>284</td>
<td>120</td>
<td>111</td>
<td>53</td>
</tr>
<tr>
<td>41–60%</td>
<td>185</td>
<td>73</td>
<td>95</td>
<td>17</td>
</tr>
<tr>
<td>61–80%</td>
<td>124</td>
<td>42</td>
<td>81</td>
<td>1</td>
</tr>
<tr>
<td>81–99%</td>
<td>103</td>
<td>25</td>
<td>78</td>
<td>0</td>
</tr>
<tr>
<td>100%</td>
<td>151</td>
<td>0</td>
<td>151</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1,022</td>
<td>350</td>
<td>593</td>
<td>79</td>
</tr>
</tbody>
</table>

QCA, quantitative coronary angiography.

*Panel-based percent stenosis except for "QCA only," which is QCA based.
†Occlusive plus nonocclusive (see Figure 1).
measurements of lesion size ($R^2=0.15$). As shown in Figure 3, agreement was best for lesions between 41% and 60% stenosis. The median QCA estimates were larger than the median panel measurements for small lesions ($\leq 40\%$), but the median panel measurements became increasingly larger than the median QCA measurements with increasing panel-based lesion size ($\geq 61\%$ stenosis). The other independent variables (e.g., status of the coronary segment, segment location, and interpanelist agreement on the presence of a lesion or on lesion size) did not significantly improve the prediction.

Change in Lesion Size

Table 2 (middle) presents the distribution of the absolute difference in the amount of change between the panel and QCA evaluations for the 122 lesions that the panel considered had changed. The correlation (Spearman) between the panel and QCA measurements of lesion change was 0.28 ($p=0.002$). The median absolute difference between the panel and QCA measurements of change was 10% (5th–95th percentile, 1–32%). (An example of an absolute difference of 10% in percent stenosis is a panel-based change estimate of 30% and a QCA-based change estimate of 20%.)

Stepwise multiple regression indicated that the panel-based amount of change was the single best predictor of the difference between the panel and QCA evaluations of the amount of change ($R^2=0.36$). As shown in Figure 4, agreement was best when the amount of change was small and worsened as the amount of change increased. The median panel estimate of change was always larger than that of QCA. The other independent variables (e.g., coronary segment status, segment location, and interpanelist agreement on the presence of a lesion or on lesion size) did not significantly improve the prediction.

Table 2 (bottom) presents the distribution of the absolute value of the amount of QCA change for the 228 lesions that the panel considered to be unchanged. Results of stepwise regression analysis revealed that panel-based lesion size, coronary segment status, segment location, interpanelist agreement on the presence of change, and interpanelist agreement on the amount of change were not significantly associated with the QCA evaluation of the amount of change for these lesions.
TABLE 2. Absolute Difference Between Panel and Quantitative Coronary Angiography Evaluations

<table>
<thead>
<tr>
<th>Difference</th>
<th>No.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>In lesion size (n=350)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–10%</td>
<td>173</td>
<td>(49%)</td>
</tr>
<tr>
<td>11–20%</td>
<td>113</td>
<td>(32%)</td>
</tr>
<tr>
<td>21–40%</td>
<td>57</td>
<td>(16%)</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>7</td>
<td>(2%)</td>
</tr>
<tr>
<td>In estimates of change in lesions that a panel considered to have changed (n=122)t</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–10%</td>
<td>61</td>
<td>(50%)</td>
</tr>
<tr>
<td>11–20%</td>
<td>40</td>
<td>(33%)</td>
</tr>
<tr>
<td>21–40%</td>
<td>18</td>
<td>(15%)</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>3</td>
<td>(2%)</td>
</tr>
<tr>
<td>In estimates of change in lesions that a panel considered unchanged (n=228)t</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–10%</td>
<td>174</td>
<td>(76%)</td>
</tr>
<tr>
<td>11–20%</td>
<td>49</td>
<td>(22%)</td>
</tr>
<tr>
<td>21–40%</td>
<td>5</td>
<td>(2%)</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>0</td>
<td>(0%)</td>
</tr>
</tbody>
</table>

QCA, quantitative coronary angiography.

*Difference=|%stenosis (QCA)−%stenosis (panel)|.
†Difference=|change in %stenosis (QCA)−change in %stenosis (panel)|.
‡Difference=|change in %stenosis (QCA)−0|.

Lesion Classification as Progression, Regression, or Unchanged

Figure 5 presents the distribution of QCA-based lesion changes at 2 years for the panel-based unchanged, progressing, and regressing lesions. The median (5th–95th percentile) QCA-based change was -6% (-28% to 10%) for panel-based regressing lesions, -2% (-16% to 13%) for unchanged lesions, and 5% (-9% to 42%) for progressing lesions. Using the 10% QCA change rule employed by Brown et al., we classified QCA-based lesion changes as progressing, regressing, or unchanged. Agreement between the panel and the QCA classifications (i.e., regression, no change, or progression) occurred for 60% (210 of 350) of the lesions (κ±SEM=0.20±0.05, p<0.001). Disagreement on the direction of change occurred for only five lesions (1%). Among the 85 angiograms, the panel found 13 “new” lesions (e.g., 0% stenosis at baseline) and seven “disappearing” lesions (e.g., 0% stenosis at 2 years). As shown in Table 3, new lesions according to QCA had a median percent stenosis of 24% at baseline and 35% at 2 years; the disappearing lesions had a QCA median percent stenosis of 27% both at baseline and at 2 years.

Discussion

The angiographic protocols used in CLAS, as well as the methods for panel and QCA lesion evaluation, were not originally designed for a comparison of methods. Consequently, the results described in this article are specific to CLAS study design and methods. Specifically, angiographic views were not optimized for QCA analysis (e.g., no cranial views were included) so that many lesions evaluated by the panel could also have been analyzed by QCA if different views were available. In addition, the majority of QCA evaluations were derived from RAO views (the LAO view was used for only 7% of the measurements), whereas the panel carried out its assessment using both RAO and LAO views. As a result, the emphasis of this comparative study is on the 350 nonocclusive lesions that were suitable for analysis by both methods.

Lesion Identification

Evaluation of CLAS angiograms by panel readers and QCA derives information from different but overlapping sets of coronary lesions (Figure 1). As we cannot assume that either the panel or QCA identified all lesions present, these sets cannot be regarded as a random sample of the entire lesion population. In fact, inherent limitations of each method resulted in a biased
sampling of the population of all lesions. Therefore, the best available estimate of the total lesion population for CLAS patients is the sum of the counts from both procedures.

The 79 lesions identified and evaluated by QCA but not by the panel were principally early lesions. Identification of early lesions is of particular value for primary atherosclerosis prevention. Unbiased identification of early lesions with QCA is possible only with a protocol such as ours, where all trackable segments are processed to detect minor vessel edge irregularities. Early lesions recognized only by QCA will not be recorded in trials in which humans trace the lesions or preselect the lesions for computer processing.

The 442 nonocclusive lesions identified and evaluated by the panel but not by QCA included 159 lesions with stenosis >60% (Figure 2, upper panel). Lack of an appropriate segment of the uninvolved vessel and the inability of the computer to track vessels more than 80% occluded were the most common reasons why QCA could not be applied to advanced lesions. Computer procedures that measure percent stenosis require uninvolved reference segments (used to determine normal vessel contours—D90 by our procedure) immediately
Table 3. Comparison of Panel and Quantitative Coronary Angiography Evaluation of "New" and "Disappearing" Lesions

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Panel</th>
<th>QCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;New&quot; (n=13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0%</td>
<td>24% (21–34%)</td>
</tr>
<tr>
<td>2-Year</td>
<td>30% (20–30%)*</td>
<td>35% (29–39%)</td>
</tr>
<tr>
<td>&quot;Disappearing&quot; (n=7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20% (20–30%)</td>
<td>27% (24–29%)</td>
</tr>
<tr>
<td>2-Year</td>
<td>0%</td>
<td>27% (24–28%)</td>
</tr>
</tbody>
</table>

QCA, quantitative coronary angiography.
*Median (25th–75th percentiles).

distal or proximal to a target lesion. Forty-six advanced lesions had no nearby uninvolved vessel segment. 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. With regard to lesion location, the most clinically important discrepancy between the panel and QCA lesion identification occurred for the left main artery (Figure 2, lower panel), in which 67% of panel-identified lesions could not be evaluated by QCA.

The fact that substantial numbers of segments could be evaluated by the panel but not by QCA is, on first inspection, rather disturbing. However, it should be pointed out that the segments rejected for QCA are generally poor-quality images that would result in high variability for any derived measurements. Consequently, imposing the acceptance criteria described previously resulted in QCA measurements that are more reliable than would be the case if poor-quality images were allowed to be analyzed.

Lesion Size, Lesion Change, and Lesion Classification

Agreement between panel and QCA lesion size measurements varied with panel-based lesion size (Figure 3). As the panel-based lesion size increased, panel estimates became increasingly larger than QCA estimates. A similar pattern was seen for determinations of lesion change (Figure 4). On average, agreement on the amount of change worsened with increasing panel-based estimates of change. These findings are consistent with those reported by Fleming and coworkers.19

On the other hand, when a 10% QCA change rule was applied, agreement with regard to the classification of lesions as unchanged, progressing, or regressing was relatively good; only two among 56 panel-based regressing lesions were classified by QCA as progressing lesions, and three among 53 panel-based progressing lesions were classified by QCA as regressing lesions. Finally, of the 75 panel-based changed lesions classified by QCA as unchanged (i.e., <10%), 30% were regarded by the panel as large changes (>20%), 35% were regarded as moderate changes (in the range 10–15%), and 25% were regarded as minor changes (5%).

The 10% change rule arising from the study of Brown et al4 is in agreement with the 8.2% cutoff arising from our data.17 Our study, however, arose from an optimal situation, as we evaluated cycle-to-cycle variability on selected lesions within the same angiographic trial, whereas Brown et al evaluated interangiogram variability. It is of interest, however, that with our cutoff of 8.2%, the agreement between the panel and QCA classification (κ=SEM=0.21±0.05) was similar to that using the Brown cutoff of 10% (0.20±0.05).

With regard to the estimates of lesion size, discrepancies at both ends of the scale are understandable in light of known physical factors in vessel edge recognition and image data processing. Both humans and computers locate the vessel edge points by detecting differences in shades of gray between contrast medium in the vessel and outside tissue densities. The angiographic process can be visualized as a series of parallel x-ray beams traversing a contrast-filled vessel, with shorter paths near the vessel edges and the longest path through the maximum diameter.20 The vessel edge is recognized at the shortest path producing a film contrast density differing from background tissue. Computer image processing detects smaller film contrast differences than do humans and is, therefore, more sensitive to early lesion formation. Thus, QCA estimates of percent stenosis are larger than panel estimates for lesions with <40% stenosis (Figure 3). For the same reason, when humans report the appearance of new lesions, QCA demonstrates that lesions already present but beneath the threshold for human recognition have grown (Table 3).

Physical factors also explain the differences between panel readings and QCA in estimating the severity of advanced lesions. In this case, panel readers recorded more severe stenosis than did QCA. The amount of contrast medium in the maximum diameter of a narrow residual channel limits the ability of humans and computers to identify the vessel lumen. Evaluation of high degrees of stenosis by QCA is limited by the number of pixels across a vessel shadow required for edge detection algorithms to function. In our system, this limiting number is approximately six to eight pixels, equivalent to a vessel narrowing of 0.4–0.5 mm. Thus, for an artery with a nondiseased (reference) diameter of 3.0 mm, stenosis >83–86% cannot be reliably measured. On the other hand, once a vessel lumen has been recognized in the narrowest part of a tight stenosis, human readers use a variety of complex maneuvers to estimate a normal diameter and to calculate the percent stenosis. These include use of information from distant segments of the same vessel, use of information from other views, and use of information derived from myocardial filling.

The use of noncontiguous reference segments and myocardial filling patterns, maneuvers that are not possible with computer algorithms currently available, presents the possibility of overinterpretation of angiograms by human readers. However, the current consensus is that human readers tend to underestimate the severity of lesions because adjacent reference segments are also diseased. This causes readers to underestimate the severity of stenotic points by diminishing the size of diameters used for "normal reference." An experiment by Weiner et al21 has directly confirmed this cause of underrecognition of stenosis severity.

Disappearing Lesions

Our findings indicate that when humans report complete disappearance of a small lesion, computer measurements do not confirm the change. This finding, which suggests that 2 years of current therapy does not
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completely restore normal vessel anatomy even in small lesions, is in accord with microscopic and functional findings of residual vessel pathology after atherosclerosis regression in animal models. It does not negate the improvements observed in larger lesions, but it does reemphasize the idea that the most effective control of atherosclerosis will be a reduction of the formation of lesions rather than a reversal of existing lesions.

Conclusions

This comparison study demonstrates the need to consider available angiographic measurement methods in relation to the goals of their use. In trials for which target lesions have been designated in advance and are known to be computer processable (e.g., trials of thrombolysis or angioplasty in straight vessel segments), the full benefit of QCA in reducing subject numbers or detecting lesser therapy effects will be realized. However, in trials of systemic therapy in which all lesions are targets (e.g., trials of lipid-lowering agents, antihypertensives, and calcium-blocking agents), the benefits of precision from QCA could be diminished by loss of measurement numbers. This loss can induce bias in both per-subject and per-lesion outcome evaluations, with selective loss of advanced lesions as a potential concern.

On the other hand, in trials of long duration, the value of a per-lesion interpretation with QCA measurements may be enhanced by a greater ability to measure changes in small lesions. Although angiographic trials are conducted in subjects with symptomatic coronary disease (who have relatively advanced lesions), a bonus that should be exploited is the chance to study the formation and growth of early lesions because this might lead to more effective primary atherosclerosis prevention. Here, the performance of QCA, if applied to all processable segments without preselection by human readers, is clearly superior to human performance.

This study is limited to measures of percent stenosis in discrete lesions. QCA also provides a plethora of other measures, including those characterizing vessel edge roughness and length of lesion involvement. We are currently evaluating those measures with regard to treatment effect.

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Comparison of computer- and human-derived coronary angiographic end-point measures for controlled therapy trials.

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