# Appendix F. Statistical analysis report for effectiveness and cost-effectiveness of echocardiography and carotid imaging in the management of stroke

Benjamin K. S. Chan, M.S.*

January 29, 2002

*Evidence-based Practice Center, Division of Medical Informatics and Outcomes Research, Oregon Health and Science University, Mail Code: BICC, 3181 SW Sam Jackson Park Road, Portland, Oregon 97201-3098, tel: 503 494 1607, fax: 503 494 4551, e-mail: chanb@ohsu.edu

# 1 Statistical methods

## 1.1 Logistic regression model

When the data was in the form of number of events ($y_i$) per number of study subjects ($n_i$) a logistic regression model was fit on the data. The model allowed for the estimation of odds ratios. Rates were estimated if the included studies were designed to allow for estimation.

If the length of follow-up varied between study we estimated the number of expected events over one month. Equation 1 was used to do this.

$$y_i = n_i \left(1 - \left(1 - \frac{y_i'}{n_i}\right)^{1/t_i}\right) \tag{1}$$

$y_i$ was rounded to the nearest integer. The units for $t_i$ was months.

The logistic regression model used to fit the data was

$$\begin{aligned}
y_i &\sim \text{Binomial}(\pi_i, n_i) \\
\text{logit}(\pi_i) &= \alpha + \eta_i + z_i\sigma^2 \\
\eta_i &= \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_j x_{ij} \\
\alpha &\sim \text{Normal}(\cdot, \cdot) \\
\beta_j &\sim \text{Normal}(\cdot, \cdot) \\
z_i &\sim \text{Normal}(0, 1) \\
\sigma^2 &\sim \text{Normal}(\cdot, \cdot) \in [0, \text{inf})
\end{aligned}$$

This model is a random effects model where $\sigma^2$ is the between-study variance.

Bayesian data analysis was used to fit the models. Posterior probabilities distributions were simulated using Gibbs sampling. Bayesian data analysis produces *credible intervals* as opposed to confidence intervals. In this report, credible intervals (in the Bayesian context) are termed confidence intervals. A credible interval for $\pi$ is an interval where 95% of the posterior probability lies between. A $p$-value shown in the results is the probability the parameter is greater than 0, $p = \text{Prob}(\beta_j > 0)$. This is different from the usual $p$-value reported from a test of a null hypothesis, where low values indicate the null hypothesis is unlikely. Values of $p$ close to 1 indicate $\beta_j > 0$ with high probability. Values of $p$ close to 0 indicate $\beta_j < 0$ with high probability. In either case, there is a high probability of a difference.

Noninformative, proper priors are used in the analysis.

## 1.2 Model for receiver operating characteristic (ROC) curves

Let the true positive rate of a test be denoted by TPR and the false positive rate be denoted by FPR. The equation that describes an ROC curve has the form

$$D = \alpha + \beta S$$

where

$$\begin{aligned}
D &= \text{logit(TPR)} - \text{logit(FPR)}, \text{ and} \\
S &= \text{logit(TPR)} + \text{logit(FPR)}
\end{aligned}$$

$\alpha$ is the main determinant of shape. $\beta$ is the determinant for symmetry about the 1:1 line.

The summary ROC meta-analysis used the following model.

$$\begin{aligned}
D_i &\sim \text{Normal}(\eta_i, \tau_i) \\
\eta_i &= \alpha + \beta S_i + z_i \sigma^2 \\
\tau_i &= \frac{1}{a+0.5} + \frac{1}{b+0.5} + \frac{1}{c+0.5} + \frac{1}{d+0.5} \\
\alpha &\sim \text{Normal}(\cdot, \cdot) \\
\beta &\sim \text{Normal}(\cdot, \cdot) \\
z_i &\sim \text{Normal}(0, 1) \\
\sigma^2 &\sim \text{Normal}(\cdot, \cdot) \in [0, \inf)
\end{aligned}$$

The model is a random effects model where $\sigma^2$ is the between-study variance. Explanatory covariates can be added to the linear predictor $\eta_i$.

Noninformative, proper priors are used in the analysis.

Summary ROC curves were plotted using the estimates for $\alpha$ and $\beta$. The relation between sensitivity and specificity is given in Equation 2.

$$\text{logit}(\text{TPR}) = \left( \frac{\alpha + (\beta + 1)\text{logit}(\text{FPR})}{1 - \beta} \right) \tag{2}$$

To draw the curves, 100 equally spaced points along the $x$-axis of FPR were taken and Equation 2 was used to calculate sensitivity (TPR).

**Maximal accuracy.** Overall accuracy is defined as

$$A = \text{Sensitivity} + \text{Specificity}$$

The point along the summary ROC curve where $A$ is maximized was crudely found from the 100 points used for plotting. Accuracy was also examined for fixed points of sensitivity and specificity. These points were at 90%, 95%, and 99%.

# 2 Yield of echocardiography

Pooled rates for TTE and TEE are shown on Table 1. Rates and odds ratios for TTE stratified by unselected and no carotid artery diseased populations are shown on Table 2. Rates and odds ratios for TEE stratified by unselected and no carotid artery diseased populations are shown on Table 3. The results are from models described in Section 1.1.

**Table 1: Pooled yield rates of echocardiography using all studies, unstratified.**

| Test | Event | $\pi$ % | 95% CI |
|---|---|---|---|
| TTE | LVT | $0.19$ | $7.688 \times 10^{-4}, 6.209$ |
| | LAT+LVT | $0.2123$ | $2.532 \times 10^{-3}, 6.357$ |
| | Myxoma | $2.767 \times 10^{-7}$ | $0.0, 0.1595$ |
| TEE | LAT | $1.766$ | $0.5288, 4.644$ |
| | LAT+LVT | $2.593$ | $1.039, 5.406$ |
| | ASA | $6.883$ | $2.405, 14.1$ |
| | AoAth | $3.364$ | $1.212, 6.845$ |
| | Myxoma | $0.0$ | — |

**Table 2: Pooled yield rates of TTE stratifying by studies of unselected patients and studies having patients without carotid artery disease.**

| Event | Stratum | $\pi$ % | 95% CI |
|---|---|---|---|
| LVT | Unselected | $0.09264$ | $1.851 \times 10^{-4}, 57.02$ |
| | Without carotid artery disease | $0.00884$ | $1.347 \times 10^{-3}, 67.0$ |
| | $p(\beta > 0) = 0.734$ | | |
| | OR: $7.903$ $(1.874 \times 10^{-4}, 81580.0)$ | | |
| LAT+LVT | Unselected | $0.06479$ | $2.909 \times 10^{-5}, 4.993$ |
| | Without carotid artery disease | $0.03386$ | $3.092 \times 10^{-7}, 4.725$ |
| | $p(\beta > 0) = 0.317$ | | |
| | OR: $0.2868$ $(2.593 \times 10^{-4}, 4512.0)$ | | |
| Myxoma | Unselected | $6.836 \times 10^{-11}$ | $0.0, 0.3539$ |
| | Without carotid artery disease | $0.0$ | — |
| | $p(\beta > 0) =$ — | | |
| | OR: — | | |

**Table 3: Pooled yield rates of TEE stratifying by studies of unselected patients and studies having patients without carotid artery disease.**

| **Event** | **Stratum** | $\pi$ **%** | **95% CI** |
|---|---|---|---|
| LAT | Unselected | $0.9752$ | $0.1314, 3.498$ |
| | Without carotid artery disease | $4.12$ | $0.7867, 12.38$ |
| | $p(\beta > 0) = 0.9102$ | | |
| | OR: $4.322$ $(0.4805, 33.99)$ | | |
| LAT+LVT | Unselected | $1.691$ | $0.4835, 5.331$ |
| | Without carotid artery disease | $4.53$ | $1.194, 11.3$ |
| | $p(\beta > 0) = 0.8926$ | | |
| | OR: $2.729$ $(0.4021, 12.14)$ | | |
| ASA | Unselected | $9.774$ | $2.488, 37.45$ |
| | Without carotid artery disease | $4.943$ | $1.197, 14.41$ |
| | $p(\beta > 0) = 0.2044$ | | |
| | OR: $0.5032$ $(0.04074, 2.625)$ | | |
| AoAth | Unselected | $3.504$ | $0.2584, 25.98$ |
| | Without carotid artery disease | $3.027$ | $0.383, 10.69$ |
| | $p(\beta > 0) = 0.4508$ | | |
| | OR: $0.894$ $(0.03474, 14.15)$ | | |
| Myxoma | Unselected | $0.0$ | — |
| | Without carotid artery disease | $0.0$ | — |
| | $p(\beta > 0) =$ — | | |
| | OR: — | | |

# 3 Accuracy of echocardiography

The results are from models described in Section 1.2.

Estimates for the summary ROC parameters $\alpha$ and $\beta$ are shown on Table 4. Plotted curves are shown on Figures 1, 2, and 3.

Sensitivities and specificities corresponding to points of maximum accuracy are shown on Table 5. Accuracy data from fixed points are shown in Table 6.

**Table 4: Estimated summary ROC curve parameters for echocardiography.**

| **Test** | $\alpha$ | **95% CI** | $\beta$ | **95% CI** |
|---|---|---|---|---|
| TTE for LVT | $2.843$ | $-0.3596, 6.646$ | $-0.5991$ | $-3.511, 2.881$ |
| excluding poor quality studies | $3.729$ | $-4.177, 10.52$ | $-0.08464$ | $-7.014, 5.083$ |
| TTE for LAT | $5.909$ | $-1.478, 13.16$ | $0.3641$ | $-1.039, 1.794$ |
| excluding poor quality studies | $4.983$ | $-1.157, 12.6$ | $0.1564$ | $-1.149, 1.638$ |
| TEE for LAT | $4.525$ | $1.126, 8.471$ | $-1.08$ | $-2.791, 0.7045$ |
| excluding poor quality studies | $4.007$ | $-2.559, 8.407$ | $-1.284$ | $-4.605, 1.03$ |

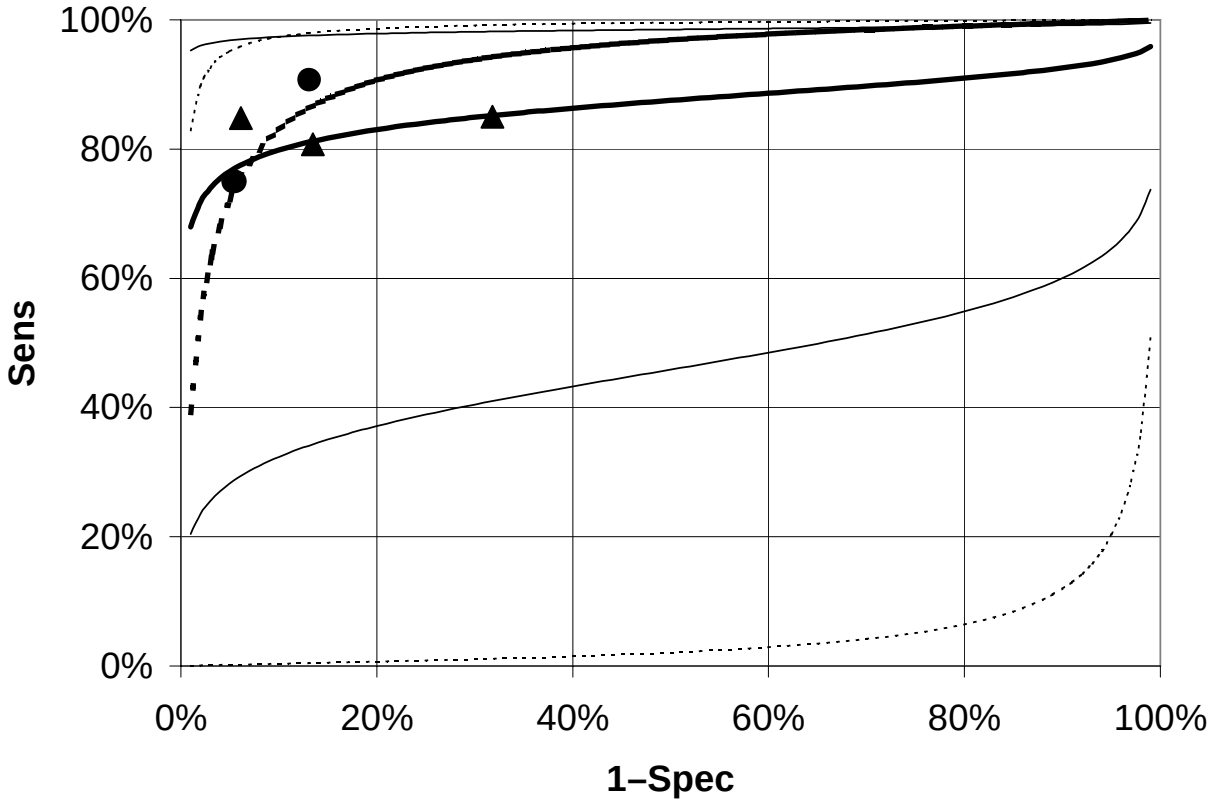
**Table 5: Sensitivity and specificity of echocardiography corresponding to the points of maximal accuracy on the summary ROC curves.**

| **Test** | **Sensitivity %** | **Specificity %** | $A_{\text{max}}$ |
|---|---|---|---|
| TTE for LVT | 76.5 | 95.0 | 171.5 |
| excluding poor quality studies | 85.3 | 88.0 | 173.3 |
| TTE for LAT | 97.2 | 93.6 | 190.8 |
| excluding poor quality studies | 93.7 | 91.2 | 184.9 |
| TEE for LAT* | 100.0 | 100.0 | 200.0 |
| excluding poor quality studies | 100.0 | 100.0 | 200.0 |

* Due to the shape of the summary ROC curve (specifically, because $\beta < -1$), maximal accuracy is achieved when both sensitivity and specificity are 100%.

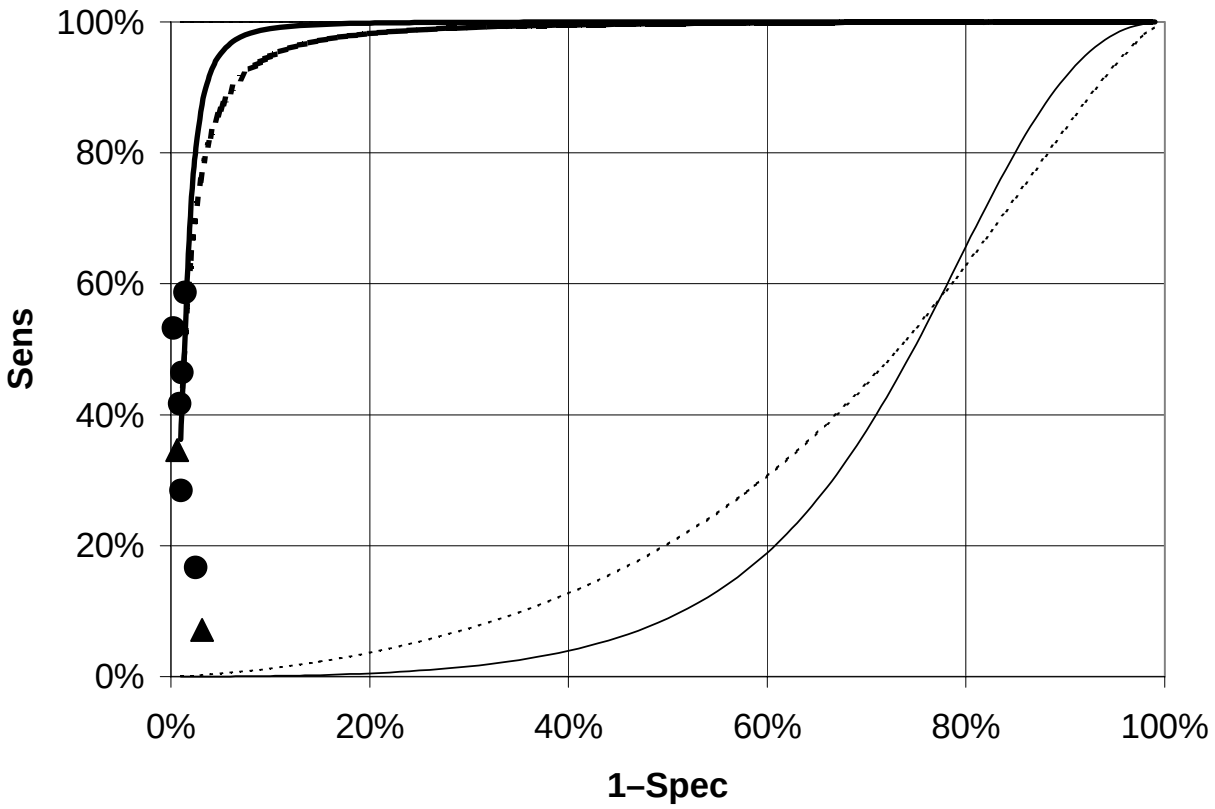
**Table 6: Sensitivity and specificity of echocardiography corresponding to fixed points of accuracy on the summary ROC curves.**

| Test | Sensitivity % | Specificity % | $A$ |
|---|---|---|---|
| TTE for LVT | 90 | 27.8 | 117.8 |
| | 95 | 2.1 | 97.1 |
| | 99 | 0.004 | 99.0 |
| | 79.8 | 90 | 169.8 |
| | 76.5 | 95 | 171.5 |
| | 68.0 | 99 | 167.0 |
| TTE for LVT, excluding poor quality studies | 90 | 81.3 | 171.3 |
| | 95 | 64.2 | 159.2 |
| | 99 | 20.2 | 119.2 |
| | 83.0 | 90 | 173.0 |
| | 72.2 | 95 | 167.2 |
| | 39.2 | 99 | 138.2 |
| TTE for LAT | 90 | 96.5 | 186.5 |
| | 95 | 95.1 | 190.1 |
| | 99 | 89.9 | 188.9 |
| | 99.0 | 90 | 189.0 |
| | 95.1 | 95 | 190.1 |
| | 36.2 | 99 | 135.2 |
| TTE for LAT, excluding poor quality studies | 90 | 93.7 | 183.7 |
| | 95 | 89.7 | 184.7 |
| | 99 | 72.3 | 171.3 |
| | 94.8 | 90 | 184.8 |
| | 86.7 | 95 | 181.7 |
| | 40.3 | 99 | 139.3 |
| TEE for LAT | 90 | 63.8 | 153.8 |
| | 95 | 100.0 | 195.0 |
| | 99 | 100.0 | 199.0 |
| | 90.6 | 90 | 180.6 |
| | 90.8 | 95 | 185.8 |
| | 91.3 | 99 | 190.3 |
| TEE for LAT, excluding poor quality studies | 90 | 97.2 | 187.2 |
| | 95 | 100.0 | 195.0 |
| | 99 | 100.0 | 199.0 |
| | 88.4 | 90 | 178.4 |
| | 89.3 | 95 | 184.3 |
| | 91.1 | 99 | 190.1 |



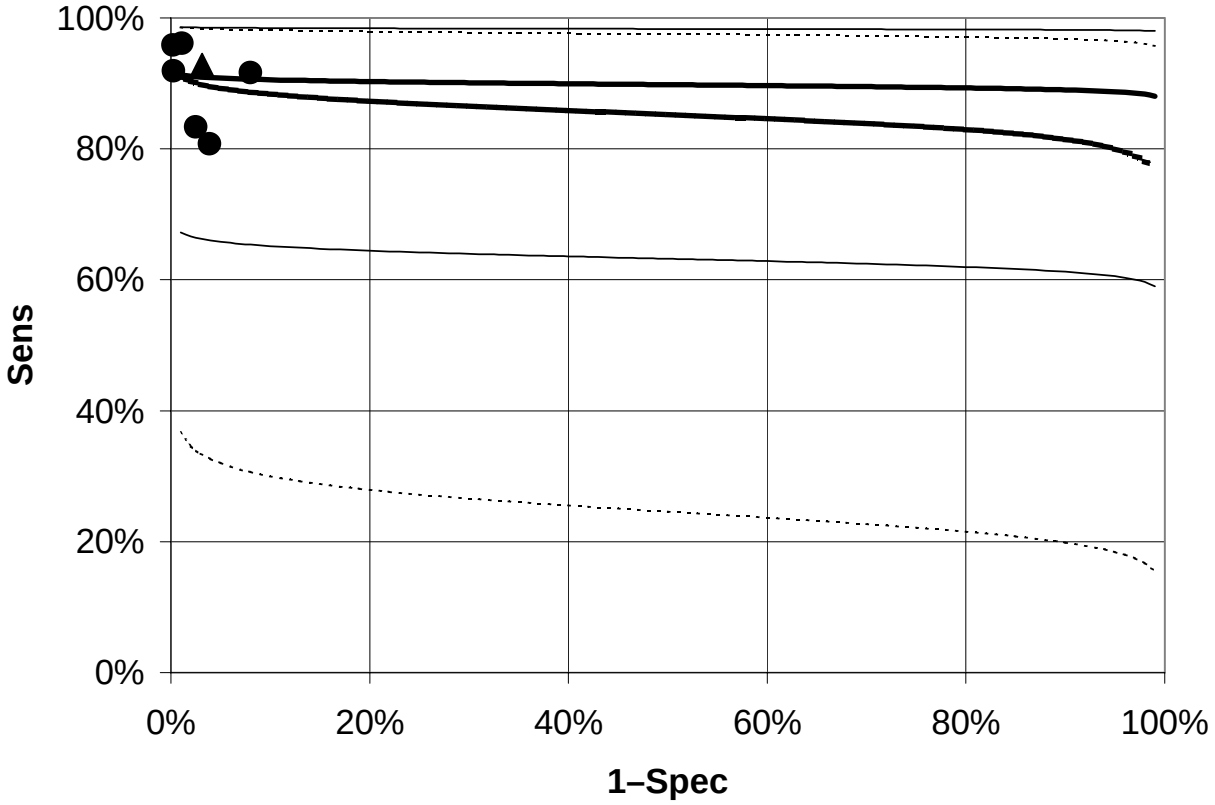

**The triangles are poor quality studies. The circles are good and fair quality studies. The solid curve is for all studies including poor quality studies. The dotted curve is for only good and fair quality studies.**

**Figure 1: Summary ROC curve (thick lines) for TTE for LVT and 95% confidence intervals (thin lines).**




**The triangles are poor quality studies. The circles are good and fair quality studies. The solid curve is for all studies including poor quality studies. The dotted curve is for only good and fair quality studies.**

**Figure 2: Summary ROC curve (thick lines) for TTE for LAT and 95% confidence intervals (think lines).**




**The triangles are poor quality studies. The circles are good and fair quality studies. The solid curve is for all studies including poor quality studies. The dotted curve is for only good and fair quality studies.**

**Figure 3: Summary ROC curve (thick lines) for TEE for LAT and 95% confidence intervals (thin lines).**

# 4 Complications of transesophageal echocardiography

Quality rating (good, fair, or poor) was examined as a potential dependent variable in the logistic regression model for transesophageal echocardiography complications. The results are from models described in Section 1.1.

Between-study variation ($\sigma^2$) from TEE studies is shown in Table 7. Including regression parameters for quality rating to the mortality model appeared to increase the between-study variance. But this was likely an artifact of overfitting the data. Including quality rating parameters in the complications model decreased the between-study variance by 52% (from 0.7849 to 0.3802).

Estimated event probabilities from TEE are shown in Table 8. The probability that complication rates are different between quality ratings of poor versus fair was 98.88%. However, mortality rates did not differ between quality ratings. The confidence intervals for the complication subsets (elderly and critically ill) are wide because the random effects model was estimated from only 3 studies.

**Table 7: Between-study variation for TEE complications.**

| Event | # studies | Dependent variables | $\sigma^2$ |
|---|---|---|---|
| Mortality | 15 | None | $0.7728$ |
| | | Quality rating | $1.003$ |
| Complications | 15 | None | $0.6907$ |
| | | Quality rating | $0.303$ |

**Table 8: Estimated complication probabilities for TEE.**

| Event | # studies | Dependent variable | Level | $\pi$ % | 95% CI |
|---|---|---|---|---|---|
| Mortality | 15 | None | — | $0.01355$ | $3.629 \times 10^{-5}, 0.03901$ |
| | | Quality rating | Poor | $0.01126$ | $8.127 \times 10^{-6}, 0.07173$ |
| | | | Fair | $0.006221$ | $3.355 \times 10^{-8}, 0.06428$ |
| | | | | $p(\beta > 0) = 0.3796$ | |
| Complications | 15 | None | — | $0.4039$ | $0.1909, 0.6902$ |
| | | Quality rating | Poor | $0.2354$ | $0.082, 0.4421$ |
| | | | Fair | $0.6714$ | $0.3045, 1.049$ |
| | | | | $p(\beta > 0) = 0.9774$ | |
| Complications (elderly) | | | | | |
| *random* | 3 | None | — | $2.778 \times 10^{-4}$ | $0, 100$ |
| *fixed* | 3 | None | — | $0.4177$ | $0.06097, 1.375$ |
| Complications (critically ill) | | | | | |
| *random* | 3 | None | — | $7.603 \times 10^{-6}$ | $0.0, 11.5$ |
| *fixed* | 3 | None | — | $0.7789$ | $0.1168, 2.598$ |

# 5 Accuracy of carotid imaging

The results are from models described in Section 1.2.

Estimates for the summary ROC parameters $\alpha$ and $\beta$ are shown on Table 9. Plotted curves are shown on Figures 1, 2, and 3.

Sensitivities and specificities corresponding to points of maximum accuracy are shown on Table 10. Accuracy data from fixed points are shown in Table 11.

**Table 9: Estimated summary ROC curve parameters for carotid imaging.**

| **Test** | $\alpha$ | **95% CI** | $\beta$ | **95% CI** |
|---|---|---|---|---|
| CUS | $3.149$ | $1.982, 4.481$ | $-0.2539$ | $-1.251, 0.7198$ |
| excluding Eliasziw (1995) | $3.492$ | $2.408, 4.7$ | $-0.04735$ | $-0.8304, 0.7223$ |
| MRA | $4.744$ | $3.105, 6.646$ | $-0.1739$ | $-1.07, 0.6748$ |
| excluding poor quality studies | $5.144$ | $3.061, 7.676$ | $-0.3108$ | $-2.446, 1.876$ |
| CUS+MRA | $6.04$ | $4.803, 7.37$ | $-0.1974$ | $-0.8365, 0.411$ |
| excluding poor quality studies | $5.925$ | $3.782, 9.333$ | $-0.1469$ | $-1.991, 1.466$ |

**Table 10: Sensitivity and specificity of carotid imaging corresponding to the points of maximal accuracy on the summary ROC curves.**

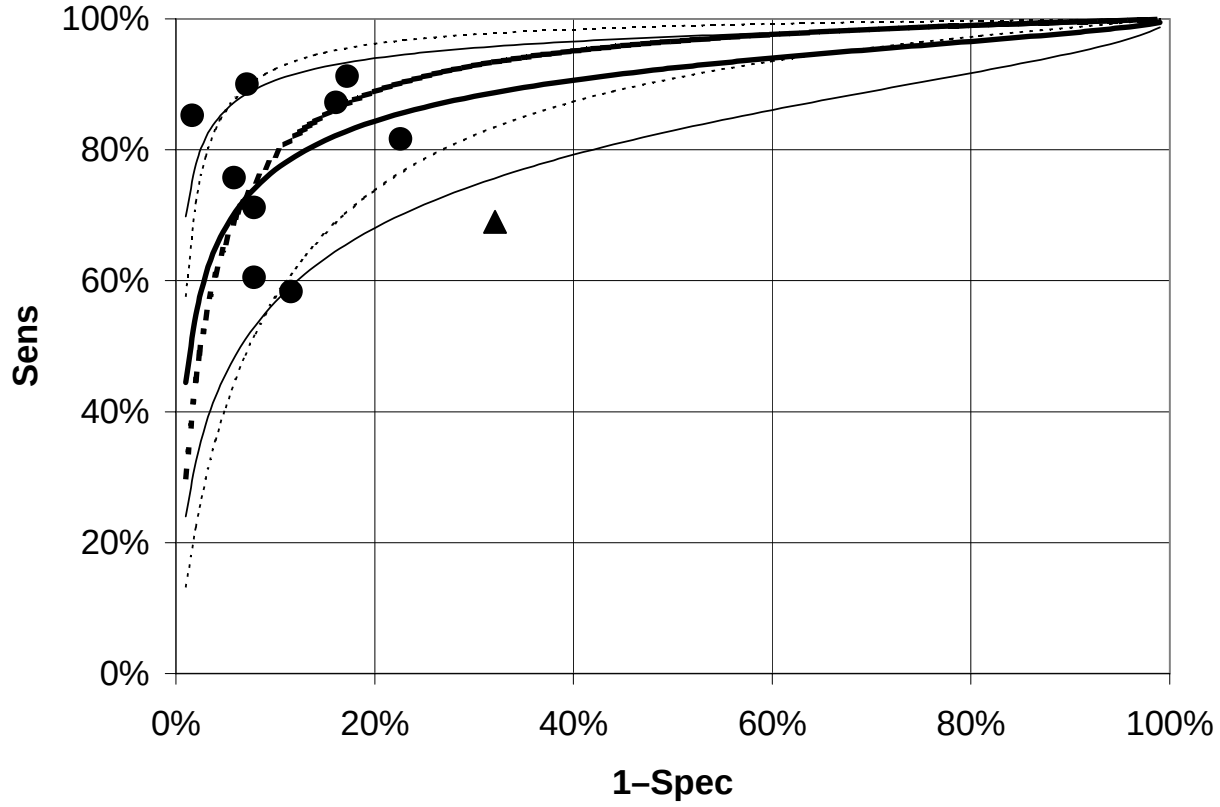
| **Test** | **Sensitivity %** | **Specificity %** | $A_{\max}$ |
|---|---|---|---|
| CUS | 78.2 | 88.8 | 167.0 |
| excluding Eliasziw (1995) | 84.3 | 86.0 | 170.3 |
| 50% stenosis cutoff | 79.8 | 91.2 | 171.0 |
| 70% stenosis cutoff | 75.4 | 87.2 | 162.6 |
| 70% stenosis cutoff excluding Eliasziw (1995) | 94.4 | 84.0 | 178.4 |
| MRA | 90.2 | 93.0 | 183.2 |
| excluding poor quality studies | 91.0 | 95.5 | 186.5 |
| 50% stenosis cutoff | 91.2 | 73.5 | 164.7 |
| 70% stenosis cutoff | 91.8 | 96.5 | 188.3 |
| CUS+MRA | 94.5 | 96.4 | 190.9 |
| excluding poor quality studies | 94.3 | 96.0 | 190.3 |
| 50% stenosis cutoff | 95.5 | 95.2 | 190.7 |
| 70% stenosis cutoff | 95.1 | 98.4 | 193.5 |
| 70% stenosis cutoff excluding poor quality studies | 95.0 | 99.9 | 194.9 |

**Table 11: Sensitivity and specificity of carotid imaging corresponding to fixed points of accuracy on the summary ROC curves.**

| Test | Sensitivity % | Specificity % | $A$ |
|---|---|---|---|
| CUS | 90 | 62.9 | 152.9 |
| | 95 | 32.6 | 127.6 |
| | 99 | 2.9 | 101.9 |
| | 76.9 | 90 | 166.9 |
| | 68.1 | 95 | 163.1 |
| | 44.5 | 99 | 143.5 |
| CUS, excluding Eliasziw (1995) | 90 | 77.7 | 167.7 |
| | 95 | 60.5 | 155.5 |
| | 99 | 2.0 | 119.0 |
| | 79.2 | 90 | 169.2 |
| | 65.8 | 95 | 160.8 |
| | 30.0 | 99 | 129.0 |
| MRA | 90 | 93.2 | 183.2 |
| | 95 | 82.6 | 177.6 |
| | 99 | 31.3 | 130.3 |
| | 92.4 | 90 | 182.4 |
| | 87.8 | 95 | 182.8 |
| | 69.2 | 99 | 168.2 |
| MRA, excluding poor quality studies | 90 | 96.4 | 186.4 |
| | 95 | 86.6 | 181.6 |
| | 99 | 21.8 | 120.8 |
| | 94.1 | 90 | 184.1 |
| | 91.5 | 95 | 186.5 |
| | 81.9 | 99 | 180.9 |
| CUS+MRA | 90 | 98.6 | 188.6 |
| | 95 | 95.8 | 190.8 |
| | 99 | 66.2 | 165.2 |
| | 97.3 | 90 | 187.3 |
| | 95.6 | 95 | 190.6 |
| | 87.7 | 99 | 186.7 |
| CUS+MRA, excluding poor quality studies | 90 | 98.2 | 188.2 |
| | 95 | 95.2 | 190.2 |
| | 99 | 68.3 | 167.6 |
| | 97.2 | 90 | 187.2 |
| | 95.1 | 95 | 190.1 |
| | 85.2 | 99 | 184.2 |

**Table 12: Sensitivity and specificity of carotid imaging corresponding to fixed points of accuracy on the summary ROC curves from cutoff subanalyses.**

| Test | Sensitivity % | Specificity % | $A$ |
|---|---|---|---|
| CUS 50% stenosis cutoff | 90 | 65.6 | 155.6 |
| | 95 | 29.0 | 124.0 |
| | 99 | 1.4 | 100.4 |
| | 80.9 | 90 | 170.9 |
| | 74.6 | 95 | 169.6 |
| | 56.9 | 99 | 155.9 |
| CUS 70% stenosis cutoff | 90 | 52.8 | 142.8 |
| | 95 | 24.2 | 119.2 |
| | 99 | 2.0 | 101.0 |
| | 72.2 | 90 | 162.2 |
| | 62.4 | 95 | 157.4 |
| | 38.2 | 99 | 137.2 |
| CUS 70% stenosis cutoff excluding Eliasziw, 1995 | 90 | 87.0 | 177.0 |
| | 95 | 83.4 | 178.4 |
| | 99 | 72.7 | 171.7 |
| | 80.4 | 90 | 170.4 |
| | 36.9 | 95 | 131.9 |
| | 0.8 | 99 | 99.8 |
| MRA 50% stenosis cutoff | 90 | 74.7 | 164.7 |
| | 95 | 68.3 | 163.3 |
| | 99 | 51.7 | 150.7 |
| | 39.0 | 90 | 129.0 |
| | 9.8 | 95 | 104.8 |
| | 0.2 | 99 | 99.2 |
| MRA 70% stenosis cutoff | 90 | 97.8 | 187.8 |
| | 95 | 90.0 | 185.0 |
| | 99 | 21.4 | 120.4 |
| | 95.0 | 90 | 185.0 |
| | 93.0 | 95 | 188.0 |
| | 86.0 | 99 | 185.0 |
| CUS+MRA 50% stenosis cutoff | 90 | 97.9 | 187.9 |
| | 95 | 95.7 | 190.7 |
| | 99 | 81.0 | 180.0 |
| | 97.9 | 90 | 187.9 |
| | 95.7 | 95 | 190.7 |
| | 81.1 | 99 | 180.1 |
| CUS+MRA 70% stenosis cutoff | 90 | 99.9 | 189.0 |
| | 95 | 98.5 | 193.5 |
| | 99 | 26.2 | 125.2 |
| | 97.3 | 90 | 187.3 |
| | 96.5 | 95 | 191.5 |
| | 94.3 | 99 | 193.3 |
| CUS+MRA 70% stenosis cutoff excluding poor quality studies | 90 | 100.0 | 190.0 |
| | 95 | 99.8 | 194.8 |
| | 99 | 0.0 | 99.0 |
| | 95.5 | 90 | 185.5 |
| | 95.4 | 95 | 190.4 |
| | 95.2 | 99 | 194.2 |




**The triangle is Eliasziw (1995). The circles are all other studies. The solid curve is for all studies including Eliasziw (1995). The dotted curve is for studies excluding Eliasziw (1995).**

**Figure 4: Summary ROC curve (thick lines) for CUS and 95% confidence intervals (thin lines).**

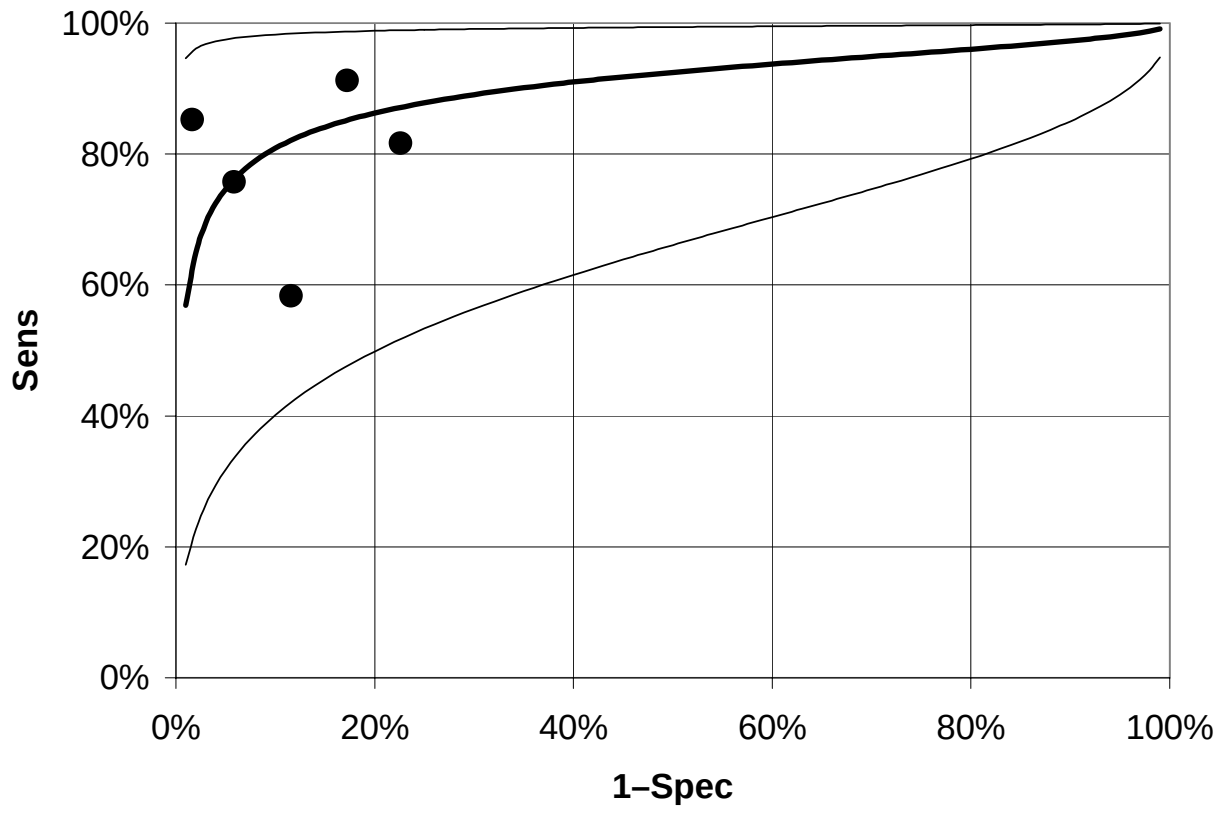
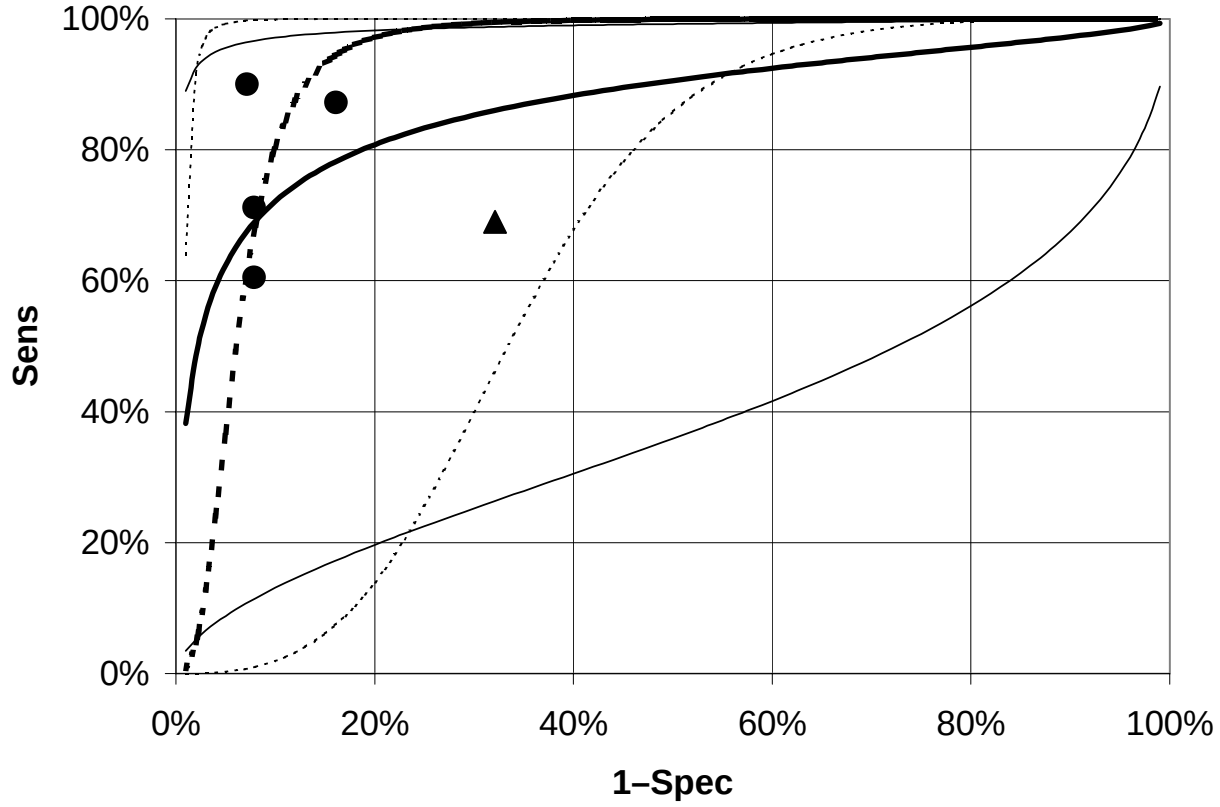
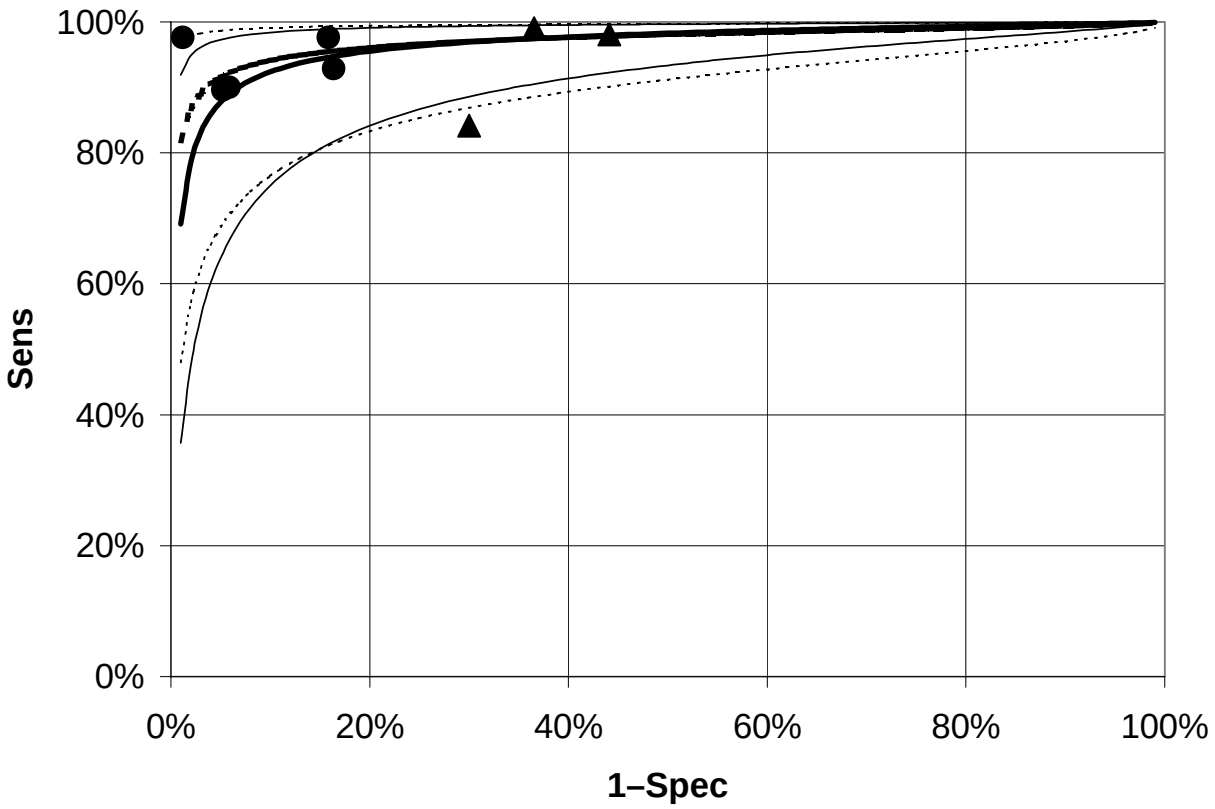



**Figure 5: Summary ROC curve (thick line) for CUS for 50% stenosis cutoff and 95% confidence intervals (thin lines).**




**The triangle is Eliasziw (1995). The circles are all other studies. The solid curve is for all studies including Eliasziw (1995). The dotted curve is for studies excluding Eliasziw (1995).**

**Figure 6: Summary ROC curve (thick lines) for CUS for 70% stenosis cutoff and 95% confidence intervals (thin lines).**




**The triangles are poor quality studies. The circles are good and fair quality studies. The solid curve is for all studies including poor quality studies. The dotted curve is for only good and fair quality studies.**

**Figure 7: Summary ROC curve (thick lines) for MRA and 95% confidence intervals (thin lines).**

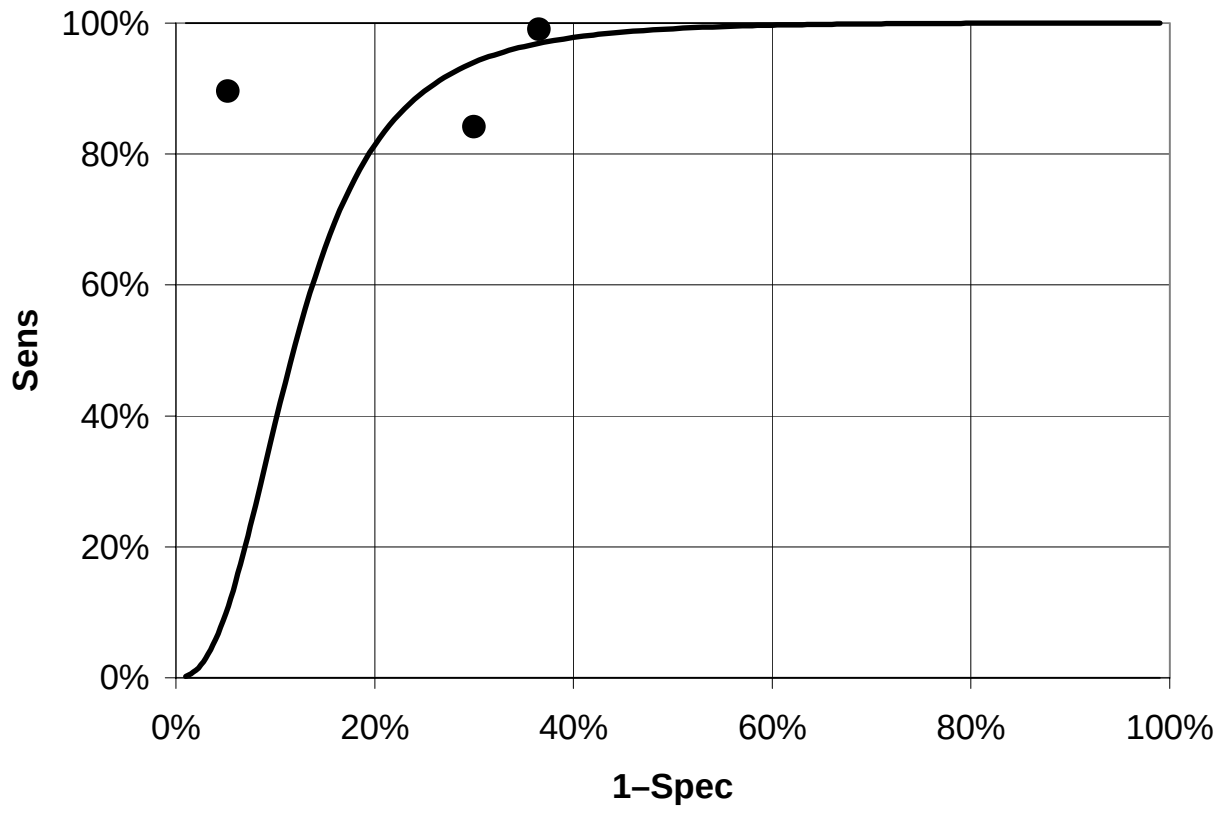



**Figure 8: Summary ROC curve (thick line) for MRA for 50% stenosis cutoff and 95% confidence intervals (thin lines).**

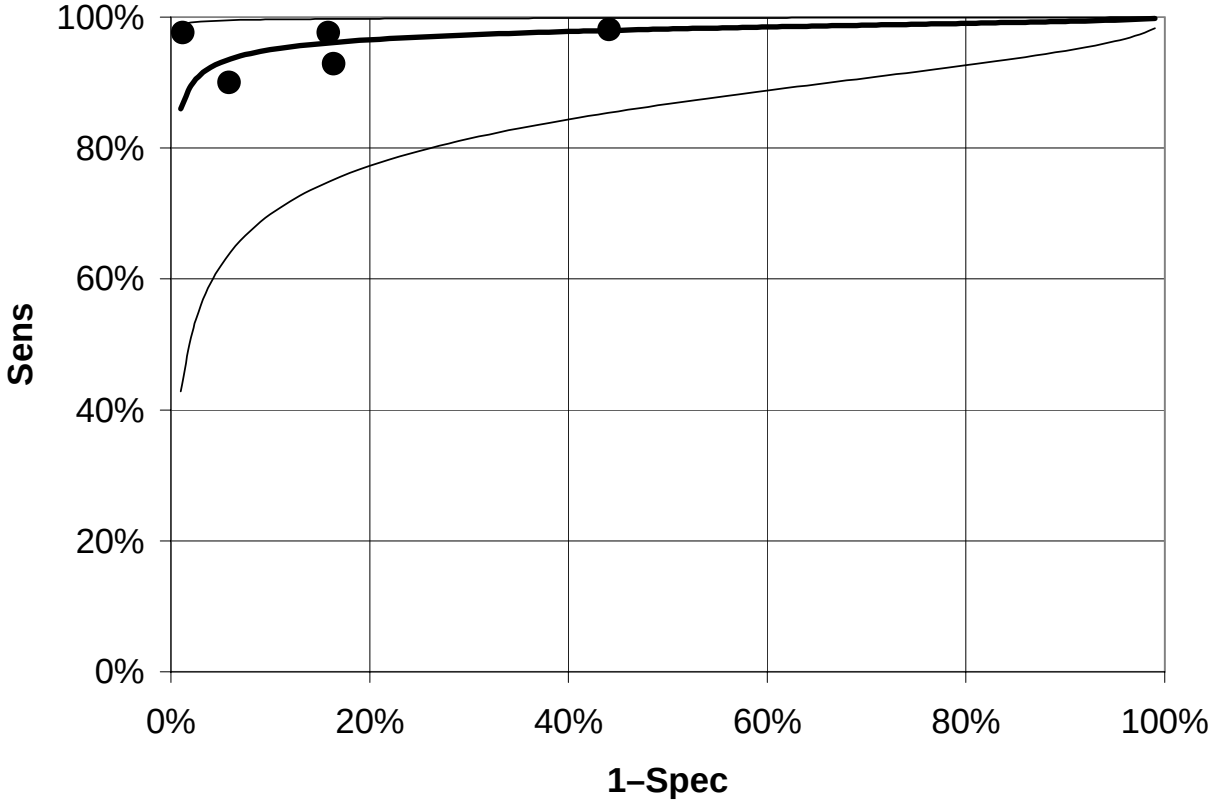
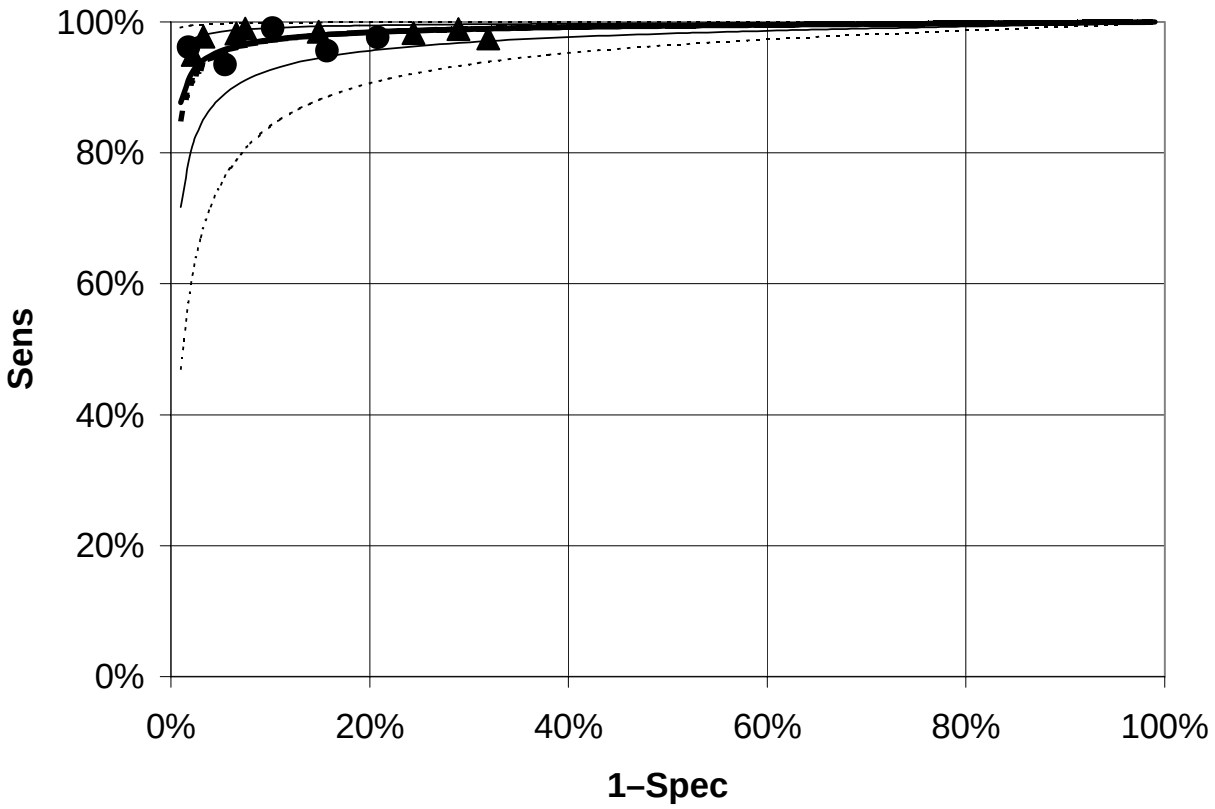



**Figure 9: Summary ROC curve (thick line) for MRA for 70% stenosis cutoff and 95% confidence intervals (thin lines).**




**The triangles are poor quality studies. The circles are good and fair quality studies. The solid curve is for all studies including poor quality studies. The dotted curve is for only good and fair quality studies.**

**Figure 10: Summary ROC curve (thick lines) for CUS+MRA and 95% confidence intervals (thin lines).**

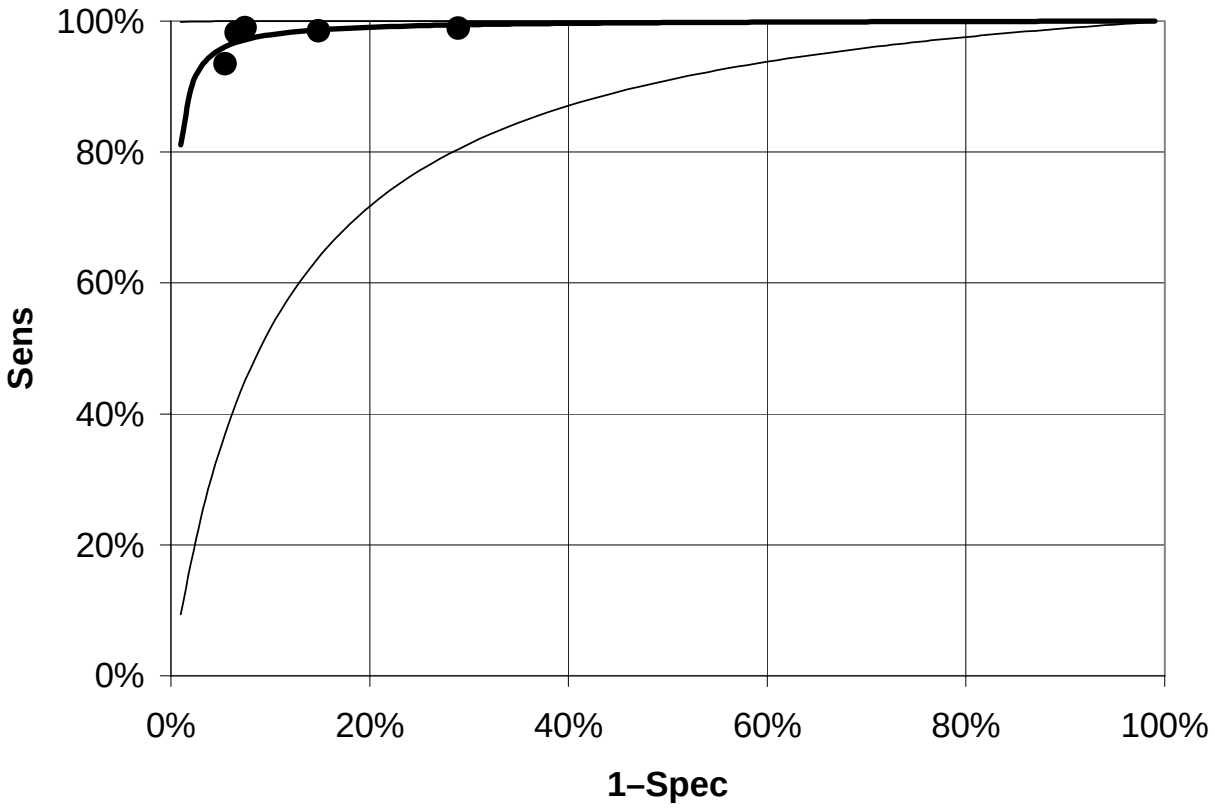
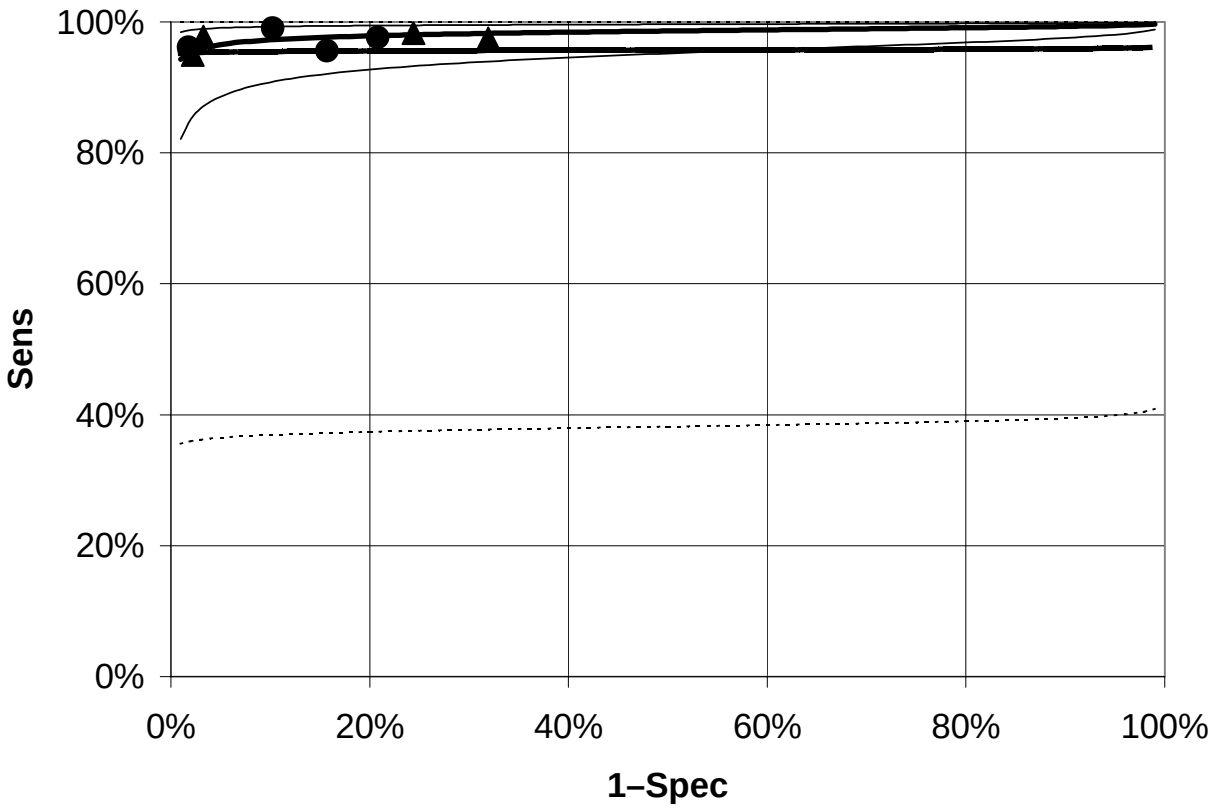



**Figure 11: Summary ROC curve (thick line) for CUS+MRA for 50% stenosis cutoff and 95% confidence intervals (thin lines).**




**The triangles are poor quality studies. The circles are good and fair quality studies. The solid curve is for all studies including poor quality studies. The dotted curve is for only good and fair quality studies.**

**Figure 12: Summary ROC curve (thick lines) for CUS+MRA for 70% stenosis cutoff and 95% confidence intervals (thin lines).**

# 6 Complications of cerebral angiography

Potential explanatory variables for the logistic regression model are shown on Table 13. The results are from models described in Section 1.1.

Between-study variation ($\sigma^2$) from cerebral angiography studies is shown in Table 14. This table shows large between-study variance for mortality and overfitting for CVA + mortality when dependent variables are included. Since only 2 of the 10 studies had deaths, no further stratification by dependent variables was done for mortality.

Estimated event probabilities from cerebral angiography are shown in Table 15. None of the dependent variables exhibited significant association with CVA + mortality.

**Table 13: Potential dependent variables for cerebral angiography complications.**

| **Factor** | **Levels** |
|---|---|
| Publication year | Pre-1990 |
| | 1990-present |
| Authorship | Radiology |
| | Surgeon |
| | Single surgeon |
| | Multiple surgeons |
| | Other |
| Quality rating | Good |
| | Fair |
| | Poor |

**Table 14: Between-study variation for cerebral angiography complications.**

| **Event** | **# studies** | **Dependent variables** | $\sigma^2$ |
|---|---|---|---|
| Mortality | 10 | None | 6.942 |
| CVA + mortality | 10 | None | 1.279 |
| | | Publication year | 1.426 |
| | | Authorship | 1.401 |
| | | Quality rating | 1.729 |

**Table 15: Estimated complication probabilities for cerebral angiography models.**

| Event | # studies | Dependent variable | Level | $\pi$ % | 95% CI |
|---|---|---|---|---|---|
| Mortality | 10 | None | — | $0.0194$ | $4.785 \times 10^{-12}, 0.1183$ |
| CVA + mortality | 10 | None | — | $1.24$ | $0.4222, 2.607$ |
| | | Publication year | Pre-1990 | $1.121$ | $0.1382, 3.608$ |
| | | | 1990-present | $1.787$ | $0.2135, 5.114$ |
| | | | | $p(\beta > 0) = 0.2674$ | |
| | | Authorship | Radiology | $1.139$ | $0.1389, 3.4$ |
| | | | Other | $1.526$ | $0.2994, 4.029$ |
| | | | | $p(\beta > 0) = 0.3396$ | |
| | | Quality rating | Good(ref) | $1.525$ | $0.1733, 5.438$ |
| | | | Fair | $3.375$ | $0.0884, 19.74$ |
| | | | Poor | $1.23$ | $0.0310, 5.954$ |
| | | | | $p(\beta_{\text{Fair}} > 0) = 0.6346$ | |
| | | | | $p(\beta_{\text{Poor}} > 0) = 0.3270$ | |

# 7 Complications of carotid endarterectomy

Between-study variation ($\sigma^2$) from CEA complications is shown in Table 17. For mortality, none of the dependent variables decreases the between-subject variability. For mortality + CVA, authorship decreases between-subject variability by 20%, and quality rating decreases between-subject variability by 12%.

Estimated event probabilities from CEA complications are shown in Tables 18 and 19. For mortality, authorship showed significant differences between single surgeon studies versus multiple surgeon studies and single surgeon studies versus other studies even though the between-subject variance was not reduced. For mortality + CVA, prospective study, RCT, CEA timing, authorship, and quality rating showed high probabilities of differences. Prospective studies and RCTs had higher rates, studies of late CEAs had higher rates, single surgeon studies had low rates followed by multiple surgeon studies followed by other studies, and poor quality studies had low rates.

## 7.1 Carotid endarterectomy timing

Between-study variation ($\sigma^2$) from CEA timing is shown in Table 21. This table shows overfitting for mortality when dependent variables are included. Since only 2 of the 10 studies had deaths, no further stratification by dependent variables was done for mortality. The dependent variables are no effect in decreasing between-study variability for mortality + CVA in the early CEA studies. However, for the late CVA studies, authorship (surgeon *vs* other) and quality rating (fair *vs* poor) lowered between-study variability by 31% and 21%, respectively.

Estimated event probabilities from CEA timing are shown in Tables 22 and 23. Consistent with the statements in the preceding paragraph, authorship and quality rating were significantly associated with mortality + CVA events for late CEA; while none of the dependent variables examined were associated with any of the other outcomes.

One study (Whittemore, 1987) had an unusually large number of late CEAs ($n = 607$). With a relatively large denominator, this study may impose a significant influence on the meta-analysis results. Scaling down Whittemore's death + CVA data by a factor of 4, decreasing the number of events to $y = 3$ and the denominator to $n = 152$ did not significantly change the results. Stratifying by authorship $\sigma^2 = 0.3746$, $p = 0.9708$, $\pi(\text{Surgeon}) = 0.01845$, and $\pi(\text{Other}) = 0.05269$.

**Table 16: Potential dependent variables for carotid endarterectomy complications.**

| Factor | Levels |
|---|---|
| Publication year | Pre-1990<br>1990-present |
| Authorship | Radiology<br>Surgeon<br>Single surgeon<br>Multiple surgeons<br>Other |
| Quality rating | Good<br>Fair<br>Poor |
| Prospective study design | Yes<br>No |
| Population-based | Yes<br>No |
| RCT | Yes<br>No |
| CEA timing | Early<br>Late |

**Table 17: Between-study variation for CEA complications.**

| **Event** | **# studies** | **Dependent variables** | $\sigma^2$ |
|---|---|---|---|
| Mortality | 42 | None | 0.5295 |
| | | Publication year | 0.5425 |
| | | Prospective study | 0.5543 |
| | | Population based | 0.5428 |
| | | RCT | 0.5667 |
| | | Early CEA | 0.5241 |
| | | Authorship | 0.5424 |
| | | Quality rating | 0.5215 |
| | | Quality rating (good/fair *vs* poor | 0.5046 |
| Mortality + CVA | 46 | None | 0.6536 |
| | | Publication year | 0.6759 |
| | | Prospective study | 0.6087 |
| | | Population based | 0.6503 |
| | | RCT | 0.6154 |
| | | Early CEA | 0.6091 |
| | | Authorship | 0.5228 |
| | | Quality rating | 0.5765 |
| | | Quality rating (good/fair *vs* poor | 0.5613 |
| Mortality + CVA | 69 | None | 0.5474 |
| (Rothwell studies included) | | Publication year | 0.5479 |
| | | Prospective study | 0.5178 |
| | | Authorship | 0.4538 |
| | | Independent ascentainment | 0.4644 |

**Table 18: Estimated event probabilities for CEA complications — mortality.**

| Event | # studies | Dependent variable | Level | $\pi$ % | 95% CI |
|---|---|---|---|---|---|
| Mortality | 42 | None | — | $1.525$ | $1.178, 1.902$ |
| | | Publication year | Pre-1990 | $1.553$ | $1.545, 2.075$ |
| | | | 1990-present | $1.495$ | $1.004, 2.16$ |
| | | | $p(\beta > 0) = 0.5898$ | | |
| | | Prospective study | Yes | $1.738$ | $1.194, 2.45$ |
| | | | No | $1.379$ | $0.9305, 1.848$ |
| | | | $p(\beta > 0) = 0.8324$ | | |
| | | Population based | Yes | $1.892$ | $0.8987, 3.428$ |
| | | | No | $1.482$ | $1.109, 1.92$ |
| | | | $p(\beta > 0) = 0.7154$ | | |
| | | RCT | Yes | $1.835$ | $0.9648, 3.181$ |
| | | | No | $1.463$ | $1.076, 1.885$ |
| | | | $p(\beta > 0) = 0.7216$ | | |
| | | CEA timing | Early | $1.108$ | $0.5396, 1.961$ |
| | | | Late | $1.588$ | $1.214, 1.999$ |
| | | | $p(\beta > 0) = 0.1212$ | | |
| | | Authorship | Single surgeon (ref) | $0.8963$ | $0.3903, 1.614$ |
| | | | Multiple surgeons | $1.75$ | $1.167, 2.478$ |
| | | | Other | $1.616$ | $1.06, 2.291$ |
| | | | $p(\beta_{\text{Multiple surgeons}} > 0) = 0.9636$ | | |
| | | | $p(\beta_{\text{Other}} > 0) = 0.9504$ | | |
| | | Quality rating | Good (ref) | $1.632$ | $0.9822, 2.505$ |
| | | | Fair | $2.13$ | $1.366, 3.131$ |
| | | | Poor | $1.124$ | $0.7336, 1.611$ |
| | | | $p(\beta_{\text{Fair}} > 0) = 0.8108$ | | |
| | | | $p(\beta_{\text{Poor}} > 0) = 0.1088$ | | |
| | | Quality rating | Good/fair (ref) | $1.857$ | $1.385, 2.427$ |
| | | | Poor | $1.147$ | $0.7809, 1.576$ |
| | | | $p(\beta > 0) = 0.0116$ | | |

**Table 19: Estimated event probabilities for CEA complications — mortality + CVA.**

| Event | # studies | Dependent variable | Level | $\pi$ % | 95% CI |
|---|---|---|---|---|---|
| Mortality + CVA | 46 | None | — | $5.328$ | $4.248, 6.461$ |
| | | Publication year | Pre-1990 | $5.479$ | $4.114, 7.209$ |
| | | | 1990-present | $5.044$ | $3.482, 6.928$ |
| | | | $p(\beta > 0) = 0.6536$ | | |
| | | Prospective study | Yes | $7.159$ | $5.347, 9.365$ |
| | | | No | $4.385$ | $3.373, 5.496$ |
| | | | $p(\beta > 0) = 0.9958$ | | |
| | | Population based | Yes | $6.376$ | $3.953, 9.499$ |
| | | | No | $5.17$ | $4.046, 6.545$ |
| | | | $p(\beta > 0) = 0.7782$ | | |
| | | RCT | Yes | $9.047$ | $5.629, 13.75$ |
| | | | No | $4.802$ | $3.87, 5.962$ |
| | | | $p(\beta > 0) = 0.9936$ | | |
| | | CEA timing | Early | $3.21$ | $1.914, 5.026$ |
| | | | Late | $5.938$ | $4.786, 7.248$ |
| | | | $p(\beta > 0) = 0.0082$ | | |
| | | Authorship | Single surgeon (ref) | $2.298$ | $1.305, 3.932$ |
| | | | Multiple surgeons | $4.482$ | $3.325, 5.898$ |
| | | | Other | $7.235$ | $5.665, 9.227$ |
| | | | $p(\beta_{\text{Multiple surgeons}} > 0) = 0.9788$ | | |
| | | | $p(\beta_{\text{Other}} > 0) = 1.0$ | | |
| | | Quality rating | Good (ref) | $6.833$ | $4.55, 9.522$ |
| | | | Fair | $6.4$ | $4.485, 8.652$ |
| | | | Poor | $3.806$ | $2.714, 5.156$ |
| | | | $p(\beta_{\text{Fair}} > 0) = 0.3994$ | | |
| | | | $p(\beta_{\text{Poor}} > 0) = 0.0216$ | | |
| | | Quality rating | Good/fair (ref) | $6.626$ | $5.193, 8.484$ |
| | | | Poor | $3.773$ | $2.706, 5.1$ |
| | | | $p(\beta > 0) = 0.0$ | | |

**Table 20: Estimated event probabilities for CEA complications — mortality + CVA. Includes studies used by Rothwell.**

| Event | # studies | Dependent variable | Level | $\pi$ % | 95% CI |
|---|---|---|---|---|---|
| Mortality + CVA | 69 | None | — | $5.024$ | $4.297, 5.831$ |
| | | Publication year | Pre-1990 | $4.784$ | $3.884, 5.807$ |
| | | | 1990-present | $5.482$ | $4.225, 6.934$ |
| | | | $p(\beta > 0) = 0.2082$ | | |
| | | Prospective study | Yes | $6.969$ | $5.254, 8.971$ |
| | | | No | $4.482$ | $3.795, 5.325$ |
| | | | $p(\beta > 0) = 0.9984$ | | |
| | | Population based | Yes | $6.376$ | $3.953, 9.499$ |
| | | | No | $5.17$ | $4.046, 6.545$ |
| | | | $p(\beta > 0) = 0.7782$ | | |
| | | Authorship | Single surgeon (ref) | $2.304$ | $1.381, 3.405$ |
| | | | Multiple surgeons | $4.544$ | $3.76, 5.421$ |
| | | | Other | $6.581$ | $5.446, 7.846$ |
| | | | $p(\beta_{\text{Multiple surgeons}} > 0) = 1.0$ | | |
| | | | $p(\beta_{\text{Other}} > 0) = 1.0$ | | |
| | | Independent ascertainment | Yes | $7.596$ | $5.873, 9.646$ |
| | | | No | $4.289$ | $3.581, 5.025$ |
| | | | $p(\beta > 0) = 0.9994$ | | |

**Table 21: Between-study variation for CEA timing.**

| Event | # studies | Dependent variables | $\sigma^2$ |
|---|---|---|---|
| Mortality, early CEA | 8 | None | 1.057 |
| | | Publication year | 1.468 |
| | | Authorship | 1.529 |
| | | Quality rating | 1.698 |
| Mortality, late CEA | 7 | None | 1.596 |
| | | Publication year | 8.313 |
| | | Authorship | 6.413 |
| | | Quality rating | 4.023 |
| Mortality | 15* | CEA timing | 0.6545 |
| Mortality + CVA, early CEA | 10 | None | 1.141 |
| | | Publication year | 1.151 |
| | | Authorship | 1.172 |
| | | Quality rating | 1.225 |
| Mortality + CVA, late CEA | 9 | None | 0.4993 |
| | | Publication year | 0.5184 |
| | | Authorship | 0.3427 |
| | | Quality rating | 0.3944 |
| | | Authorship, Quality rating | 0.4576 |
| Mortality + CVA | 19* | CEA timing | 0.6545 |

* Number of data points; some studies contributed more than 1 data point.

**Table 22: Estimated event probabilities for CEA timing — mortality.**

| Event | # studies | Dependent variable | Level | $\pi$ % | 95% CI |
|---|---|---|---|---|---|
| Mortality, early CEA | 8 | None | — | $0.9912$ | $0.1095, 2.538$ |
| | | Publication year | Pre-1990 | $1.991$ | $0.06401, 8.866$ |
| | | | 1990-present | $0.6812$ | $8.472 \times 10^{-3}, 2.572$ |
| | | | | $p(\beta > 0) = 0.7756$ | |
| | | Authorship | Surgeon | $1.076$ | $0.05087, 3.297$ |
| | | | Other | $1.996$ | $1.534 \times 10^{-3}, 10.76$ |
| | | | | $p(\beta > 0) = 0.3138$ | |
| | | Quality rating | Fair | $1.526$ | $7.912 \times 10^{-3}, 5.951$ |
| | | | Poor | $1.433$ | $7.858 \times 10^{-3}, 5.783$ |
| | | | | $p(\beta > 0) = 0.4232$ | |
| Mortality, late CEA | 7 | None | — | $0.994$ | $0.05687, 2.644$ |
| | | Publication year | Pre-1990 | $0.6429$ | $5.985 \times 10^{-15}, 2.366$ |
| | | | 1990-present | $3.993$ | $7.94 \times 10^{-5}, 48.26$ |
| | | | | $p(\beta > 0) = 0.1552$ | |
| | | Authorship | Surgeon | $0.9001$ | $2.384 \times 10^{-5}, 6.119$ |
| | | | Other | $5.042$ | $8.557 \times 10^{-14}, 68.7$ |
| | | | | $p(\beta > 0) = 0.5478$ | |
| | | Quality rating | Fair | $4.796$ | $1.2 \times 10^{-4}, 58.47$ |
| | | | Poor | $0.4281$ | $6.175 \times 10^{-5}, 1.981$ |
| | | | | $p(\beta > 0) = 0.7744$ | |
| Mortality | 15* | CEA timing | Early | $0.9665$ | $0.196, 2.25$ |
| | | | Late | $0.981$ | $0.1653, 2.094$ |
| | | | | $p(\beta > 0) = 0.5344$ | |
| | | | | OR: $1.058$ $(0.2393, 5.717)$ | |

* Number of data points; some studies contributed more than 1 data point.

**Table 23: Estimated event probabilities for CEA timing — mortality + CVA.**

| Event | # studies | Dependent variable | Level | $\pi$ % | 95% CI |
|---|---|---|---|---|---|
| Mortality + CVA, early CEA | 10 | None | — | $3.754$ | $1.289, 7.57$ |
| | | Publication year | Pre-1990 | $5.837$ | $1.324, 14.81$ |
| | | | 1990-present | $2.74$ | $0.5226, 7.263$ |
| | | | $p(\beta > 0) = 0.8364$ | | |
| | | Authorship | Surgeon | $3.996$ | $1.188, 8.858$ |
| | | | Other | $4.204$ | $0.4798, 14.33$ |
| | | | $p(\beta > 0) = 0.4376$ | | |
| | | Quality rating | Fair | $3.303$ | $0.3441, 12.01$ |
| | | | Poor | $4.684$ | $1.383, 11.15$ |
| | | | $p(\beta > 0) = 0.2656$ | | |
| Mortality + CVA, late CEA | 9 | None | — | $2.818$ | $1.45, 4.563$ |
| | | Publication year | Pre-1990 | $2.361$ | $0.929, 4.647$ |
| | | | 1990-present | $3.796$ | $1.325, 7.363$ |
| | | | $p(\beta > 0) = 0.1834$ | | |
| | | Authorship | Surgeon | $1.929$ | $0.7756, 3.317$ |
| | | | Other | $5.185$ | $2.314, 9.769$ |
| | | | $p(\beta > 0) = 0.9788$ | | |
| | | Quality rating | Fair | $5.297$ | $1.979, 10.18$ |
| | | | Poor | $2.028$ | $0.85, 3.633$ |
| | | | $p(\beta > 0) = 0.9574$ | | |
| Mortality + CVA | 19* | CEA timing | Early | $3.863$ | $1.785, 6.661$ |
| | | | Late | $2.706$ | $1.227, 4.826$ |
| | | | $p(\beta > 0) = 0.2076$ | | |
| | | | OR: $0.702$ $(0.2541, 1.883)$ | | |

* Number of data points; some studies contributed more than 1 data point.