

A simplified approach to the pooled analysis of calibration of clinical prediction rules for systematic reviews of validation studies.

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APPENDICES (online only)

APPENDIX 1

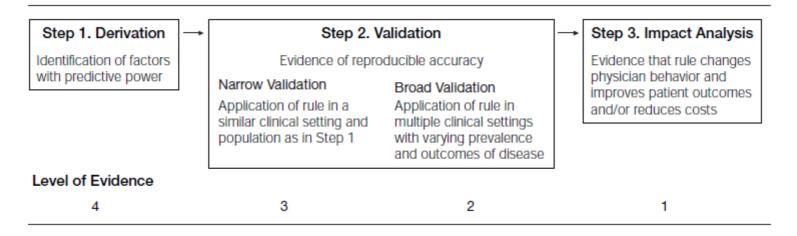


Fig. A1.1 Steps in the development of a clinical prediction rule

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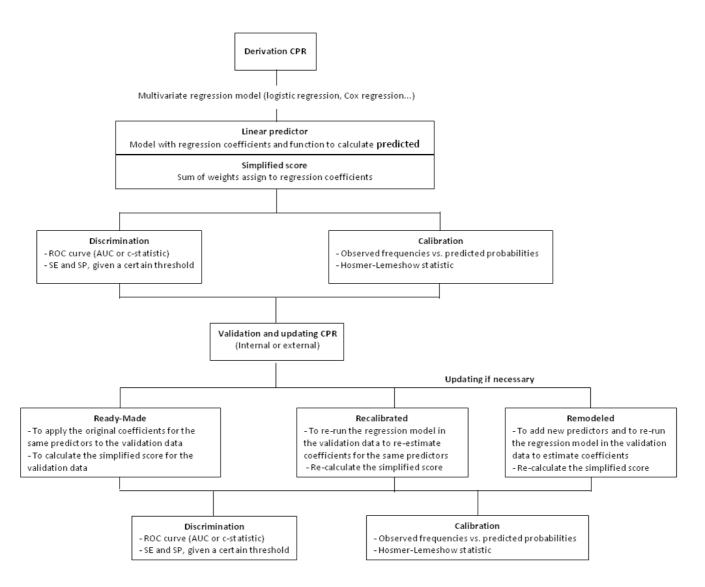


Fig. A1.2 Flow-chart of the process of derivation and validation of a clinical prediction rule (CPR)

Footnote: Recalibration may not always mean that the model is refitted; Remodelling may be also considered as a model revision or extension.

| Study | Predicted n/N | Observed n/N | | | RR (random) 95% CI | | 10 yeaı risk |
|---|------------------|-----------------|-------|---|-----------------------|------------------------------|-----------------|
| or sub-category | n/IN | n/IN | | | 95% CI | Score | risk |
| Framingham CHD calibration by | observed risk | | | | | | |
| Germany Augsberg women | 82/2925 | 32/2925 | | | - | Anderson | 1 |
| Germany Munster women | 89/3155 | 31/3155 | | | _ | Anderson | 1 |
| France PRIME | 463/7359 | 197/7359 | | | - | ■ Wilson | 5 |
| Germany Augsberg men | 292/2861 | 146/2861 | | | - | Anderson | 5 |
| Germany Munster men | 544/5527 | 307/5527 | | | | Anderson | 5 |
| Europe INSIGHT | 285/4127 | 124/4127 | | | - | ■ Anderson | 8 |
| UK Caerphilly & Speedwell 1 | 343/3213 | 27/3213 | | | | Anderson | 9 |
| Northern Ireland PRIME | 161/2399 | 120/2399 | | | | Wilson | 10 |
| Scotland WOSCOPS Pravastatin | 103/1803 | 81/1803 | | | ├ | Anderson | 10 |
| UK Caerphilly & Speedwell 2 | 325/2467 | 238/2467 | | | - | Anderson | 10 |
| UK BRHS | 1062/6643 | 677/6643 | | | - | Anderson | 10 |
| USA Los Angeles | 115/1029 | 84/1029 | | | | Wilson | 12 |
| USA Normative Aging Study | 222/1393 | 206/1393 | | | | Anderson | 15 |
| Scotland WOSCOPS control | 95/1251 | 88/1251 | | | | Anderson | 16 |
| UK Whickham | 401/1700 | 529/1700 | | | - | Anderson | 16 |
| USA Johns Hopkins 2 | 64/736 | 95/736 | | | | Wilson | 20 |
| USA Johns Hopkins 1 | 21/256 | 56/256 | | _ | | Wilson | 22 |
| Germany angiography | 6/42 | 10/42 | | | | Wilson | 24 |
| UK diabetic women | 31/396 | 67/396 | | | | Anderson | 42 |
| UK diabetic men | 52/542 | 105/542 | | | _ | Anderson | 48 |
| Total (95% CI) | 49824 | 100,012 | 49824 | | _ | 7 110010011 | |
| Total events: 4759 (Predicted), 3469 | | | 17021 | | | | |
| Test for heterogeneity: $\chi^2 = 366.84$, | | $^{2} = 94.8\%$ | | | | | |
| | | | | | | | |
| Framingham CVD calibration by | observed risk | | | | | | |
| Australia women | 94/1045 | 87/1045 | | | | Wilson | 8 |
| New Zealand women | 79/1716 | 86/1716 | | | ■ | Anderson | 10 |
| Australia men | 115/755 | 105/755 | | | | Wilson | 14 |
| New Zealand men | 277/4638 | 325/4638 | | | | Anderson | 14 |
| Europe INSIGHT | 601/4127 | 231/4127 | | | | | 15 |
| N Europe/USA LIFE | 410/9194 | 479/9194 | | | | Anderson | 52 |
| UK diabetics | 64/428 | 96/428 | | | | Anderson | 53 |
| Total (95% CI) | 21903 | | 21903 | | | | |
| Total events: 1640 (Predicted), 1409 | (Observed) | | | | | | |
| Test for heterogeneity: $\chi^2 = 172.37$, | | = 96.5% | | | | | |
| | | | | 1 | _ , | 1 | |
| | | | | | 0.5 1 2 | 5 | |

Fig. A1.3 Studies examining the predicted to observed ratio of Framingham Anderson and Wilson risk scores, ordered by the observed 10-year risk (%) in the test populations. Reproduced with the written permission from the paper by Brindle et al (Heart, 2006*)

^{*}Reference: Brindle PM et al. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. Heart 2006; 92: 1752-59.

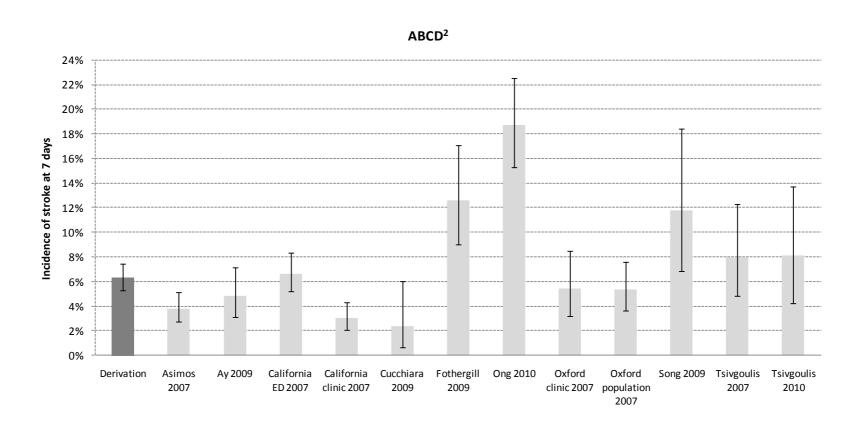


Fig. A1.4 Incidence rate of stroke at 7 days across the various studies of the ABCD²rule

Table A1.1 Stroke incidence at 7 days across the derivation and validation studies of ABCD² rule

| Study | Total % (N) | | Low risk (0-3 score) % (n) | | Intermediate risk (4-5 score) % (n) | | High risk (6-7 score) % (n) | |
|-------------------------|----------------|--------|----------------------------|-------|---|-------|-----------------------------------|-------|
| CED & OPB (derivation)* | 6.28 | (1910) | 1.35 | (520) | 6.51 | (921) | 11.3 | (469) |
| Asimos 2007 | 3.80 | (1054) | 0 | (231) | 3.76 | (559) | 7.20 | (264) |
| Ay 2009 | 4.82 | (477) | 1.23 | (162) | 6.17 | (227) | 7.95 | (88) |
| California ED* | 6.64 | (1069) | 3.09 | (259) | 5.93 | (506) | 10.86 | (304) |
| California Clinic data* | 3.01 | (962) | 0.47 | (426) | 4.28 | (397) | 7.19 | (139) |
| Cucchiara 2009 | 2.40 | (167) | 1.64 | (61) | 1.18 | (85) | 9.52 | (21) |
| Fothergill 2009 | 12.63 | (285) | 5.63 | (71) | 13.33 | (150) | 18.75 | (64) |
| Ong 2010 | 18.72 | (470) | 8.28 | (145) | 19.47 | (226) | 32.32 | (99) |
| Oxford Clinic data* | 5.40 | (315) | 0.62 | (162) | 9.24 | (119) | 14.71 | (34) |
| Oxford Population data* | 5.34 | (543) | 0.77 | (261) | 4.63 | (216) | 25.76 | (66) |
| Song 2009 | 11.76 | (136) | 2.78 | (72) | 20.69 | (58) | 33.33 | (6) |
| Tsivgoulis 2007 | 7.96 | (226) | 1.19 | (84) | 9.73 | (113) | 20.69 | (29) |
| Tsivgoulis 2010 | 8.11 | (148) | 2.82 | (71) | 8.93 | (56) | 23.81 | (21) |

*Note: Databases form the derivation/validation study by Johnston (2007)

APPENDIX 2

A2.1 Simplified approach to derive the predicted values of the target outcome or disease (30-day mortality of pneumonia) predicted by CRB-65 rule

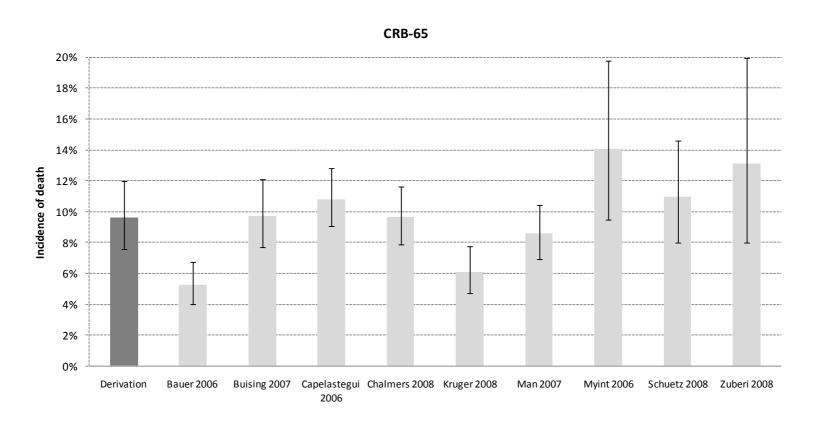


Fig. A2.1 Mortality rate across the various studies of CRB-65

| Table A2 1A | Mortality rate | (at 30-days) acro | ss the derivation an | d validation studie | es of CRR65 rule |
|---------------------------|------------------|-------------------|----------------------|---------------------|------------------|
| $1 autc \Delta 2.1\Delta$ | with tall y rate | tai 50-uavsi acio | ss me derivation an | u vanuauon stuur | o of CKDO3 fulc |

| Study | To | otal (N) | | risk e) % (n) | | diate risk re) % (n) | C | h risk ore) % (n) |
|-------------------|-------|-------------|------|------------------|-------|-------------------------|-------|----------------------|
| Lim 2003 | 9.61 | (718) | 1.20 | (167) | 8.13 | (455) | 31.25 | (96) |
| Bauer 2006 | 5.26 | (1084) | 0 | (299) | 6.26 | (735) | 22.00 | (50) |
| Buising 2007 | 9.73 | (740) | 0 | (100) | 4.85 | (433) | 24.64 | (207) |
| Capelastegui 2006 | 10.82 | (1100) | 0 | (201) | 10.13 | (819) | 45.00 | (80) |
| Chalmers 2008 | 9.63 | (1007) | 1.84 | (217) | 7.47 | (629) | 28.57 | (161) |
| Kruger 2008 | 6.10 | (1032) | 0.76 | (262) | 6.97 | (703) | 17.91 | (67) |
| Man 2007 | 8.56 | (1016) | 2.34 | (128) | 7.41 | (783) | 24.76 | (105) |
| Myint 2006 | 14.06 | (192) | 0 | (3) | 10.45 | (134) | 23.64 | (55) |
| Schuetz 2008 | 10.99 | (373) | 3.67 | (109) | 13.51 | (259) | 40.00 | (5) |
| Zuberi 2008 | 13.14 | (137) | 0 | (34) | 13.83 | (94) | 55.56 | (9) |

The distribution pattern in the initial derivation study of the CPR is used as a "predictive model" to which all validation studies are related. The number of deaths as target outcome as predicted by the **CRB-65 severity index** (rule) is compared to the observed number of deaths in each of the validation studies, across the three risk strata as defined by the CPR (low risk: score = 0; intermediate risk: score = 1 or 2; and high risk: score = 3 or 4). In order to calculate the predicted number of deaths, the proportionate mortality estimate (%) from the original derivation study was applied according to the three risk strata: low risk (mortality=1.2%), intermediate risk (mortality=8.2%) and high risk (mortality=31.3%). The calculation of the absolute risk (mortality or incidence of death) using the distribution in the derivation study ¹ as a predictive model is shown on Table A2.2A below.

Table A2.1B Results on derivation data for CRB-65 rule

| CRB-65 risk stratification | N | Deaths observed (n) | Deaths observed (%) |
|-------------------------------|-----|---------------------|---------------------|
| Low risk (0 score) | 167 | 2 | 2/167 = 1.20% |
| Intermediate risk (1-2 score) | 455 | 37 | 37/455 = 8.10% |
| High risk (3-4 score) | 96 | 30 | 30/96 = 31.3% |

We show an example on data from a validation study by Man et al (2007).² - the blue arrow indicates how the estimate of observed deaths (percentage) is used to be applied to the data from the validation study to produce the predicted number of deaths and to compare those to the observed deaths as in the last column of Table A2.2B.

Table A2.1C Results on validation data for CRB-65 rule

| CRB-65 risk stratification | N | Deaths predicted (%)* | Deaths predicted (n) | Deaths observed (n)** |
|-------------------------------|-----|-----------------------|----------------------|-----------------------|
| Low risk (0 score) | 128 | 1.2% | 1.5 (≈2) | 3 |
| Intermediate risk (1-2 score) | 783 | 8.1% | 63.4 (≈63) | 58 |
| High risk (3-4 score) | 105 | 31.3% | 32.9 (≈33) | 26 |

Notes: *Using original derivation study as a predictive model; ** actual number of deaths reported in each stratum of risk; values in the parentheses are rounded numbers.

¹ Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58(5): 377–382.

² Man SY, Lee N, IpM, et al. Prospective comparison of three predictive rules for assessing severity of community-acquired pneumonia in Hong Kong. Thorax 2007; 62(4): 348–353.

A2.2 Predicted values from coefficients of the logistic regression model in the derivation study of the CRB-65 rule

In order to confirm our new simplified approach, we generated "individual-level data" by creating dummy variables of the CRB-65 rule (considering those as a *proxy* for the original data given the distribution in the derivation study) and applied a logistic regression model to predict the outcome. From the derivation study it was possible to reconstruct the data with the outcome "death" as a dependent, binary variable (yes=1; no=0) and the CRB-65 score as a single, independent semi-quantitative variable. In fact, the CRB-65 score is not a true continuous variable and thus we avoided an assumption of linearity by including CRB-65 score in the models as a discrete, categorical variable, with the lowest CRB-65 stratum (score 0) as the reference category. This was achieved by converting the CRB-65 score into two dummy dichotomous variables (one for the intermediate risk at score 1 or 2; the other – for high risk at score of 3 or 4) and include these into a multiple linear regression model as two separate covariates (predictors). An extract of the data transformation is shown below in Table A2.2A.

A2.2A Reconstruction of the individual-level dataset from the derivation study (dummy variables)

Table A2.2A Creation of dummy variables for the CRB-65 score by using derivation study data

| CRB-65 | Deaths | N | Patient | Death | CRB-65 | Dummy Intermediate | Dummy High |
|--------|--------|------|----------|-------|--------|-----------------------|-----------------------|
| 0 | 2 | 167 | 1 ationt | Death | CRD-03 | (X_{INT}) | (X_{HIGH}) |
| 1 | 14 | 266 | | 1 | 0 | 0 | 0 |
| 2 | 23 | 189 | 1 | 1 | | | |
| 3 | 28 | 85 | 2 | 1 | 0 | 0 | 0 |
| 4 | 2 | 11 / | • • • | • • • | | ••• | ••• |
| | | | 167 | 0 | 0 | 0 | 0 |
| | | 1 | 168 | 1 | 1 | 1 | 0 |
| | | | 169 | 1 | 1 | 1 | 0 |
| | | - 1 | ••• | | ••• | | |
| | | 1 | 433 | 0 | 1 | 1 | 0 |
| | | 1 | 434 | 1 | 2 | . 1 | 0 |
| | | | 435 | 1 | 2 | 1 | 0 |
| | | | ••• | | ••• | | |
| | | | 622 | 0 | 2 | 1 | 0 |
| | | | 623 | 1 | 3 | 0 | 1 |
| | | | 624 | 1 | 3 | 0 | 1 |
| | | | | ••• | | ••• | ••• |
| | | | 707 | 0 | 3 | 0 | 1 |
| | | | 708 | 1 | 4 | ş 0 | 1 |
| | | | 709 | 1 | 4 | 0 | 1 |
| | | 1 | | ••• | ••• | ••• | ••• |
| | | | | | | | |

The equation {A1} of the prediction logistic model is of the form:

718

$$Log\left(\frac{risk \ of \ death}{1-risk \ of \ death}\right) = linear \ predictor \ Y = \alpha + \beta_{INT} \ X_{INT} + \beta_{HIGH} \ X_{HIGH} \qquad \{A1\},$$

0

where α is the coefficient of the intercept and β_{INT} and β_{HIGH} are the regression coefficients of the dummy variable intermediate and high risk, respectively. The predicted probability of death for each individual patient can be calculated from equation $\{A2\}$:

$$P = \frac{e^{Y}}{(1+e^{Y})} \tag{A2}.$$

In the derivation study, the linear model was described by equation [3]:

$$Y = -4.413 + 1.988 X_{INT} + 3.624 X_{HIGH}$$
 {A3}.

For instance, a patient with score 0 will have Y = -4.413, resulting in a probability of 0.012 (1.2%, 95% CI 0.3-4.7%). A patient with a score of 1-2 will produce Y = -4.413+1.988 = -2.425 that equals to a probability of 0.081 (8.1%, 95% CI 5.9-11.0%). Similarly, a patient with a score of 3-4 will have Y = -4.413+3.624 = -0.789, resulting in a probability of 0.313 (31.3%, 95% CI 22.8-41.2%).

Using the above logistic regression approach as shown on the data from the derivation study (Table A2.2A) it was possible to approximate the individual-level data in each of the validation studies of the CRB-65 rule. As an example only, we present below one such computation as applied to the validation study of Man et al (2007) as in Table A2.2B below.

A2.2B Reconstruction of the individual-level dataset from the validation study (dummy variables)

Table A2.2B Creation of dummy variables for the CRB-65 rule by using validation study data

| CRB-65 | Deaths | N |
|--------|--------|-----|
| 0 | 3 | 128 |
| 1 | 25 | 489 |
| 2 | 33 | 294 |
| 3 | 22 | 95 |
| 4 | 4 | 10 |

| Patient | Death | CRB- 65 | Dummy Intermediate $(X_{INT,VAL})$ | Dummy High (X _{HIGH,VAL}) |
|---------|-------|------------|--|---|
| 1 | 1 | 0 | 0 | 0 |
| 2 | 1 | 0 | 0 | 0 |
| | | | | |
| 128 | 0 | 0 | 0 | 0 |
| 129 | 1 | 1 | 1 | 0 |
| 130 | 1 | 1 | 1 | 0 |
| | | ••• | ••• | |
| 617 | 0 | 1 | 1 | 0 |
| 618 | 1 | 2 | 1 | 0 |
| 619 | 1 | 2 | 1 | 0 |
| | | | *** | |
| 911 | 0 | 2 | - 1 | 0 |
| 912 | 1 | 3 | 0 | 1 |
| 913 | 1 | 3 | 0 | 1 |
| | ••• | | | *** |
| 1006 | 0 | 3 :- | 0 | 1 |
| 1007 | 1 | 4 | 0 | 1 |
| 1008 | 1 | 4 | 0 | 1 |
| | *** | | ••• | *** |
| 1016 | 0 | 4 | 0 | 1 |

The linear predictor Y_{VAL} on the data from the validation study was calculated after the equation [4]:

$$Y_{VAL} = \alpha_{DER} + \beta_{INT,DER} X_{INT,VAL} + \beta_{HIGH,DER} X_{HIGH,VAL}$$
 (A4),

where α_{DER} (-4.413) is the intercept as well as $\beta_{\text{INT,DER}}$ (1.988) and $\beta_{\text{HIGH,DER}}$ (3.624) are the dummy variable coefficients from the derivation study (as shown above), while $X_{\text{INT,VAL}}$ and $X_{\text{HIGH,VAL}}$ are the CRB-65 values as dummy variables of intermediate and high risk, respectively, from the validation study. The predicted probability of death for each individual patient (Table A2.2C) was calculated as:

$$P = \frac{e^{Y_{VAL}}}{\left(1 + e^{Y_{VAL}}\right)} \tag{A5}.$$

Table A2.2C Reconstructed individual-level dataset from the validation study of the CRB-65 rule by Man et al (2007)

| Patient | Death | CRB-65 | Dummy Intermediate $(X_{INT,VAL})$ | Dummy High $(X_{HIGH,VAL})$ | Y_{VAL} | P |
|---------|-------|--------|------------------------------------|-----------------------------|-----------|--------|
| 1 | 1 | 0 | 0 | 0 | -4.413 | 0.0119 |
| 2 | 1 | 0 | 0 | 0 | -4.413 | 0.0119 |
| | • • • | • • • | • • • | • • • | | • • • |
| 128 | 0 | 0 | 0 | 0 | -4.413 | 0.0119 |
| 129 | 1 | 1 | 1 | 0 | -2.425 | 0.0813 |
| 130 | 1 | 1 | 1 | 0 | -2.425 | 0.0813 |
| • • • | • • • | | • • • | • • • | | ••• |
| 617 | 0 | 1 | 1 | 0 | -2.425 | 0.0813 |
| 618 | 1 | 2 | 1 | 0 | -2.425 | 0.0813 |
| 619 | 1 | 2 | 1 | 0 | -2.425 | 0.0813 |
| ••• | • • • | | • • • | • • • | • • • | ••• |
| 911 | 0 | 2 | 1 | 0 | -2.425 | 0.0813 |
| 912 | 1 | 3 | 0 | 1 | -0.789 | 0.313 |
| 913 | 1 | 3 | 0 | 1 | -0.789 | 0.313 |
| • • • | ••• | • • • | • • • | • • • | | • • • |
| 1006 | 0 | 3 | 0 | 1 | -0.789 | 0.3125 |
| 1007 | 1 | 4 | 0 | 1 | -0.789 | 0.3125 |
| 1008 | 1 | 4 | 0 | 1 | -0.789 | 0.3125 |
| • • • | | | ••• | ••• | | ••• |
| 1016 | 0 | 4 | 0 | 1 | -0.789 | 0.3125 |

The predicted number of deaths was obtained by adding up the individual probabilities within each stratum of the CRB-65 rule and then compared with the observed number of deaths (Table A2.2D).

Table A2.2D. Results on the data from a validation study of the CRB-65 rule by Man et al (2007)

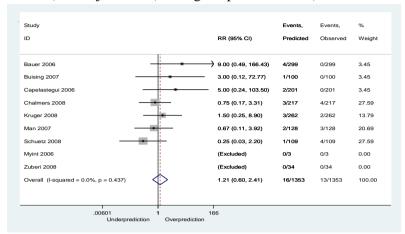
| CRB-65 risk stratification | Observed deaths (n)* | N | Predicted deaths (n)** |
|-------------------------------|----------------------|-----|------------------------|
| Low risk (0 score) | 3 | 128 | 1.5 (≈2) |
| Intermediate risk (1-2 score) | 58 | 783 | 63.7 (≈64) |
| High risk (3-4 score) | 26 | 105 | 32.8 (≈33) |

Notes: *Actual number of deaths reported in each stratum of risk; **values in the parentheses are rounded numbers.

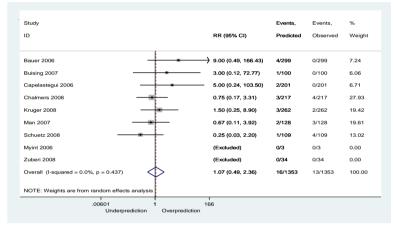
It is clear that the predicted numbers of deaths in Table A2.2D as obtained by our new simplified approach in each risk stratum of the CRB-65 rule (2, 63 and 33) in the validation study by Man et al (2007) do correspond exactly to the numbers of deaths in each stratum of Table A2.1C (2, 64 and 33) as predicted by the logistic regression model with the reconstructed dummy variables (as considered to be our "gold standard" as a reference for our new approach).

A2.3. Results of the meta analysis of the validation studies of CRB-65 rule (Forest plots)

A2.3.1A) No adjustment (the original prediction rule) – fixed effects



A2.3.1B) No adjustment (the original prediction rule) – random effects



A2.3.1C) Adjustment of the intercept – fixed effects

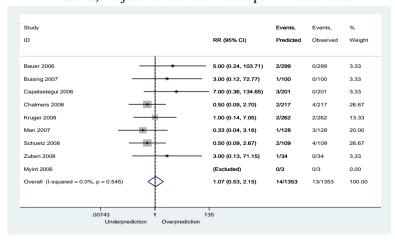
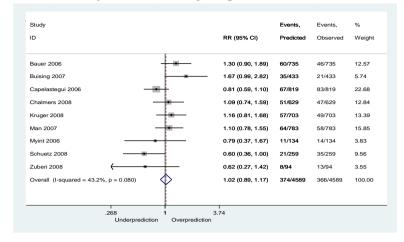
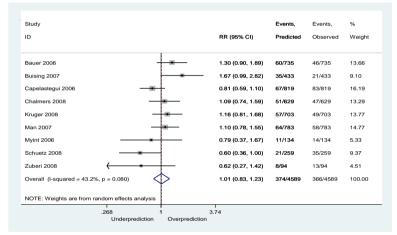


Fig. A2.3.1 CRB-65 (low risk)

A2.3.2A) No adjustment (the original prediction rule) – fixed effects



A2.3.2B) No adjustment (the original prediction rule) - random effects



A2.3.2C) Adjustment of the intercept – fixed effects

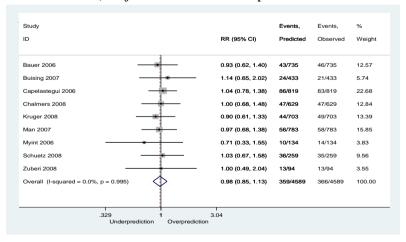
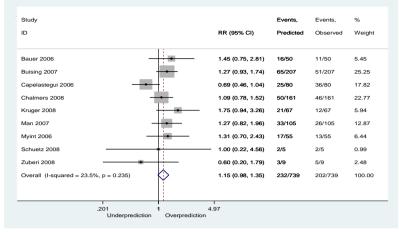
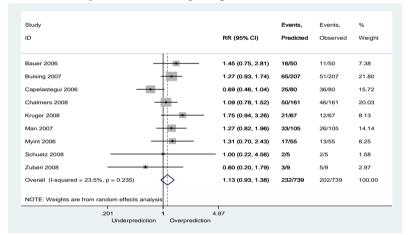


Fig. A2.3.2 CRB-65 (intermediate risk)

A2.3.3A) No adjustment (the original prediction rule) – fixed effects



A2.3.3B) No adjustment (the original prediction rule) – random effects



A2.3.3C) Adjustment of the intercept – fixed effects

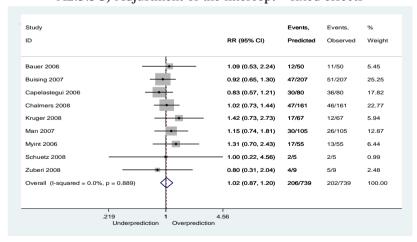


Figure A2.3.3 CRB-65 (high risk)

A2.4. Performance and pooled results of the meta analysis of the validation studies of CRB-65 rule

Table A2.4. Performance of the CRB65 rule in validation studies

| | Discrimination | n (c-statistic) | Calibration (H-L p-value*) | | |
|-------------------|----------------|-----------------|----------------------------|---------------|--|
| Study | No adjustment | Adjustment of | No adjustment | Adjustment of | |
| | (original CPR) | intercept | (original CPR) | intercept | |
| Bauer 2006 | 0.695 | 0.695 | 0.028 | 0.404 | |
| Buising 2007 | 0.759 | 0.759 | 0.009 | 0.691 | |
| Capelastegui 2006 | 0.700 | 0.700 | 0.003 | 0.156 | |
| Chalmers 2008 | 0.717 | 0.717 | 0.644 | 0.762 | |
| Kruger 2008 | 0.661 | 0.661 | 0.065 | 0.437 | |
| Man 2007 | 0.638 | 0.638 | 0.258 | 0.417 | |
| Myint 2006 | 0.618 | 0.618 | 0.479 | 0.475 | |
| Schuetz 2008 | 0.622 | 0.622 | 0.001 | 0.743 | |
| Zuberi 2008 | 0.725 | 0.725 | 0.073 | 0.771 | |

Note: *H-L, Hosmer-Lemeshow "goodness-of-fit" p-value (a non-significant p-value means good fit – the higher the p-value, the better the fit)

Table A2.5. Pooled RRs with 95% CIs from the meta-analysis of the validation studies of CRB65 rule*

| | | No adjustment (original CPR) | | Adjustment of intercept | |
|-------------------------------|----------------|------------------------------|------------------|-------------------------|------------------|
| CRB-65 score (mortality risk) | \mathbf{I}^2 | Fixed effects | Random effects | \mathbf{I}^2 | Fixed effects |
| Low risk (0 score) | 0.0% | 1.21 (0.60-2.41) | 1.08 (0.49-2.36) | 0.0% | 1.07 (0.53-2.15) |
| Intermediate risk (1-2 score) | 43.2% | 1.02 (0.89-1.17) | 1.01 (0.83-1.23) | 0.0% | 0.98 (0.85-1.13) |
| High risk (3-4 score) | 23.5% | 1.15 (0.98-1.35) | 1.13 (0.93-1.38) | 0.0% | 1.02 (0.87-1.20) |

Note: *Abbreviations: RR, risk ratio, CI, confidence interval; I², coefficient of heterogeneity