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# Table 1 . Meta analysis of Net adverse clinical event – overall and stratified analysis

 Study | RR [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

 Provisional GPI use

BRAVE 4 |  **1.073 0.720 1.600 4.95**

BRIGHT (hep alone) |  **0.670 0.496 0.904 6.65**

ISAR-REACT 3 |  **0.951 0.787 1.151 9.05**

NAPLES III |  **1.504 0.841 2.688 2.99**

MATRIX |  **0.901 0.794 1.023 10.47**

 Sub-total |

 D+L pooled RR |  **0.917 0.781 1.077 34.11**

 M-H pooled RR |  **0.908 0.826 0.999**

---------------------+---------------------------------------------------

 Planned GPI use in h

ACUITY-PCI (Biv alon |  **0.869 0.752 1.004 10.09**

ACUITY-PCI (Biv+GPI) |  **1.120 0.979 1.281 10.30**

BRIGHT (hep +GPI) |  **0.513 0.386 0.681 6.97**

EUROMAX |  **0.734 0.562 0.957 7.34**

Horizons AMI |  **0.762 0.630 0.923 9.03**

ISAR-REACT 4 |  **1.012 0.773 1.324 7.28**

NAPLES |  **0.569 0.384 0.844 5.03**

REPLACE-2 |  **0.924 0.791 1.080 9.84**

 Sub-total |

 D+L pooled RR |  **0.812 0.689 0.957 65.89**

 M-H pooled RR |  **0.880 0.822 0.941**

---------------------+---------------------------------------------------

Overall |

 D+L pooled RR |  **0.854 0.760 0.959 100.00**

 M-H pooled RR |  **0.889 0.842 0.939**

---------------------+---------------------------------------------------

Test(s) of heterogeneity:

 Heterogeneity degrees of statistic freedom P I-squared\*\* Tau-squared

Provisional GPI use  **7.77 4 0.101 48.5% 0.0147**

Planned GPI use in h **36.34 7 0.000 80.7% 0.0424**

Overall **44.34 12 0.000 72.9% 0.0292** \*\* I-squared: the variation in RR attributable to heterogeneity)

Note: between group heterogeneity not calculated; only valid with inverse variance method Significance test(s) of RR=1

Provisional GPI use z=  **1.05**  p = **0.292**

Planned GPI use in h z=  **2.48**  p = **0.013**

Overall z=  **2.67**  p = **0.008**

-------------------------------------------------------------------------

Figure 1. Forrest plot for Net adverse clinical event -overall and stratified analysis.



#  Table 2 . Net adverse clinical event – Egger’s test - overall analysis

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **13** Root MSE =  **1.899**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.0292239 .1379818 0.21 0.836 -.2744719 .3329198** |
| bias  |  **-1.547531 1.359083 -1.14 0.279 -4.538853 1.443791** |

Test of H0: no small-study effects P = **0.279**

# Figure 2. Funnel plot of Net adverse clinical event - overall analysis.



# Table 3. Net adverse clinical event -sensitivity analysis

------------------------------------------------------------------------------

 Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

 **BRAVE 4** | **.88607401 .83823705 .93664086**

 **BRIGHT (hep alone)**| **.8982746 .84940946 .94995093**

 **HEAT-PPCI** | **.88917506 .8416189 .93941838**

 **ACUITY-PCI (Biv alone)**|**.89259613 .84110981 .94723403**

 **ACUITY-PCI (Biv+GPI)**| **.85037959 .80062789 .90322286**

 **BRIGHT (hep +GPI)** | **.90985847 .86020523 .96237779**

 **EUROMAX** | **.89717984 .84815764 .94903547**

 **Horizons AMI** | **.90190077 .8515811 .95519388**

 **ISAR-REACT 4** | **.88415694 .83587396 .93522882**

 **PROTECT-TIMI 30** | **.88917506 .8416189 .93941838**

 **AMYDA-7 BIVALVE** | **.88917506 .8416189 .93941838**

 **ISAR-REACT 3** | **.88350892 .83420831 .93572319**

 **NAPLES III** | **.88451791 .83698922 .93474561**

 **CACHET** | **.88917506 .8416189 .93941838**

 **Deshpande et al** | **.88917506 .8416189 .93941838**

 **NAPLES** | **.89640474 .84798241 .94759208**

 **REPLACE-1** | **.88917506 .8416189 .93941838**

 **REPLACE-2** | **.88420355 .83375579 .93770379**

 **TENACITY** | **.88917506 .8416189 .93941838**

 **MATRIX** | **.88638186 .83394033 .94212121**

-------------------+----------------------------------------------------------

 **Combined** | **.88917505 .8416189 .93941838**

------------------------------------------------------------------------------

 0.80

 0.89

 0.84

 0.94

 0.96

 BRAVE 4

 BRIGHT (hep alone)

 HEAT-PPCI

 ACUITY-PCI (Biv alone)

 ACUITY-PCI (Biv+GPI)

 BRIGHT (hep +GPI)

 EUROMAX

 Horizons AMI

 ISAR-REACT 4

 PROTECT-TIMI 30

 AMYDA-7 BIVALVE

 ISAR-REACT 3

 NAPLES III

 CACHET

 Deshpande et al

 NAPLES

 REPLACE-1

 REPLACE-2

 TENACITY

 MATRIX

 Lower CI Limit

 Estimate

 Upper CI Limit

 Meta-analysis estimates, given named study is omitted

# Table 4 . Net adverse clinical event – Egger’s test for provisional GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **5** Root MSE =  **1.531**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |  **-.1747461 .1580587 -1.11 0.350 -.6777595 .3282672** |
| bias  |   **.8160568 1.453901 0.56 0.614 -3.810904 5.443018** |

Test of H0: no small-study effects P = **0.614**

# Figure 3. Funnel plot of Net adverse clinical event for provisional GPI use in heparin arm.



# Table 5 . Net adverse clinical event – Egger’s test for planned GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **8** Root MSE =  **1.729**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.2778815 .1376709 2.02 0.090 -.058987 .61475** |
| bias  |  **-4.362168 1.363194 -3.20 0.019 -7.697783 -1.026553** |

Test of H0: no small-study effects P = **0.019**

# Figure 4. Funnel plot of Net adverse clinical event for planned GPI use in heparin arm.



# Table 6 . Meta analysis of MACE – overall and stratified analysis

 Study | RR [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

 Provisional GPI use

AMYDA-7 BIVALVE |  **1.253 0.694 2.264 1.17**

BRAVE 4 |  **0.886 0.430 1.826 0.78**

BRIGHT (hep alone) |  **0.897 0.582 1.383 2.18**

HEAT-PPCI |  **1.523 1.086 2.134 3.58**

ISAR-REACT 3 |  **1.161 0.911 1.480 6.95**

NAPLES III |  **1.640 0.784 3.430 0.75**

MATRIX |  **0.947 0.828 1.083 22.61**

 Sub-total |

 D+L pooled RR |  **1.110 0.934 1.319 38.01**

 M-H pooled RR |  **1.048 0.945 1.162**

---------------------+---------------------------------------------------

 Planned GPI use in h

ACUITY-PCI (Biv alon |  **1.071 0.895 1.281 12.74**

ACUITY-PCI (Biv+GPI) |  **1.136 0.952 1.355 13.11**

BRIGHT (hep +GPI) |  **1.021 0.653 1.596 2.04**

CACHET |  **0.122 0.007 2.123 0.05**

EUROMAX |  **1.085 0.773 1.523 3.55**

Horizons AMI |  **0.991 0.755 1.300 5.53**

ISAR-REACT 4 |  **1.047 0.820 1.336 6.87**

NAPLES |  **0.814 0.446 1.488 1.12**

PROTECT-TIMI 30 |  **1.327 0.818 2.154 1.74**

REPLACE-1 |  **0.821 0.513 1.312 1.85**

REPLACE-2 |  **1.081 0.902 1.295 12.53**

TENACITY |  **0.936 0.470 1.865 0.86**

 Sub-total |

 D+L pooled RR |  **1.064 0.981 1.154 61.99**

 M-H pooled RR |  **1.061 0.978 1.150**

---------------------+---------------------------------------------------

Overall |

 D+L pooled RR |  **1.056 0.991 1.126 100.00**

 M-H pooled RR |  **1.056 0.991 1.125**

---------------------+---------------------------------------------------

Test(s) of heterogeneity:

 Heterogeneity degrees of statistic freedom P I-squared\*\* Tau-squared

Provisional GPI use  **10.04 6 0.123 40.2% 0.0188**

Planned GPI use in h **5.97 11 0.876 0.0% 0.0000**

Overall **16.08 18 0.587 0.0% 0.0000** \*\* I-squared: the variation in RR attributable to heterogeneity)

Note: between group heterogeneity not calculated; only valid with inverse variance method Significance test(s) of RR=1

Provisional GPI use z=  **1.19**  p = **0.235**

Planned GPI use in h z=  **1.50**  p = **0.134**

Overall z=  **1.68**  p = **0.094**

-------------------------------------------------------------------------

#  Figure 5. Forrest plot for MACE -overall and stratified analysis.



# Table 7 . MACE – Egger’s test - overall analysis.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **19** Root MSE =  **.9721**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.0617495 .0621153 0.99 0.334 -.0693023 .1928012** |
| bias  |  **-.0583248 .4372584 -0.13 0.895 -.9808593 .8642097** |

Test of H0: no small-study effects P = **0.895**

# Figure 6. Funnel plot of MACE - overall analysis.



# Table 8. MACE -sensitivity analysis

------------------------------------------------------------------------------

 Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

 **AMYDA-7 BIVALVE** | **1.0536858 .98823416 1.1234723**

 **BRAVE 4** | **1.0572944 .99174339 1.1271782**

 **BRIGHT (hep alone)**| **1.0597433 .99358523 1.1303065**

 **HEAT-PPCI** | **1.0409526 .97547907 1.1108207**

 **ISAR-REACT 3** | **1.0480626 .98104048 1.1196635**

 **NAPLES III** | **1.0519546 .98673493 1.1214851**

 **ACUITY-PCI (Biv alone)**|**1.0535985 .98410916 1.1279945**

 **ACUITY-PCI (Biv+GPI)**| **1.044278 .97525591 1.118185**

 **BRIGHT (hep +GPI)** | **1.056555 .9906469 1.126848**

 **CACHET** | **1.058583 .99316096 1.1283146**

 **Deshpande et al** | **1.0557876 .99057829 1.1252896**

 **EUROMAX** | **1.0546962 .98841131 1.1254264**

 **Horizons AMI** | **1.0598259 .99254572 1.1316667**

 **ISAR-REACT 4** | **1.0564234 .98890448 1.1285523**

 **NAPLES** | **1.0588226 .99306256 1.1289371**

 **PROTECT-TIMI 30** | **1.0516701 .98615634 1.121536**

 **REPLACE-1** | **1.060953 .99482143 1.1314808**

 **REPLACE-2** | **1.0522114 .98289466 1.1264166**

 **TENACITY** | **1.0568912 .99134016 1.1267767**

 **MATRIX** | **1.088663 1.0125695 1.1704749**

-------------------+----------------------------------------------------------

 **Combined** | **1.0557876 .99057827 1.1252896**

------------------------------------------------------------------------------

 0.98

 1.06

 0.99

 1.13

 1.17

 AMYDA-7 BIVALVE

 BRAVE 4

 BRIGHT (hep alone)

 HEAT-PPCI

 ISAR-REACT 3

 NAPLES III

 ACUITY-PCI (Biv alone)

 ACUITY-PCI (Biv+GPI)

 BRIGHT (hep +GPI)

 CACHET

 Deshpande et al

 EUROMAX

 Horizons AMI

 ISAR-REACT 4

 NAPLES

 PROTECT-TIMI 30

 REPLACE-1

 REPLACE-2

 TENACITY

 MATRIX

 Lower CI Limit

 Estimate

 Upper CI Limit

 Meta-analysis estimates, given named study is omitted

# Table 9 . MACE – Egger’s test for provisional GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **7** Root MSE =  **1.225**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **-.084014 .1170927 -0.72 0.505 -.3850105 .2169824** |
| bias  |   **1.085961 .8372537 1.30 0.251 -1.066268 3.23819** |

Test of H0: no small-study effects **0.251**

# Figure 7. Funnel plot of MACE for provisional GPI use in heparin arm.



# Table 10 . MACE – Egger’s test for planned GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **12** Root MSE =  **1.104**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.3133407 .0959582 3.27 0.008 .0995326 .5271488** |
| bias  |  **-1.909295 .5968164 -3.20 0.010 -3.239084 -.5795047** |

Test of H0: no small-study effects P = **0.010**

# Figure 8. Funnel plot of MACE for planned GPI use in heparin arm.



# Table 11 . Meta analysis of myocardial infarction – overall and stratified analysis.

 Study | RR [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

 Provisional GPI use

AMYDA-7 BIVALVE |  **1.206 0.651 2.234 1.59**

BRAVE 4 |  **1.022 0.258 4.046 0.32**

BRIGHT (hep alone) |  **0.774 0.290 2.066 0.63**

HEAT-PPCI |  **3.007 1.358 6.657 0.95**

ISAR-REACT 3 |  **1.160 0.905 1.486 9.80**

NAPLES III |  **3.007 0.123 73.607 0.06**

MATRIX |  **1.011 0.869 1.177 26.16**

 Sub-total |

 D+L pooled RR |  **1.142 0.927 1.408 39.50**

 M-H pooled RR |  **1.088 0.962 1.230**

---------------------+---------------------------------------------------

 Planned GPI use in h

ACUITY-PCI (Biv alon |  **1.154 0.931 1.432 13.03**

ACUITY-PCI (Biv+GPI) |  **1.166 0.940 1.445 13.07**

BRIGHT (hep +GPI) |  **1.159 0.391 3.431 0.51**

EUROMAX |  **1.935 0.904 4.142 1.04**

Horizons AMI |  **1.032 0.638 1.672 2.60**

ISAR-REACT 4 |  **0.953 0.735 1.235 8.93**

NAPLES |  **0.814 0.446 1.488 1.66**

REPLACE-1 |  **0.948 0.561 1.603 2.19**

REPLACE-2 |  **1.124 0.928 1.362 16.41**

TENACITY |  **0.785 0.370 1.664 1.07**

 Sub-total |

 D+L pooled RR |  **1.095 0.991 1.210 60.50**

 M-H pooled RR |  **1.098 0.994 1.213**

---------------------+---------------------------------------------------

Overall |

 D+L pooled RR |  **1.089 1.007 1.177 100.00**

 M-H pooled RR |  **1.094 1.012 1.182**

---------------------+---------------------------------------------------

Test(s) of heterogeneity:

 Heterogeneity degrees of statistic freedom P I-squared\*\* Tau-squared

Provisional GPI use  **8.39 6 0.211 28.5% 0.0191**

Planned GPI use in h **5.92 9 0.748 0.0% 0.0000**

Overall **14.34 16 0.573 0.0% 0.0000** \*\* I-squared: the variation in RR attributable to heterogeneity)

Note: between group heterogeneity not calculated; only valid with inverse variance method Significance test(s) of RR=1

Provisional GPI use z=  **1.25**  p = **0.211**

Planned GPI use in h z=  **1.78**  p = **0.075**

Overall z=  **2.14**  p = **0.032**

-------------------------------------------------------------------------

#  Figure 9. Forrest plot of myocardial infarction - overall and stratified analysis.



# Table 12 . Myocardial infarction– Egger’s test - overall analysis.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **17** Root MSE =  **.9586**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.0442002 .065134 0.68 0.508 -.0946297 .1830301** |
| bias  |   **.3068515 .3986511 0.77 0.453 -.5428533 1.156556** |

Test of H0: no small-study effects P = **0.453**

# Figure 10. Funnel plot of myocardial infarction - overall analysis.



# Table 13. Myocardial infarction – sensitivity analysis

------------------------------------------------------------------------------

 Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

 **AMYDA-7 BIVALVE** | **1.0868356 1.0049911 1.1753454**

 **BRAVE 4** | **1.0888549 1.0073621 1.1769402**

 **BRIGHT (hep alone)**| **1.0909786 1.0092059 1.179377**

 **HEAT-PPCI** | **1.0780264 .99709541 1.1655264**

 **ISAR-REACT 3** | **1.0811979 .99629998 1.1733302**

 **NAPLES III** | **1.0879833 1.0066576 1.1758791**

 **ACUITY-PCI (Biv alone)**|**1.0791124 .99288344 1.1728301**

 **ACUITY-PCI (Biv+GPI)**| **1.0775094 .99139005 1.1711098**

 **BRIGHT (hep +GPI)** | **1.0882869 1.0067606 1.176415**

 **CACHET** | **1.088636 1.0072845 1.1765575**

 **Deshpande et al** | **1.088636 1.0072845 1.1765575**

 **EUROMAX** | **1.0820681 1.0007995 1.1699359**

 **Horizons AMI** | **1.0901773 1.0076733 1.1794364**

 **ISAR-REACT 4** | **1.1029795 1.0167689 1.1964997**

 **NAPLES** | **1.0939885 1.0115759 1.1831152**

 **PROTECT-TIMI 30** | **1.088636 1.0072845 1.1765575**

 **REPLACE-1** | **1.0920001 1.0095241 1.1812142**

 **REPLACE-2** | **1.0817974 .9936949 1.1777111**

 **TENACITY** | **1.0924854 1.010424 1.1812114**

 **MATRIX** | **1.1174525 1.0208836 1.2231562**

-------------------+----------------------------------------------------------

 **Combined** | **1.088636 1.0072846 1.1765576**

------------------------------------------------------------------------------

 0.99

 1.09

 1.01

 1.18

 1.22

 AMYDA-7 BIVALVE

 BRAVE 4

 BRIGHT (hep alone)

 HEAT-PPCI

 ISAR-REACT 3

 NAPLES III

 ACUITY-PCI (Biv alone)

 ACUITY-PCI (Biv+GPI)

 BRIGHT (hep +GPI)

 CACHET

 Deshpande et al

 EUROMAX

 Horizons AMI

 ISAR-REACT 4

 NAPLES

 PROTECT-TIMI 30

 REPLACE-1

 REPLACE-2

 TENACITY

 MATRIX

 Lower CI Limit

 Estimate

 Upper CI Limit

 Meta-analysis estimates, given named study is omitted

# Table 14 . Myocardial infarction– Egger’s test for provisional GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **7** Root MSE =  **1.139**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |  **-.0156471 .1044941 -0.15 0.887 -.2842579 .2529636** |
| bias  |   **.7564582 .6264099 1.21 0.281 -.8537798 2.366696** |

 Test of H0: no small-study effects **0.281**

# Figure 11. Funnel plot of myocardial infarction for provisional GPI use in heparin arm.



# Table 15 . Myocardial infarction – Egger’s test for planned GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **10** Root MSE =  **1.433**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.2711206 .1473085 1.84 0.103 -.0685733 .6108146** |
| bias  |  **-1.356216 .8106135 -1.67 0.133 -3.225494 .5130625** |

Test of H0: no small-study effects P = **0.133**

# Figure 12. Funnel plot of myocardial infarction for planned GPI use in heparin arm.



# Table 16. Meta analysis of major bleeding according to the TIMI scale – overall and stratified analysis.

 Study | RR [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

 Provisional GPI use

AMYDA-7 BIVALVE |  **0.513 0.047 5.608 0.91**

BRAVE 4 |  **0.895 0.329 2.432 4.29**

BRIGHT (hep alone) |  **0.362 0.116 1.130 3.48**

HEAT-PPCI |  **1.145 0.696 1.886 10.40**

ISAR-REACT 3 |  **0.498 0.250 0.994 7.26**

 Sub-total |

 D+L pooled RR |  **0.723 0.449 1.165 26.34**

 M-H pooled RR |  **0.769 0.545 1.085**

---------------------+---------------------------------------------------

 Planned GPI use in h

ACUITY-PCI (Biv alon |  **0.371 0.228 0.604 10.62**

ACUITY-PCI (Biv+GPI) |  **1.066 0.750 1.517 13.61**

BRIGHT (hep +GPI) |  **0.284 0.094 0.858 3.65**

CACHET |  **0.176 0.010 3.210 0.63**

EUROMAX |  **0.620 0.321 1.198 7.69**

Horizons AMI |  **0.605 0.436 0.840 14.18**

ISAR-REACT 4 |  **0.843 0.436 1.628 7.71**

PROTECT-TIMI 30 |  **0.224 0.012 4.142 0.62**

REPLACE-1 |  **0.774 0.355 1.689 6.18**

REPLACE-2 |  **0.734 0.407 1.324 8.76**

 Sub-total |

 D+L pooled RR |  **0.639 0.482 0.848 73.66**

 M-H pooled RR |  **0.659 0.553 0.785**

---------------------+---------------------------------------------------

Overall |

 D+L pooled RR |  **0.664 0.525 0.839 100.00**

 M-H pooled RR |  **0.680 0.582 0.794**

---------------------+---------------------------------------------------

Test(s) of heterogeneity:

 Heterogeneity degrees of

 statistic freedom P I-squared\*\* Tau-squared

Provisional GPI use  **5.85 4 0.211 31.6% 0.0907**

Planned GPI use in h **17.17 9 0.046 47.6% 0.0827**

Overall **23.62 14 0.051 40.7% 0.0727** \*\* I-squared: the variation in RR attributable to heterogeneity)

Note: between group heterogeneity not calculated; only valid with inverse variance method Significance test(s) of RR=1

Provisional GPI use z=  **1.33**  p = **0.182**

Planned GPI use in h z=  **3.11**  p = **0.002**

Overall z=  **3.43**  p = **0.001**

-------------------------------------------------------------------------

#  Figure 13. Forrest plot for major bleeding according to the TIMI scale - overall and stratified analysis.



# Table 17 . Major bleeding according to the TIMI scale – Egger’s test - overall analysis.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **15** Root MSE =  **1.249**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |  **-.1035338 .2059937 -0.50 0.624 -.5485562 .3414886** |
| bias  |  **-.9519265 .6574418 -1.45 0.171 -2.372243 .4683901** |

Test of H0: no small-study effects P = **0.171**

# Figure 14. Funnel plot of major bleeding according to the TIMI scale - overall and stratified analysis.



# Table 18. Major bleeding according to the TIMI scale – sensitivity analysis

------------------------------------------------------------------------------

 Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

 **AMYDA-7 BIVALVE** | **.6635114 .5213064 .84450793**

 **BRAVE 4** | **.65255398 .5102033 .83462155**

 **BRIGHT (hep alone)**| **.67858857 .53476161 .86109853**

 **HEAT-PPCI** | **.62806439 .49798635 .79211992**

 **ISAR-REACT 3** | **.67742103 .52870655 .86796594**

 **NAPLES III** | **.66380316 .52512425 .83910543**

 **ACUITY-PCI (Biv alone)**|**.73026663 .5929783 .89934039**

 **ACUITY-PCI (Biv+GPI)**| **.62097806 .49908412 .77264273**

 **BRIGHT (hep +GPI)** | **.68761283 .54623753 .86557841**

 **CACHET** | **.66914326 .5284673 .8472665**

 **Deshpande et al** | **.66380316 .52512425 .83910543**

 **EUROMAX** | **.66415834 .51515901 .85625273**

 **Horizons AMI** | **.66662639 .50883341 .87335205**

 **ISAR-REACT 4** | **.64758706 .50301832 .83370519**

 **NAPLES** | **.66380316 .52512425 .83910543**

 **PROTECT-TIMI 30** | **.66756326 .52634555 .84666938**

 **REPLACE-1** | **.65393388 .508798 .84047019**

 **REPLACE-2** | **.65330243 .50514638 .84491169**

 **TENACITY** | **.66380316 .52512425 .83910543**

 **MATRIX** | **.66380316 .52512425 .83910543**

-------------------+----------------------------------------------------------

 **Combined** | **.66380317 .52512428 .83910544**

------------------------------------------------------------------------------

 0.50

 0.66

 0.53

 0.84

 0.90

 AMYDA-7 BIVALVE

 BRAVE 4

 BRIGHT (hep alone)

 HEAT-PPCI

 ISAR-REACT 3

 NAPLES III

 ACUITY-PCI (Biv alone)

 ACUITY-PCI (Biv+GPI)

 BRIGHT (hep +GPI)

 CACHET

 Deshpande et al

 EUROMAX

 Horizons AMI

 ISAR-REACT 4

 NAPLES

 PROTECT-TIMI 30

 REPLACE-1

 REPLACE-2

 TENACITY

 MATRIX

 Lower CI Limit

 Estimate

 Upper CI Limit

 Meta-analysis estimates, given named study is omitted

# Table 19 . Major bleeding according to the TIMI scale – Egger’s test for provisional GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **5** Root MSE =  **1.162**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.2723267 .4920181 0.55 0.619 -1.293494 1.838148** |
| bias  |  **-1.405382 1.22444 -1.15 0.334 -5.302098 2.491334** |

 Test of H0: no small-study effects **0.334**

# Figure 15. Funnel plot of major bleeding according to the TIMI scale for provisional GPI use in heparin arm.



# Table 20. Major bleeding according to the TIMI scale– Egger’s test for planned GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **10** Root MSE =  **1.201**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.1098097 .210593 0.52 0.616 -.3758186 .5954379** |
| bias  |  **-1.700378 .6861978 -2.48 0.038 -3.282753 -.1180034** |

Test of H0: no small-study effects P = **0.038**

# Figure 16. Funnel plot of major bleeding according to the TIMI scale for planned GPI use in heparin arm.



# Table 21. Meta analysis of TVR/TLR– overall and stratified analysis.

 Study | RR [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

 Provisional GPI use

AMYDA-7 BIVALVE |  **0.205 0.046 0.924 1.48**

BRAVE 4 |  **0.682 0.194 2.388 2.07**

BRIGHT (hep alone) |  **0.918 0.422 1.998 4.72**

HEAT-PPCI |  **4.009 1.647 9.761 3.78**

ISAR-REACT 3 |  **1.114 0.580 2.137 6.20**

NAPLES III |  **1.671 0.402 6.946 1.63**

MATRIX |  **1.483 0.968 2.270 10.74**

 Sub-total |

 D+L pooled RR |  **1.198 0.723 1.986 30.62**

 M-H pooled RR |  **1.312 0.999 1.724**

---------------------+---------------------------------------------------

 Planned GPI use in h

ACUITY-PCI (Biv alon |  **1.026 0.761 1.384 14.85**

ACUITY-PCI (Biv+GPI) |  **1.163 0.870 1.556 15.18**

BRIGHT (hep +GPI) |  **1.324 0.561 3.123 4.02**

EUROMAX |  **1.438 0.777 2.661 6.73**

Horizons AMI |  **1.384 0.894 2.141 10.46**

ISAR-REACT 4 |  **1.573 0.613 4.039 3.43**

REPLACE-1 |  **0.657 0.271 1.593 3.81**

REPLACE-2 |  **0.837 0.536 1.307 10.21**

TENACITY |  **3.211 0.337 30.594 0.68**

NAPLES | (Excluded)

 Sub-total |

 D+L pooled RR |  **1.118 0.954 1.309 69.38**

 M-H pooled RR |  **1.119 0.956 1.310**

---------------------+---------------------------------------------------

Overall |

 D+L pooled RR |  **1.174 0.972 1.418 100.00**

 M-H pooled RR |  **1.165 1.017 1.336**

---------------------+---------------------------------------------------

Test(s) of heterogeneity:

 Heterogeneity degrees of statistic freedom P I-squared\*\* Tau-squared

Provisional GPI use  **14.42 6 0.025 58.4% 0.2429**

Planned GPI use in h **6.44 8 0.598 0.0% 0.0000**

Overall **21.79 15 0.113 31.2% 0.0392** \*\* I-squared: the variation in RR attributable to heterogeneity)

Note: between group heterogeneity not calculated; only valid with inverse variance method Significance test(s) of RR=1

Provisional GPI use z=  **0.70**  p = **0.484**

Planned GPI use in h z=  **1.38**  p = **0.169**

Overall z=  **1.67**  p = **0.096**

-------------------------------------------------------------------------

#  Figure 17. Forrest plot for TVR/TLR - overall and stratified analysis.



# Table 22 . TVR/TLR – Egger’s test - overall analysis.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **16** Root MSE =  **1.247**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.1261706 .1795084 0.70 0.494 -.2588367 .5111778** |
| bias  |   **.0927414 .6355927 0.15 0.886 -1.270469 1.455952** |

Test of H0: no small-study effects P = **0.886**

# Figure 18. Funnel plot of TVR/TLR - overall analysis.



# Table 23. TVR/TLR – sensitivity analysis

------------------------------------------------------------------------------

 Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

 **AMYDA-7 BIVALVE** | **1.1924336 1.0125729 1.4042425**

 **BRAVE 4** | **1.1881658 .97946286 1.4413389**

 **BRIGHT (hep alone)**| **1.1895267 .97497118 1.451298**

 **HEAT-PPCI** | **1.1255293 .97667921 1.2970648**

 **ISAR-REACT 3** | **1.1792639 .96238691 1.4450151**

 **NAPLES III** | **1.1674707 .96055067 1.4189649**

 **ACUITY-PCI (Biv alone)**|**1.2014459 .96817565 1.4909199**

 **ACUITY-PCI (Biv+GPI)**| **1.1778547 .94350851 1.4704072**

 **BRIGHT (hep +GPI)** | **1.1687083 .95743865 1.4265969**

 **CACHET** | **1.1740144 .97199774 1.4180176**

 **Deshpande et al** | **1.1740144 .97199774 1.4180176**

 **EUROMAX** | **1.1574142 .94635695 1.4155414**

 **Horizons AMI** | **1.1528214 .93747032 1.4176419**

 **ISAR-REACT 4** | **1.1620877 .95455801 1.414736**

 **NAPLES** | **1.1740144 .97199774 1.4180176**

 **PROTECT-TIMI 30** | **1.1740144 .97199774 1.4180176**

 **REPLACE-1** | **1.200528 .99276793 1.4517666**

 **REPLACE-2** | **1.2196287 1.0025905 1.4836507**

 **TENACITY** | **1.1660144 .9634096 1.411227**

 **MATRIX** | **1.142019 .93244284 1.3986996**

-------------------+----------------------------------------------------------

 **Combined** | **1.1740145 .97199774 1.4180176**

------------------------------------------------------------------------------

 0.93

 1.17

 0.97

 1.42

 1.49

 AMYDA-7 BIVALVE

 BRAVE 4

 BRIGHT (hep alone)

 HEAT-PPCI

 ISAR-REACT 3

 NAPLES III

 ACUITY-PCI (Biv alone)

 ACUITY-PCI (Biv+GPI)

 BRIGHT (hep +GPI)

 CACHET

 Deshpande et al

 EUROMAX

 Horizons AMI

 ISAR-REACT 4

 NAPLES

 PROTECT-TIMI 30

 REPLACE-1

 REPLACE-2

 TENACITY

 MATRIX

 Lower CI Limit

 Estimate

 Upper CI Limit

 Meta-analysis estimates, given named study is omitted

# Table 24 . TVR/TLR – Egger’s test for provisional GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **7** Root MSE =  **1.59**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.6938053 .5548737 1.25 0.266 -.7325429 2.120153** |
| bias  |  **-1.210532 1.444479 -0.84 0.440 -4.923683 2.502619** |

 Test of H0: no small-study effects P = **0.440**

# Figure 19. Funnel plot of TVR/TLR for provisional GPI use in heparin arm.



# Table 25 . TVR/TLR – Egger’s test for planned GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **9** Root MSE =  **1.579**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.354645 .2882178 1.23 0.258 -.3268817 1.036172** |
| bias  |   **-.960919 1.011273 -0.95 0.374 -3.3522 1.430362** |

Test of H0: no small-study effects P = **0.374**

# Figure 20. Funnel plot of TVR/TLR for planned GPI use in heparin arm.



# Table 26. Meta analysis of Death– overall and stratified analysis.

 Study | RR [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

 Provisional GPI use

AMYDA-7 BIVALVE |  **3.075 0.126 75.044 0.24**

BRAVE 4 |  **1.022 0.363 2.875 2.27**

BRIGHT (hep alone) |  **1.077 0.495 2.345 4.01**

HEAT-PPCI |  **1.182 0.779 1.793 13.99**

ISAR-REACT 3 |  **0.747 0.167 3.336 1.09**

NAPLES III |  **1.671 0.613 4.555 2.41**

MATRIX |  **0.709 0.510 0.987 22.22**

 Sub-total |

 D+L pooled RR |  **0.922 0.733 1.160 46.23**

 M-H pooled RR |  **0.921 0.734 1.156**

---------------------+---------------------------------------------------

 Planned GPI use in h

ACUITY-PCI (Biv alon |  **1.190 0.688 2.061 8.06**

ACUITY-PCI (Biv+GPI) |  **1.280 0.746 2.198 8.31**

BRIGHT (hep +GPI) |  **0.861 0.412 1.796 4.49**

EUROMAX |  **0.958 0.596 1.542 10.74**

Horizons AMI |  **0.661 0.439 0.997 14.44**

ISAR-REACT 4 |  **1.168 0.543 2.511 4.15**

PROTECT-TIMI 30 |  **6.042 0.247 147.851 0.24**

REPLACE-1 |  **0.141 0.007 2.717 0.28**

REPLACE-2 |  **0.586 0.231 1.487 2.80**

TENACITY |  **0.214 0.010 4.428 0.26**

 Sub-total |

 D+L pooled RR |  **0.916 0.727 1.153 53.77**

 M-H pooled RR |  **0.902 0.732 1.112**

---------------------+---------------------------------------------------

Overall |

 D+L pooled RR |  **0.916 0.784 1.071 100.00**

 M-H pooled RR |  **0.911 0.781 1.062**

---------------------+---------------------------------------------------

Test(s) of heterogeneity:

 Heterogeneity degrees of statistic freedom P I-squared\*\* Tau-squared

Provisional GPI use  **5.94 6 0.429 0.0% 0.0000**

Planned GPI use in h **9.87 9 0.361 8.8% 0.0124**

Overall **15.82 16 0.466 0.0% 0.0000** \*\* I-squared: the variation in RR attributable to heterogeneity)

Note: between group heterogeneity not calculated; only valid with inverse variance method Significance test(s) of RR=1

Provisional GPI use z=  **0.69**  p = **0.488**

Planned GPI use in h z=  **0.75**  p = **0.455**

Overall z=  **1.10**  p = **0.270**

-------------------------------------------------------------------------

#  Figure 21. Forrest plot for Death – overall and stratified analysis.



# Table 27 . Death – Egger’s test – overall analysis.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **17** Root MSE =  **1.016**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |  **-.1617567 .1551914 -1.04 0.314 -.4925395 .169026** |
| bias  |   **.2648793 .4734475 0.56 0.584 -.7442503 1.274009** |

Test of H0: no small-study effects P = **0.584**

# Figure 22. Funnel plot of Death – overall analysis.



# Table 28. Death – sensitivity analysis

------------------------------------------------------------------------------

 Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

 **AMYDA-7 BIVALVE** | **.91584444 .78132206 1.0735278**

 **BRAVE 4** | **.92048275 .77965105 1.0867535**

 **BRIGHT (hep alone)**| **.91561604 .7752555 1.0813888**

 **HEAT-PPCI** | **.87889177 .74296308 1.0396893**

 **ISAR-REACT 3** | **.92490113 .78454578 1.0903661**

 **NAPLES III** | **.9025923 .7708835 1.0568041**

 **ACUITY-PCI (Biv alone)**|**.89530826 .76102269 1.0532891**

 **ACUITY-PCI (Biv+GPI)**| **.88871974 .75525343 1.0457717**

 **BRIGHT (hep +GPI)** | **.92641127 .78278786 1.0963862**

 **CACHET** | **.91610426 .78392351 1.0705725**

 **Deshpande et al** | **.91610426 .78392351 1.0705725**

 **EUROMAX** | **.91938895 .77206385 1.0948266**

 **Horizons AMI** | **.96786523 .81781733 1.145443**

 **ISAR-REACT 4** | **.91021323 .77255106 1.0724056**

 **NAPLES** | **.91610426 .78392351 1.0705725**

 **PROTECT-TIMI 30** | **.91199976 .78026658 1.0659735**

 **REPLACE-1** | **.92088342 .78784275 1.0763903**

 **REPLACE-2** | **.92798001 .79231662 1.0868722**

 **TENACITY** | **.91964418 .78679019 1.0749313**

 **MATRIX** | **.98551124 .82590497 1.1759615**

-------------------+----------------------------------------------------------

 **Combined** | **.91610425 .78392353 1.0705725**

------------------------------------------------------------------------------

 0.74

 0.92

 0.78

 1.07

 1.18

 AMYDA-7 BIVALVE

 BRAVE 4

 BRIGHT (hep alone)

 HEAT-PPCI

 ISAR-REACT 3

 NAPLES III

 ACUITY-PCI (Biv alone)

 ACUITY-PCI (Biv+GPI)

 BRIGHT (hep +GPI)

 CACHET

 Deshpande et al

 EUROMAX

 Horizons AMI

 ISAR-REACT 4

 NAPLES

 PROTECT-TIMI 30

 REPLACE-1

 REPLACE-2

 TENACITY

 MATRIX

 Lower CI Limit

 Estimate

 Upper CI Limit

 Meta-analysis estimates, given named study is omitted

# Table 29 . Death – Egger’s test for provisional GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **7** Root MSE =  **.9336**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |  **-.3058277 .1991782 -1.54 0.185 -.8178317 .2061763** |
| bias  |   **.8686555 .6438672 1.35 0.235 -.7864578 2.523769** |

 Test of H0: no small-study effects P = **0.235**

# Figure 23. Funnel plot of death for provisional GPI use in heparin arm.



# Table 30 . Death – Egger’s test for planned GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **10** Root MSE =  **1.295**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.0931804 .2744768 0.34 0.743 -.5397642 .726125** |
| bias  |  **-.8379252 .7406179 -1.13 0.291 -2.545793 .8699426** |

Test of H0: no small-study effects P = **0.291**

# Figure 24. Funnel plot of Death for planned GPI use in heparin arm.



# Table 31. Meta analysis of major bleeding not related to CABG– overall and stratified analysis.

 Study | RR [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

 Provisional GPI use

BRAVE 4 |  **1.177 0.762 1.819 8.96**

ISAR-REACT 3 |  **0.671 0.498 0.903 10.81**

NAPLES III |  **1.276 0.586 2.777 5.24**

MATRIX |  **0.556 0.393 0.786 10.15**

 Sub-total |

 D+L pooled RR |  **0.803 0.555 1.163 35.16**

 M-H pooled RR |  **0.726 0.599 0.880**

---------------------+---------------------------------------------------

 Planned GPI use in h

ACUITY-PCI (Biv alon |  **0.517 0.404 0.662 11.46**

ACUITY-PCI (Biv+GPI) |  **1.106 0.908 1.346 12.04**

EUROMAX |  **0.426 0.276 0.656 8.98**

Horizons AMI |  **0.598 0.464 0.771 11.37**

ISAR-REACT 4 |  **0.551 0.330 0.918 7.97**

NAPLES |  **0.251 0.028 2.227 1.02**

REPLACE-2 |  **0.580 0.435 0.773 10.94**

TENACITY |  **0.214 0.025 1.815 1.06**

 Sub-total |

 D+L pooled RR |  **0.590 0.433 0.804 64.84**

 M-H pooled RR |  **0.674 0.603 0.753**

---------------------+---------------------------------------------------

Overall |

 D+L pooled RR |  **0.663 0.527 0.833 100.00**

 M-H pooled RR |  **0.687 0.624 0.756**

---------------------+---------------------------------------------------

Test(s) of heterogeneity:

 Heterogeneity degrees of statistic freedom P I-squared\*\* Tau-squared

Provisional GPI use  **9.32 3 0.025 67.8% 0.0914**

Planned GPI use in h **37.48 7 0.000 81.3% 0.1276**

Overall **47.22 11 0.000 76.7% 0.1037** \*\* I-squared: the variation in RR attributable to heterogeneity)

Note: between group heterogeneity not calculated; only valid with inverse variance method Significance test(s) of RR=1

Provisional GPI use z=  **1.16**  p = **0.246**

Planned GPI use in h z=  **3.34**  p = **0.001**

Overall z=  **3.52**  p = **0.000**

-------------------------------------------------------------------------

#  Figure 25. Forrest plot for major bleeding not related to CABG of overall and stratified analysis.



# Table 32 . Major bleeding not related to CABG – Egger’s test – overall analysis.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **12** Root MSE =  **2.094**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |  **-.1914865 .2231915 -0.86 0.411 -.6887881 .3058151** |
| bias  |  **-1.123392 1.299958 -0.86 0.408 -4.019878 1.773095** |

Test of H0: no small-study effects P = **0.408**

# Figure 26. Funnel plot of major bleeding not related to CABG – overall analysis.



# Table 33. Major bleeding not related to CABG – sensitivity analysis

------------------------------------------------------------------------------

 Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

 **AMYDA-7 BIVALVE** | **.66252995 .52672356 .83335167**

 **BRAVE 4** | **.62677717 .49640757 .79138523**

 **BRIGHT (hep alone)**| **.66252995 .52672356 .83335167**

 **HEAT-PPCI** | **.66252995 .52672356 .83335167**

 **ISAR-REACT 3** | **.6605491 .51008004 .85540527**

 **NAPLES III** | **.63918567 .50580621 .80773687**

 **ACUITY-PCI (Biv alone)**|**.68389463 .53458476 .8749069**

 **ACUITY-PCI (Biv+GPI)**| **.61222625 .51569438 .72682774**

 **BRIGHT (hep +GPI)** | **.66252995 .52672356 .83335167**

 **CACHET** | **.66252995 .52672356 .83335167**

 **Deshpande et al** | **.66252995 .52672356 .83335167**

 **EUROMAX** | **.69229025 .54719746 .87585527**

 **Horizons AMI** | **.6700651 .51681238 .86876261**

 **ISAR-REACT 4** | **.6730231 .52730614 .85900778**

 **NAPLES** | **.66917789 .53105819 .84322035**

 **PROTECT-TIMI 30** | **.66252995 .52672356 .83335167**

 **REPLACE-1** | **.66252995 .52672356 .83335167**

 **REPLACE-2** | **.67256147 .52118504 .86790466**

 **TENACITY** | **.67059141 .53258783 .84435445**

 **MATRIX** | **.67531353 .52612114 .86681259**

-------------------+----------------------------------------------------------

 **Combined** | **.66252997 .52672355 .8333517**

------------------------------------------------------------------------------

 0.50

 0.66

 0.53

 0.83

 0.88

 AMYDA-7 BIVALVE

 BRAVE 4

 BRIGHT (hep alone)

 HEAT-PPCI

 ISAR-REACT 3

 NAPLES III

 ACUITY-PCI (Biv alone)

 ACUITY-PCI (Biv+GPI)

 BRIGHT (hep +GPI)

 CACHET

 Deshpande et al

 EUROMAX

 Horizons AMI

 ISAR-REACT 4

 NAPLES

 PROTECT-TIMI 30

 REPLACE-1

 REPLACE-2

 TENACITY

 MATRIX

 Lower CI Limit

 Estimate

 Upper CI Limit

 Meta-analysis estimates, given named study is omitted

# Table 34 . Major bleeding not related to CABG – Egger’s test for provisional GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **4** Root MSE =  **1.52**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |  **-.9858838 .5001462 -1.97 0.187 -3.137839 1.166072** |
| bias  |   **3.598529 2.526955 1.42 0.290 -7.274081 14.47114** |

Test of H0: no small-study effects P = **0.290**

#  Figure 27. Funnel plot of major bleeding not related to CABG for provisional GPI use in heparin arm.



# Table 35. Major bleeding not related to CABG – Egger’s test for planned GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **8** Root MSE =  **1.925**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.1082584 .207551 0.52 0.621 -.3996007 .6161175** |
| bias  |  **-2.932309 1.142382 -2.57 0.043 -5.727617 -.1369999** |

Test of H0: no small-study effects P = **0.043**

# Figure 28. Funnel plot of major bleeding not related to CABG for planned GPI use in heparin arm.



# Table 36. Meta analysis of stent thrombosis– overall and stratified analysis.

 Study | RR [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

 Provisional GPI use

AMYDA-7 BIVALVE |  **21.528 1.270 364.908 0.97**

BRAVE 4 |  **0.767 0.173 3.393 3.27**

HEAT-PPCI |  **4.009 1.647 9.761 7.73**

ISAR-REACT 3 |  **1.329 0.561 3.147 8.11**

NAPLES III |  **1.002 0.142 7.083 1.98**

MATRIX |  **1.711 1.001 2.925 15.00**

 Sub-total |

 D+L pooled RR |  **1.884 1.053 3.370 37.06**

 M-H pooled RR |  **2.063 1.432 2.972**

---------------------+---------------------------------------------------

 Planned GPI use in h

ACUITY-PCI (Biv alon |  **1.041 0.639 1.694 16.54**

ACUITY-PCI (Biv+GPI) |  **1.235 0.773 1.973 17.17**

EUROMAX |  **2.885 1.142 7.291 7.26**

Horizons AMI |  **1.301 0.812 2.085 17.07**

ISAR-REACT 4 |  **1.200 0.368 3.916 4.88**

 Sub-total |

 D+L pooled RR |  **1.275 0.986 1.648 62.94**

 M-H pooled RR |  **1.289 0.999 1.663**

---------------------+---------------------------------------------------

Overall |

 D+L pooled RR |  **1.501 1.130 1.993 100.00**

 M-H pooled RR |  **1.514 1.230 1.863**

---------------------+---------------------------------------------------

Test(s) of heterogeneity:

 Heterogeneity degrees of statistic freedom P I-squared\*\* Tau-squared

Provisional GPI use  **8.47 5 0.132 41.0% 0.1946**

Planned GPI use in h **3.69 4 0.450 0.0% 0.0000**

Overall **14.64 10 0.146 31.7% 0.0649** \*\* I-squared: the variation in RR attributable to heterogeneity)

Note: between group heterogeneity not calculated; only valid with inverse variance method Significance test(s) of RR=1

Provisional GPI use z=  **2.13**  p = **0.033**

Planned GPI use in h z=  **1.85**  p = **0.064**

Overall z=  **2.80**  p = **0.005**

-------------------------------------------------------------------------

#  Figure 29. Forrest plot for stent thrombosis of overall and stratified analysis.



# Table 37 . Stent thrombosis – Egger’s test – overall analysis.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **11** Root MSE =  **1.155**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.0264354 .2789029 0.09 0.927 -.6044867 .6573575** |
| bias  |   **1.03694 .7743228 1.34 0.213 -.7147003 2.788579** |

Test of H0: no small-study effects P = **0.213**

Figure 30. Funnel plot of stent thrombosis – overall analysis.



# Table 38. Stent thrombosis – sensitivity analysis

------------------------------------------------------------------------------

 Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

 **AMYDA-7 BIVALVE** | **1.4387457 1.1237028 1.8421147**

 **BRAVE 4** | **1.5406985 1.1480197 2.067693**

 **BRIGHT (hep alone)**| **1.5007819 1.1299909 1.9932427**

 **HEAT-PPCI** | **1.3479025 1.0800966 1.68211**

 **ISAR-REACT 3** | **1.5318828 1.1183677 2.0982945**

 **NAPLES III** | **1.5228317 1.1299176 2.0523767**

 **ACUITY-PCI (Biv alone)**|**1.6132212 1.1831936 2.1995406**

 **ACUITY-PCI (Biv+GPI)**| **1.5806361 1.1289723 2.2129955**

 **BRIGHT (hep +GPI)** | **1.5007819 1.1299909 1.9932427**

 **CACHET** | **1.5007819 1.1299909 1.9932427**

 **Deshpande et al** | **1.5007819 1.1299909 1.9932427**

 **EUROMAX** | **1.4179361 1.0718459 1.8757759**

 **Horizons AMI** | **1.5670418 1.1149621 2.2024245**

 **ISAR-REACT 4** | **1.5302778 1.1272832 2.0773399**

 **NAPLES** | **1.5007819 1.1299909 1.9932427**

 **PROTECT-TIMI 30** | **1.5007819 1.1299909 1.9932427**

 **REPLACE-1** | **1.5007819 1.1299909 1.9932427**

 **REPLACE-2** | **1.5007819 1.1299909 1.9932427**

 **MATRIX** | **1.4845403 1.0680157 2.0635092**

-------------------+----------------------------------------------------------

 **Combined** | **1.5007819 1.1299909 1.9932428**

------------------------------------------------------------------------------

 1.07

 1.50

 1.13

 1.99

 2.21

 AMYDA-7 BIVALVE

 BRAVE 4

 BRIGHT (hep alone)

 HEAT-PPCI

 ISAR-REACT 3

 NAPLES III

 ACUITY-PCI (Biv alone)

 ACUITY-PCI (Biv+GPI)

 BRIGHT (hep +GPI)

 CACHET

 Deshpande et al

 EUROMAX

 Horizons AMI

 ISAR-REACT 4

 NAPLES

 PROTECT-TIMI 30

 REPLACE-1

 REPLACE-2

 MATRIX

 Lower CI Limit

 Estimate

 Upper CI Limit

 Meta-analysis estimates, given named study is omitted

# Table 39 . Stent thrombosis – Egger’s test for provisional GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **6** Root MSE =  **1.406**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.4346029 .5787841 0.75 0.494 -1.172359 2.041565** |
| bias  |   **.4337149 1.218646 0.36 0.740 -2.949788 3.817218** |

Test of H0: no small-study effects P = **0.740**

# Figure 31. Funnel plot of stent thrombosis for provisional GPI use in heparin arm.



# Table 40 . Stent thrombosis – Egger’s test for planned GPI use in heparin arm.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **5** Root MSE =  **1.784**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |   **.7601033 .5740376 1.32 0.277 -1.06674 2.586947** |
| bias  |  **-1.628443 1.673515 -0.97 0.402 -6.954314 3.697428** |

Test of H0: no small-study effects P = **0.402**

# Figure 32. Funnel plot of stent thrombosis for planned GPI use in heparin arm.



# Table 41. Meta analysis of acute stent thrombosis– overall and stratified analysis.

 Study | RR [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

 Provisional GPI use

HEAT-PPCI |  **3.341 1.348 8.280 27.51**

MATRIX |  **1.535 0.765 3.082 34.85**

 Sub-total |

 D+L pooled RR |  **2.141 1.005 4.558 62.35**

 M-H pooled RR |  **2.105 1.222 3.627**

---------------------+---------------------------------------------------

 Planned GPI use in h

EUROMAX |  **6.110 1.371 27.237 14.65**

Horizons AMI |  **5.256 1.808 15.281 23.00**

 Sub-total |

 D+L pooled RR |  **5.530 2.320 13.181 37.65**

 M-H pooled RR |  **5.539 2.325 13.197**

---------------------+---------------------------------------------------

Overall |

 D+L pooled RR |  **3.089 1.589 6.006 100.00**

 M-H pooled RR |  **2.927 1.861 4.602**

---------------------+---------------------------------------------------

Test(s) of heterogeneity:

 Heterogeneity degrees of statistic freedom P I-squared\*\* Tau-squared

Provisional GPI use  **1.78 1 0.182 43.9% 0.1333**

Planned GPI use in h **0.03 1 0.872 0.0% 0.0000**

Overall **5.46 3 0.141 45.1% 0.2037** \*\* I-squared: the variation in RR attributable to heterogeneity)

Note: between group heterogeneity not calculated; only valid with inverse variance method Significance test(s) of RR=1

Provisional GPI use z=  **1.97**  p = **0.048**

Planned GPI use in h z=  **3.86**  p = **0.000**

Overall z=  **3.33**  p = **0.001**

-------------------------------------------------------------------------

#  Figure 33. Forrest plot for acute stent thrombosis of overall and stratified analysis.



# Table 42 . Acute stent thrombosis – Egger’s test – overall analysis.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **4** Root MSE =  **.7011**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |  **-.8569056 .6443904 -1.33 0.315 -3.629494 1.915683** |
| bias  |   **4.047514 1.354312 2.99 0.096 -1.779621 9.874649** |

Test of H0: no small-study effects P = **0.096**

# Figure 34. Funnel plot of acute stent thrombosis – overall analysis.



# Table 43. Acute stent thrombosis – sensitivity analysis

------------------------------------------------------------------------------

 Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

 **AMYDA-7 BIVALVE** | **3.0893335 1.5891356 6.0057693**

 **BRAVE 4** | **3.0893335 1.5891356 6.0057693**

 **BRIGHT (hep alone)**| **3.0893335 1.5891356 6.0057693**

 **HEAT-PPCI** | **3.2178967 1.2086517 8.5672817**

 **ISAR-REACT 3** | **3.0893335 1.5891356 6.0057693**

 **NAPLES III** | **3.0893335 1.5891356 6.0057693**

 **ACUITY-PCI (Biv alone)**|**3.0893335 1.5891356 6.0057693**

 **ACUITY-PCI (Biv+GPI)**| **3.0893335 1.5891356 6.0057693**

 **BRIGHT (hep +GPI)** | **3.0893335 1.5891356 6.0057693**

 **CACHET** | **3.0893335 1.5891356 6.0057693**

 **Deshpande et al** | **3.0893335 1.5891356 6.0057693**

 **EUROMAX** | **2.7576222 1.3230337 5.7477603**

 **Horizons AMI** | **2.6321776 1.2390066 5.591866**

 **ISAR-REACT 4** | **3.0893335 1.5891356 6.0057693**

 **NAPLES** | **3.0893335 1.5891356 6.0057693**

 **PROTECT-TIMI 30** | **3.0893335 1.5891356 6.0057693**

 **REPLACE-1** | **3.0893335 1.5891356 6.0057693**

 **REPLACE-2** | **3.0893335 1.5891356 6.0057693**

 **TENACITY** | **3.0893335 1.5891356 6.0057693**

 **MATRIX** | **4.3461185 2.3204412 8.1401529**

-------------------+----------------------------------------------------------

 **Combined** | **3.0893336 1.5891356 6.0057693**

------------------------------------------------------------------------------

 1.21

 3.09

 1.59

 6.01

 8.57

 AMYDA-7 BIVALVE

 BRAVE 4

 BRIGHT (hep alone)

 HEAT-PPCI

 ISAR-REACT 3

 NAPLES III

 ACUITY-PCI (Biv alone)

 ACUITY-PCI (Biv+GPI)

 BRIGHT (hep +GPI)

 CACHET

 Deshpande et al

 EUROMAX

 Horizons AMI

 ISAR-REACT 4

 NAPLES

 PROTECT-TIMI 30

 REPLACE-1

 REPLACE-2

 TENACITY

 MATRIX

 Lower CI Limit

 Estimate

 Upper CI Limit

 Meta-analysis estimates, given named study is omitted

The number of studies is too small to perform Egger’s test analysis separately for provisional and planned use of GPI in heparin arm.

# Table 44. Meta analysis of subacute stent thrombosis– overall and stratified analysis.

 Study | RR [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

 Provisional GPI use

HEAT-PPCI |  **9.020 0.486 167.289 5.84**

MATRIX |  **1.996 0.855 4.658 32.38**

 Sub-total |

 D+L pooled RR |  **2.244 0.995 5.064 38.22**

 M-H pooled RR |  **2.408 1.084 5.352**

---------------------+---------------------------------------------------

 Planned GPI use in h

EUROMAX |  **1.273 0.343 4.728 20.45**

Horizons AMI |  **0.732 0.406 1.317 41.33**

 Sub-total |

 D+L pooled RR |  **0.803 0.469 1.372 61.78**

 M-H pooled RR |  **0.803 0.471 1.370**

---------------------+---------------------------------------------------

Overall |

 D+L pooled RR |  **1.313 0.623 2.769 100.00**

 M-H pooled RR |  **1.158 0.754 1.780**

---------------------+---------------------------------------------------

Test(s) of heterogeneity:

 Heterogeneity degrees of statistic freedom P I-squared\*\* Tau-squared

Provisional GPI use  **0.97 1 0.324 0.0% 0.0000**

Planned GPI use in h **0.57 1 0.450 0.0% 0.0000**

Overall **5.85 3 0.119 48.7% 0.2607** \*\* I-squared: the variation in RR attributable to heterogeneity)

Note: between group heterogeneity not calculated; only valid with inverse variance method Significance test(s) of RR=1

Provisional GPI use z=  **1.95**  p = **0.052**

Planned GPI use in h z=  **0.80**  p = **0.422**

Overall z=  **0.72**  p = **0.474**

-------------------------------------------------------------------------

#  Figure 35. Forrest plot for subacute stent thrombosis of overall and stratified analysis.



# Table 45 . Subacute stent thrombosis – Egger’s test – overall analysis.

Egger's test for small-study effects:

Regress standard normal deviate of intervention effect estimate against its standard error Number of studies = **4** Root MSE =  **1.078**

|  |  |
| --- | --- |
|  Std\_Eff  |  Coef. Std. Err. t P>|t| [95% Conf. Interval] |
|  slope  |  **-.7508739 .546697 -1.37 0.303 -3.103121 1.601374** |
| bias  |   **2.064681 1.196008 1.73 0.226 -3.081328 7.21069** |

Test of H0: no small-study effects P = **0.226**

# Figure 36. Funnel plot of subacute stent thrombosis – overall analysis.



# Table 46. Subacute stent thrombosis – sensitivity analysis

------------------------------------------------------------------------------

 Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

 **AMYDA-7 BIVALVE** | **1.3132013 .62269944 2.7693903**

 **BRAVE 4** | **1.3132013 .62269944 2.7693903**

 **BRIGHT (hep alone)**| **1.3132013 .62269944 2.7693903**

 **HEAT-PPCI** | **1.1455907 .57973701 2.263747**

 **ISAR-REACT 3** | **1.3132013 .62269944 2.7693903**

 **NAPLES III** | **1.3132013 .62269944 2.7693903**

 **ACUITY-PCI (Biv alone)**|**1.3132013 .62269944 2.7693903**

 **ACUITY-PCI (Biv+GPI)**| **1.3132013 .62269944 2.7693903**

 **BRIGHT (hep +GPI)** | **1.3132013 .62269944 2.7693903**

 **CACHET** | **1.3132013 .62269944 2.7693903**

 **Deshpande et al** | **1.3132013 .62269944 2.7693903**

 **EUROMAX** | **1.4328589 .51144731 4.0142646**

 **Horizons AMI** | **1.9171011 .96001577 3.8283503**

 **ISAR-REACT 4** | **1.3132013 .62269944 2.7693903**

 **NAPLES** | **1.3132013 .62269944 2.7693903**

 **PROTECT-TIMI 30** | **1.3132013 .62269944 2.7693903**

 **REPLACE-1** | **1.3132013 .62269944 2.7693903**

 **REPLACE-2** | **1.3132013 .62269944 2.7693903**

 **TENACITY** | **1.3132013 .62269944 2.7693903**

 **MATRIX** | **1.0793663 .43194792 2.6971581**

-------------------+----------------------------------------------------------

 **Combined** | **1.3132014 .62269945 2.7693903**

------------------------------------------------------------------------------

 0.43

 1.31

 0.62

 2.77

 4.01

 AMYDA-7 BIVALVE

 BRAVE 4

 BRIGHT (hep alone)

 HEAT-PPCI

 ISAR-REACT 3

 NAPLES III

 ACUITY-PCI (Biv alone)

 ACUITY-PCI (Biv+GPI)

 BRIGHT (hep +GPI)

 CACHET

 Deshpande et al

 EUROMAX

 Horizons AMI

 ISAR-REACT 4

 NAPLES

 PROTECT-TIMI 30

 REPLACE-1

 REPLACE-2

 TENACITY

 MATRIX

 Lower CI Limit

 Estimate

 Upper CI Limit

 Meta-analysis estimates, given named study is omitted

The number of studies is too small to perform Egger’s test analysis separately for provisional and planned use of GPI in heparin arm.

# Table 47. Risk of bias

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Random sequence generation (selection bias) | Blinding of participants and personel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias)  | Selective reporting (reporting bias) |
| CACHET (2002)  |   |   |   |   |   |
| REPLACE-2 (2003)  |   |   |   |   |   |
| REPLACE-1 (2004)  |   |   |   |   |   |
| PROTECT-TIMI 30 (2006)  |   |   |   |   |   |
| ACUITY-PCI (Biv alone, 2007) |   |   |   |   |   |
| ACUITY-PCI (Biv+GPI, 2007)  |   |   |   |   |   |
| Horizons AMI (2008)  |   |   |   |   |   |
| ISAR-REACT 3 (2008)  |   |   |   |   |   |
| NAPLES (2009)  |   |   |   |   |   |
| TENACITY (2011)  |   |   |   |   |   |
| ISAR-REACT 4 (2011)  |   |   |   |   |   |
| ARMYDA-7 BIVALVE (2012)  |   |   |   |   |   |
| Deshpande et al. (2012)  |   |   |   |   |   |
| EUROMAX (2013)  |   |   |   |   |   |
| BRIGHT (hep +GPI, 2014)  |   |   |   |   |   |
| BRIGHT (hep alone, 2014)  |   |   |   |   |   |
| HEAT-PPCI (2014) |   |   |   |   |   |
| NAPLES III (2014)  |   |   |   |   |   |
| BRAVE 4 (2014) |   |   |   |   |   |
| MATRIX (2015)  |   |   |   |   |   |
|   | low risk of bias |  |  |  |  |
|   | unclear risk of bias |  |  |  |  |
|   | high risk of bias |  |  |  |  |