Results of Meta-analyses

Supplement to: Makam RCP, Hoaglin DC, McManus DD, Wang V, Gore JM, Spencer FA, Pradhan R, Tran H, Yu H, Goldberg RJ. Efficacy and safety of direct oral anticoagulants approved for cardiovascular indications: systematic review and meta-analysis.

Results of Meta-analyses: Non-valvular atrial fibrillation

Efficacy

Data Used

Trial	Drug	Sample Size	Stroke or Systemic Embolism (PO)	Systemic Embolism	Any Stroke	Hemorrhagic Stroke	Death from Any Cause	Death from Vascular Causes	Myocardial Infarction
ARISTOTLE	Apixaban	9120	212	15	199	40	603		90
ENGAGE-AF	Edoxaban	7035	182	15	281	49	773	530	133
RE-LY – 150	Dabigatran	6076	134		122	12	438	274	97
ROCKET I	Rivaroxaban	6958	188	5	184	29	208	170	101
ARISTOTLE	Warfarin	9081	265	17	250	78	669		102
ENGAGE-AF	Warfarin	7036	232	23	317	90	839	611	141
RE-LY – 150	Warfarin	6022	202		186	45	487	317	75
ROCKET I	Warfarin	7004	241	22	221	50	250	193	126

Stroke or systemic embolism

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) + (-1 + arm | id)

   AIC   BIC logLik deviance df.resid
  14.2 14.7 -1.1   2.2   2

Scaled residuals:
    Min   1Q Median   3Q   Max
-0.99625 -0.24489 0.01467 0.28001 0.87612

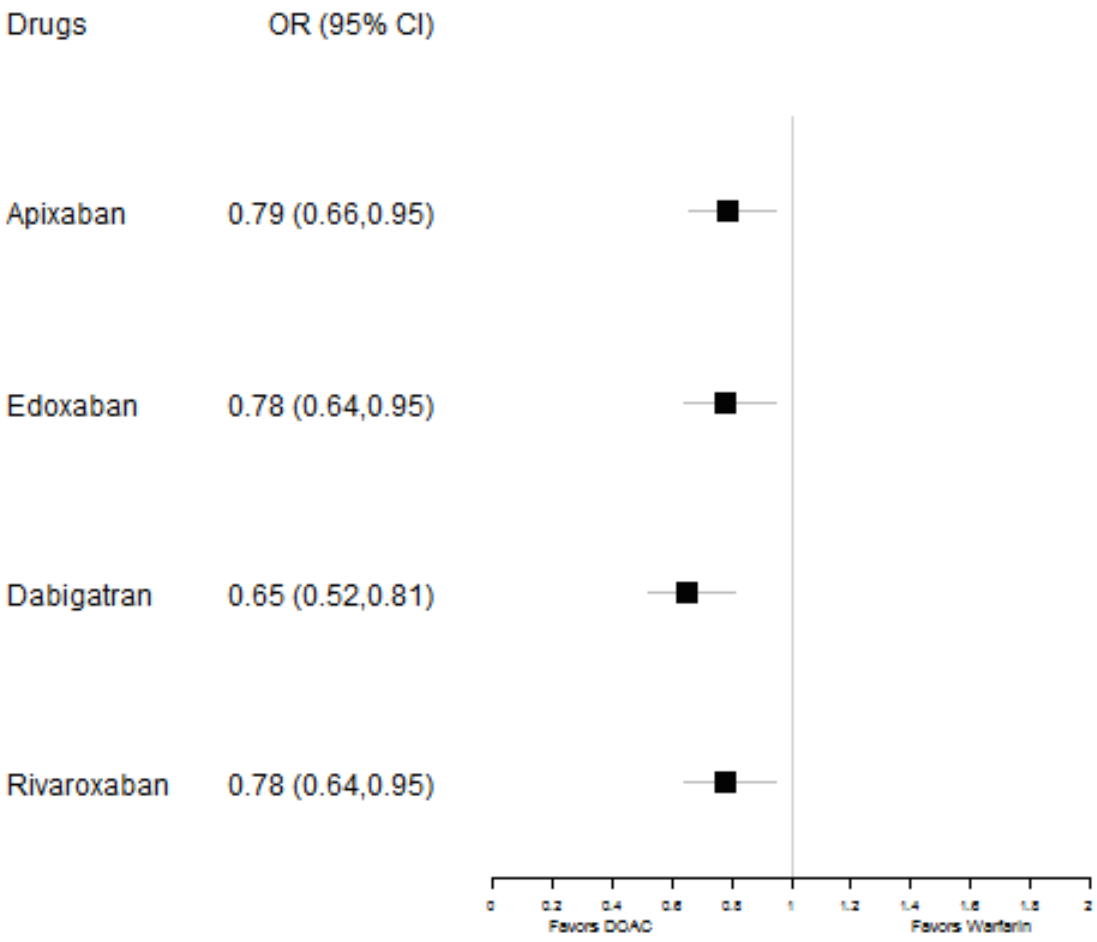
Random effects:
 Groups Name Variance Std.Dev.
 id   arm 0   0
Number of obs: 8, groups: id, 4

Fixed effects:
                 Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.48348   0.05131 -67.90 < 2e-16 ***
as.factor(arm)1 -0.28148   0.05031   -5.59 2.21e-08 ***
as.factor(id)2   0.11877   0.06815   1.74   0.0814 .
as.factor(id)3   0.06000   0.07223   0.83   0.4062
as.factor(id)4   0.16306   0.06753   2.41   0.0158 *

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
            (Intr) as.()1 as.()2 as.()3
as.fctr(r)1 -0.426
as.fctr(d)2 -0.616 0.000
as.fctr(d)3 -0.581 -0.001 0.438
as.fctr(d)4 -0.622 0.002 0.468 0.442

Odds Ratio of Studies for Stroke or Systemic Embolism (PO)



Systemic embolism

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) + (-1 + arm | id)

AIC	BIC	logLik	deviance	df.resid
15.7	14.6	-2.8	5.7	1

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.43128	-0.59779	0.04713	0.79839	1.05525

Random effects:

Groups	Name	Variance	Std.Dev.
id	arm	0.009755	0.09877

Number of obs: 6, groups: id, 3

Fixed effects:

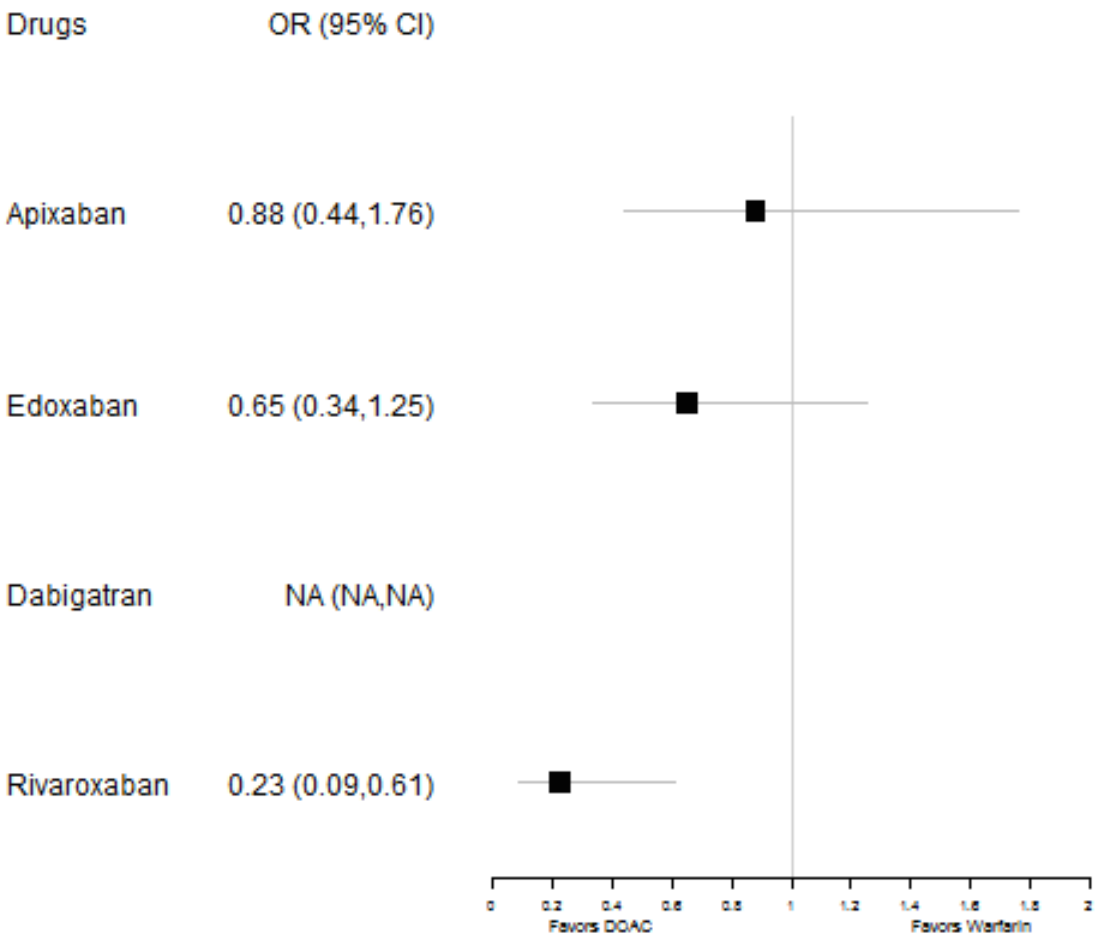
	Estimate	Std. Error	z value	Pr(>|z|)	
(Intercept)	-6.1055	0.2783	-21.937	<2e-16	***
as.factor(arm)1	-0.5800	0.2611	-2.222	0.0263	*
as.factor(id)2	0.4368	0.2821	1.549	0.1215	
as.factor(id)4	0.1206	0.5722	0.211	0.8331	

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:

	(Intr)	as.()1	as.()2
as.fctr(r)1	0.158		
as.fctr(d)2	-0.768	-0.262	
as.fctr(d)4	-0.836	-0.475	0.639

Odds Ratio of Studies for Systemic Embolism



Any stroke

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Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite
Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial  ( logit )
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +      (-1 + arm | id)

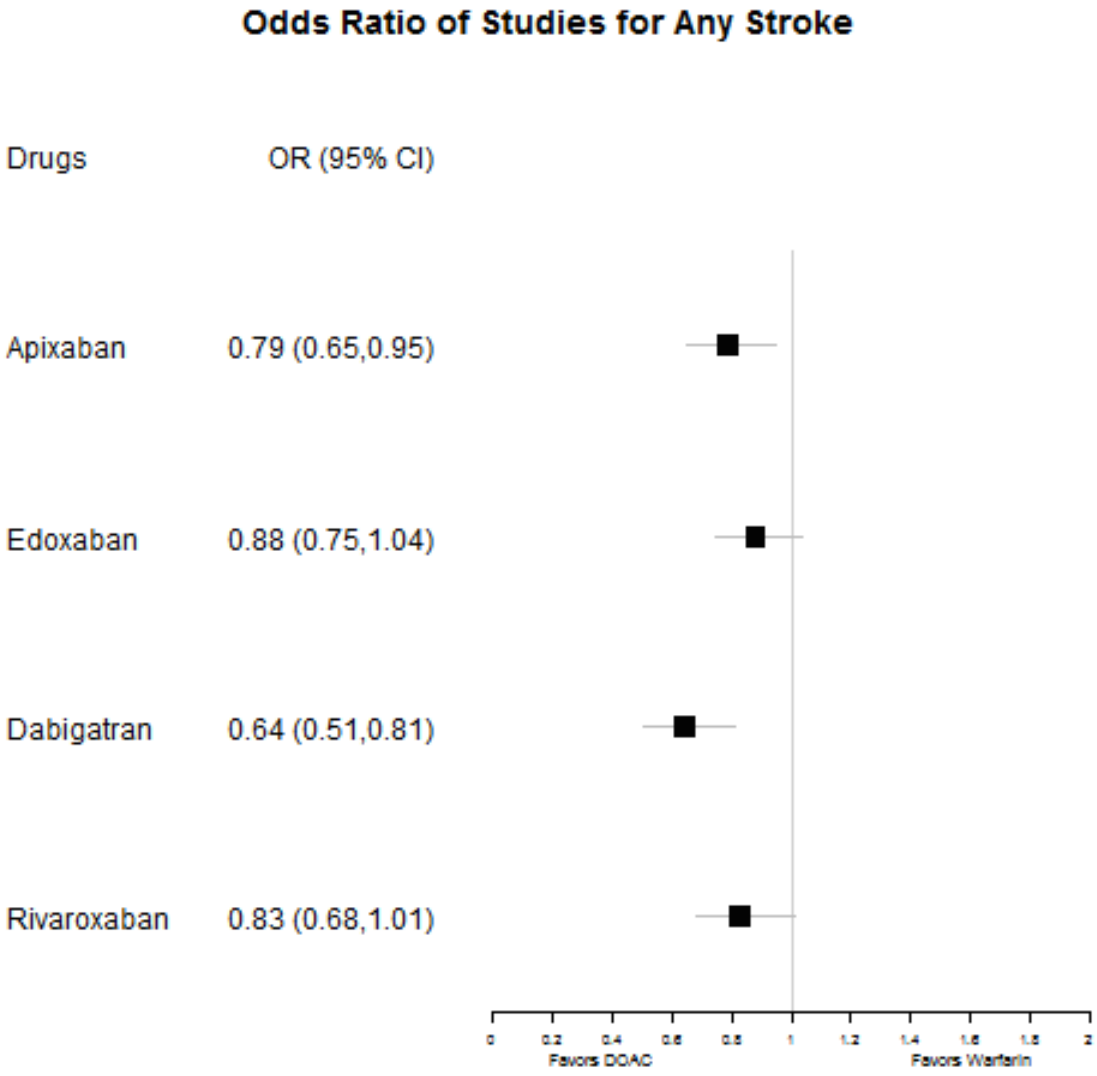
    AIC      BIC   logLik deviance df.resid
   17.0     17.5     -2.5      5.0        2

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.38088 -0.39535 -0.00596  0.43917  1.24798

Random effects:
 Groups Name Variance Std.Dev.
 id     arm  0        0
Number of obs: 8, groups:  id, 4

Fixed effects:
             Estimate Std. Error z value Pr(>|z|)
(Intercept)    -3.57156    0.05255  -67.97  < 2e-16 ***
as.factor(arm)1 -0.22261    0.04872   -4.57  4.9e-06 ***
as.factor(id)2   0.56235    0.06349    8.86  < 2e-16 ***
as.factor(id)3   0.03259    0.07495    0.43    0.664
as.factor(id)4   0.16591    0.06948    2.39    0.017 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
          (Intr) as.()1 as.()2 as.()3
as.fctr(r)1 -0.416
as.fctr(d)2 -0.684 -0.001
as.fctr(d)3 -0.580 -0.001  0.480
as.fctr(d)4 -0.626  0.002  0.518  0.439
```


Odds Ratio of Studies for Any Stroke
Drugs
OR (95% CI)
Apixaban
0.79 (0.65,0.95)
Edoxaban
0.88 (0.75,1.04)
Dabigatran
0.64 (0.51,0.81)
Rivaroxaban
0.83 (0.68,1.01)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Favors DOAC
Favors Warfarin

Hemorrhagic stroke

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) + (-1 + arm | id)

   AIC   BIC logLik deviance df.resid
  17.0 17.4 -2.5   5.0   2

Scaled residuals:
    Min   1Q Median   3Q   Max
-1.59536 -0.33959 0.02125 0.48220 1.12681

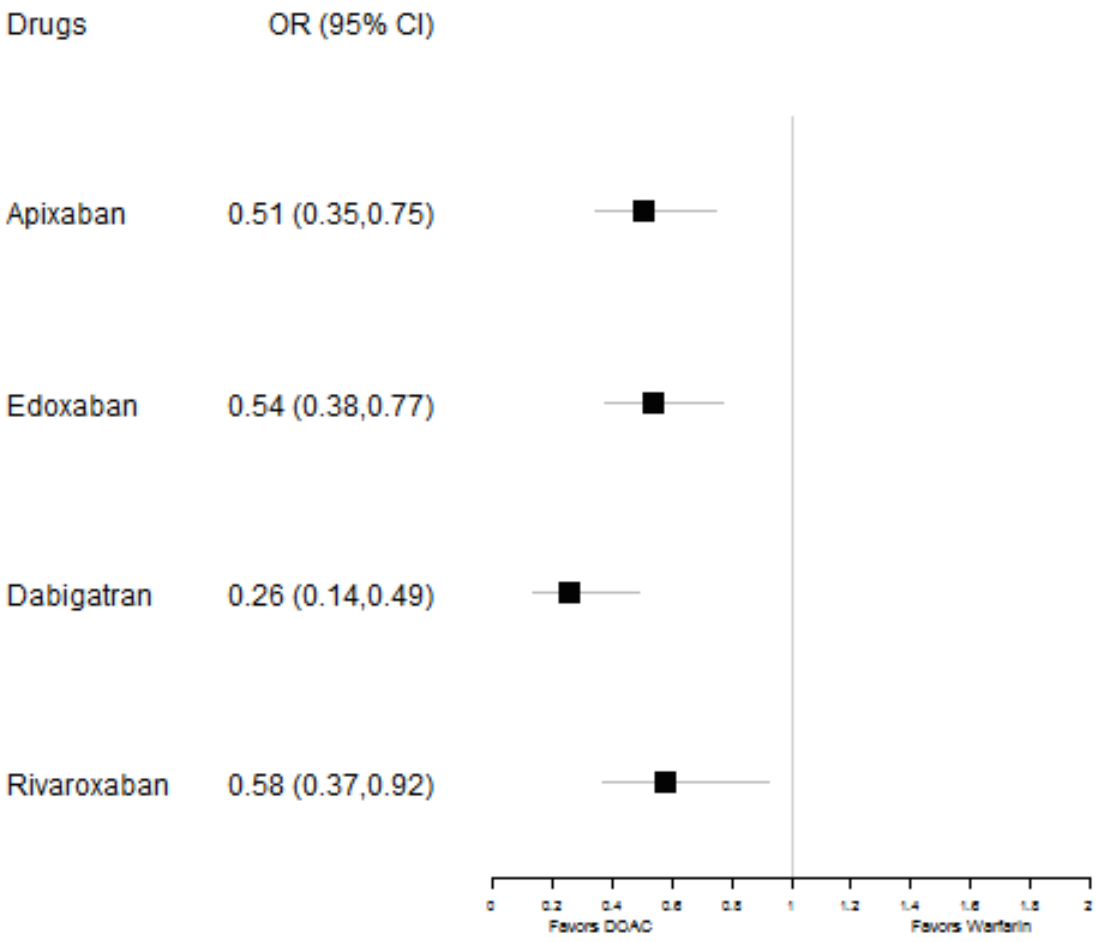
Random effects:
 Groups Name Variance Std.Dev.
 id arm 0 0
Number of obs: 8, groups: id, 4

Fixed effects:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.73703 0.09907 -47.82 < 2e-16 ***
as.factor(arm)1 -0.71079 0.10756 -6.61 3.89e-11 ***
as.factor(id)2 0.42421 0.12574 3.37 0.000742 ***
as.factor(id)3 -0.32039 0.16178 -1.98 0.047657 *
as.factor(id)4 -0.13888 0.14586 -0.95 0.341011

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
        (Intr) as.()1 as.()2 as.()3
as.fctr(r)1 -0.361
as.fctr(d)2 -0.685 0.000
as.fctr(d)3 -0.533 0.000 0.420
as.fctr(d)4 -0.591 0.002 0.465 0.362

Odds Ratio of Studies for Hemorrhagic Stroke



Death from any cause

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Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite
Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial  ( logit )
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +      (-1 + arm | id)

    AIC      BIC   logLik deviance df.resid
   12.7     13.2     -0.4      0.7        2

Scaled residuals:
    Min      1Q  Median      3Q     Max
-0.50637 -0.13996  0.00019  0.14102  0.47788

Random effects:
 Groups Name Variance Std.Dev.
 id     arm  0        0
Number of obs: 8, groups:  id, 4

Fixed effects:
             Estimate Std. Error z value Pr(>|z|)
(Intercept)    -2.53133    0.03283  -77.10  < 2e-16 ***
as.factor(arm)1 -0.11691    0.03203   -3.65 0.000263 ***
as.factor(id)2   0.54349    0.03932   13.82  < 2e-16 ***
as.factor(id)3   0.09713    0.04490    2.16 0.030526 *
as.factor(id)4  -0.79588    0.05571  -14.29  < 2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
          (Intr) as.()1 as.()2 as.()3
as.fctr(r)1 -0.464
as.fctr(d)2 -0.654 -0.001
as.fctr(d)3 -0.573 -0.001  0.479
as.fctr(d)4 -0.464  0.003  0.386  0.338
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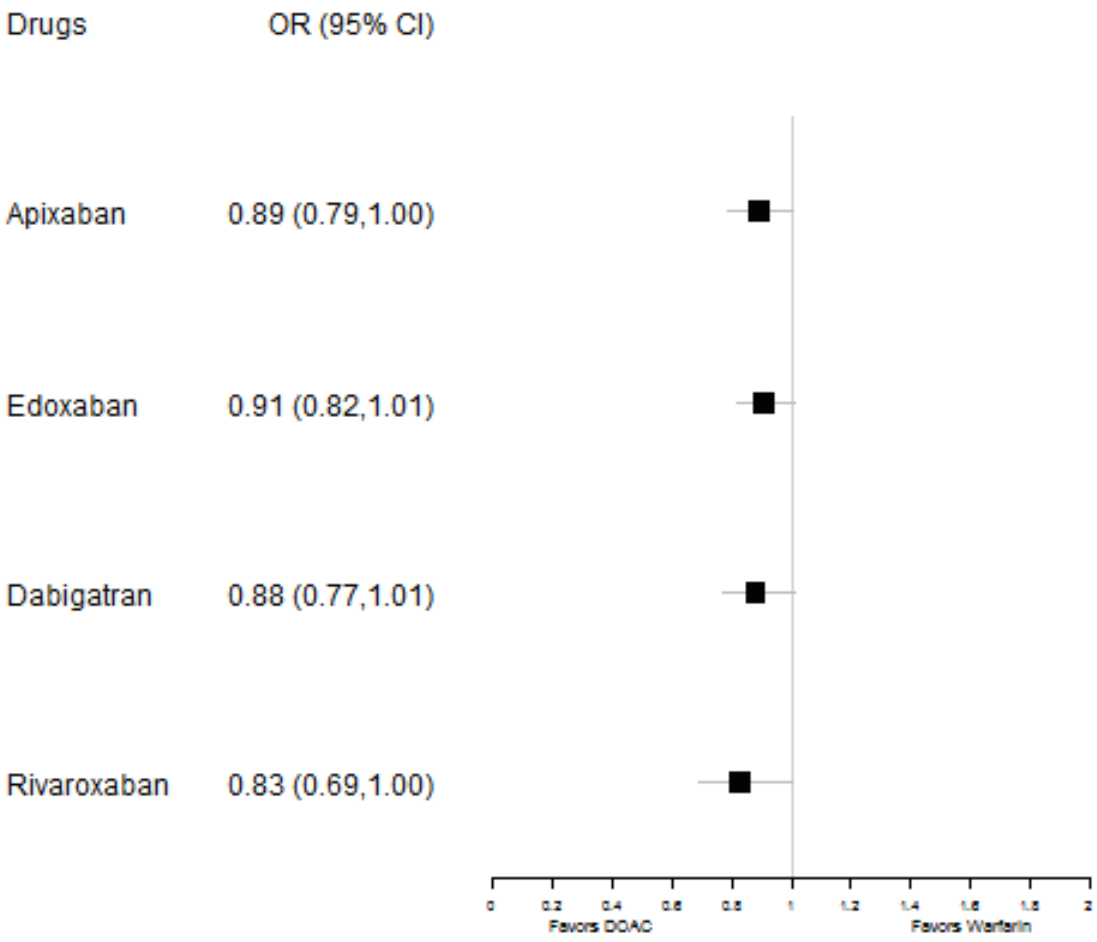
Odds Ratio of Studies for Death from Any Cause



Death from vascular causes

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) + (-1 + arm | id)

   AIC   BIC logLik deviance df.resid
  10.1   9.0   0.0   0.1   1

Scaled residuals:
     Min   1Q   Median   3Q   Max
-0.177361 -0.082998 -0.001193 0.077870 0.191178

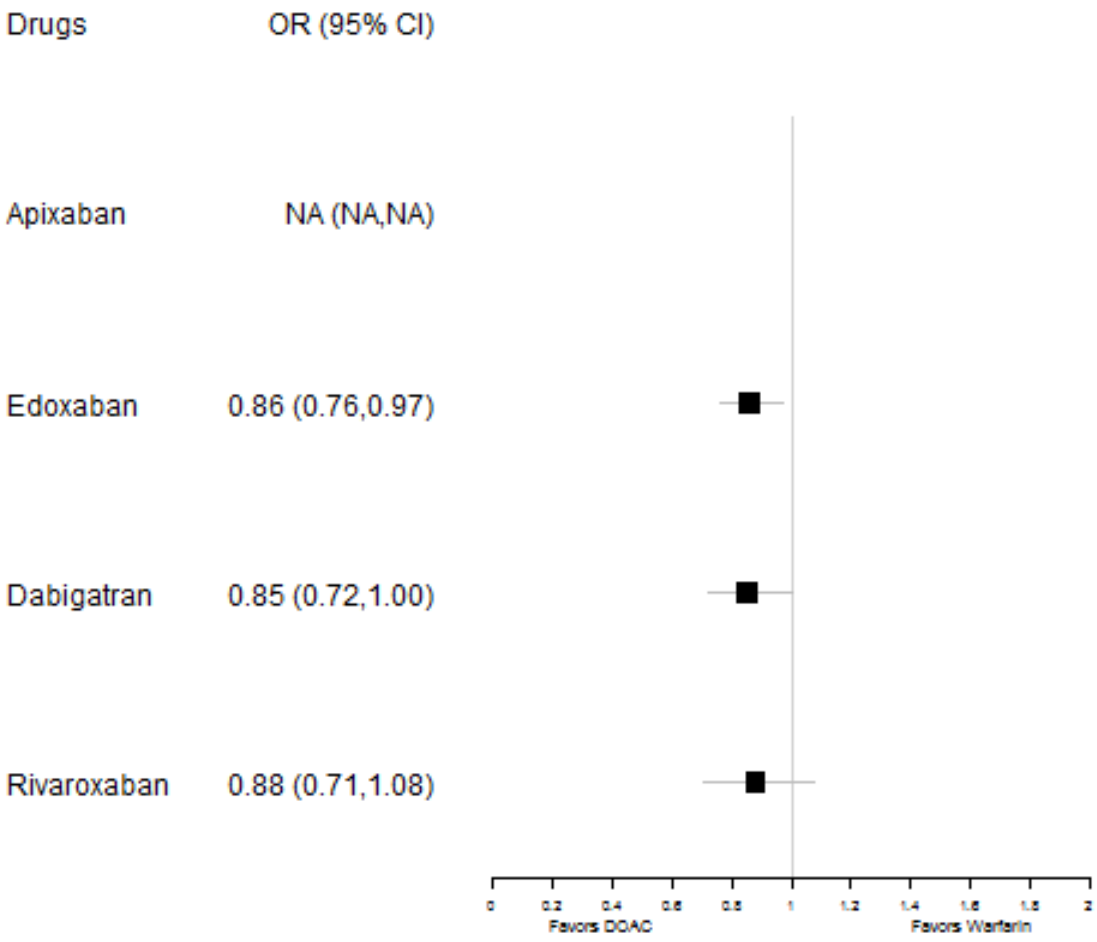
Random effects:
 Groups Name Variance Std.Dev.
 id   arm 0   0
Number of obs: 6, groups: id, 3

Fixed effects:
                Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.35440   0.03746 -62.86 < 2e-16 ***
as.factor(arm)1 -0.15130   0.04523   -3.34 0.000823 ***
as.factor(id)3 -0.54109   0.05228 -10.35 < 2e-16 ***
as.factor(id)4 -1.19626   0.06151 -19.45 < 2e-16 ***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
            (Intr) as.()1 as.()3
as.fctr(r)1 -0.566
as.fctr(d)3 -0.487 0.000
as.fctr(d)4 -0.417 0.004 0.297

Odds Ratio of Studies for Death from Vascular Causes



Myocardial infarction

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Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite
Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial  ( logit )
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +      (-1 + arm | id)

   AIC     BIC   logLik deviance df.resid
  17.7    18.2    -2.9     5.7       2

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.39079 -0.49761 -0.00034  0.48434  1.42209

Random effects:
 Groups Name Variance Std.Dev.
 id     arm  0        0
Number of obs: 8, groups:  id, 4

Fixed effects:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)    -4.51394    0.07989  -56.51  < 2e-16 ***
as.factor(arm)1 -0.05500    0.06856   -0.80  0.42243
as.factor(id)2   0.62200    0.09479    6.56 5.33e-11 ***
as.factor(id)3   0.30222    0.10565    2.86  0.00423 **
as.factor(id)4   0.43823    0.09870    4.44 9.00e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
         (Intr) as.()1 as.()2 as.()3
as.fctr(r)1 -0.419
as.fctr(d)2 -0.695  0.001
as.fctr(d)3 -0.623 -0.001  0.526
as.fctr(d)4 -0.668  0.002  0.563  0.505
```
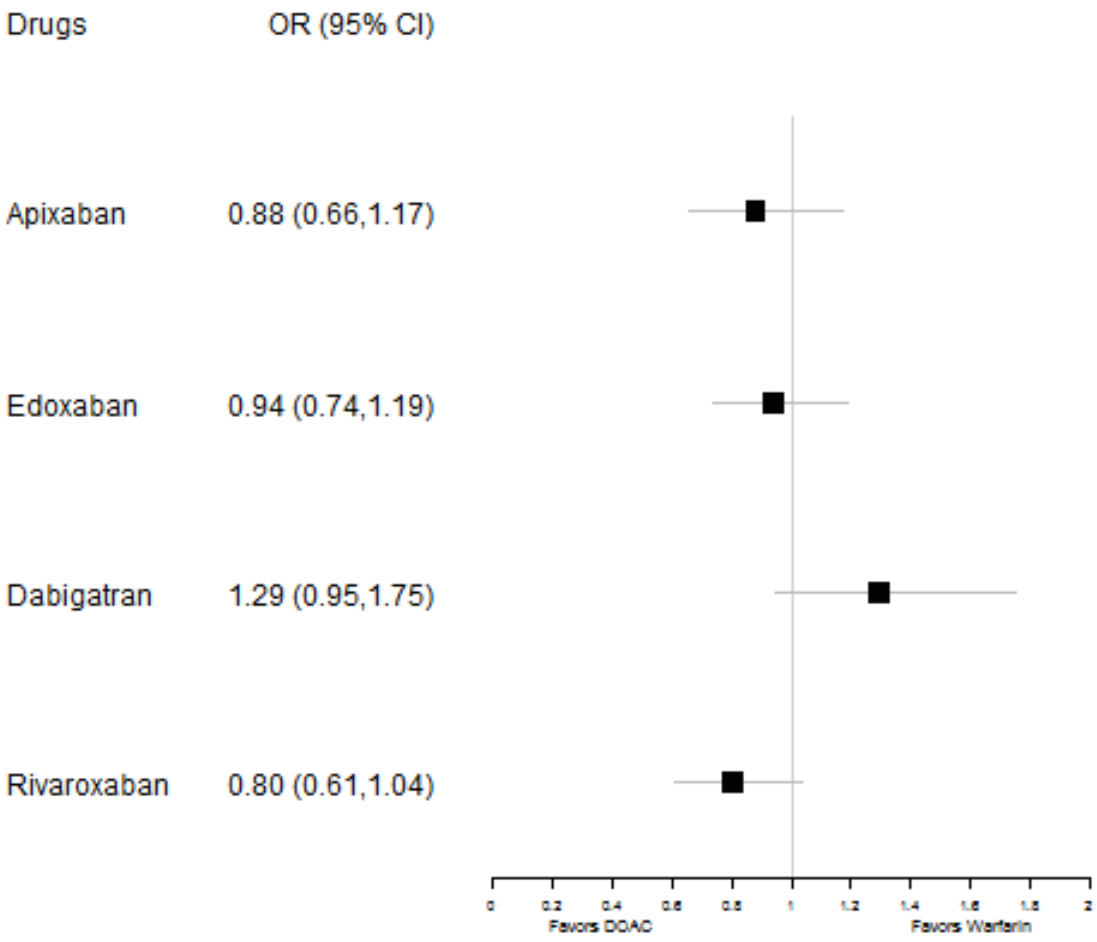

Odds Ratio of Studies for Myocardial Infarction



Safety

Data Used

STUDY	Drug	Sample Size	Major Bleeding	Fatal Bleeding	Intracranial Bleeding	Gastrointestinal Bleeding
ARISTOTLE	Apixaban	9088	327	34	52	105
ENGAGE AF-TIMI 48 (high dose)	Edoxaban	7012	418	32	61	232
RE-LY - 150	Dabigatran	6076	399		38	188
ROCKET AF	Rivaroxaban	7111	395	27	55	224
ARISTOTLE	Warfarin	9052	462	55	122	119
ENGAGE AF-TIMI 48 (high dose)	Warfarin	7012	524	59	132	190
RE-LY - 150	Warfarin	6022	421		90	126
ROCKET AF	Warfarin	7125	386	55	84	154

Major bleeding

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +   (-1 + arm | id)

    AIC   BIC   logLik deviance df.resid
   24.0   24.5   -6.0   12.0   2

Scaled residuals:
    Min   1Q Median   3Q   Max
-0.55360 -0.30118 -0.00809 0.30982 0.49351

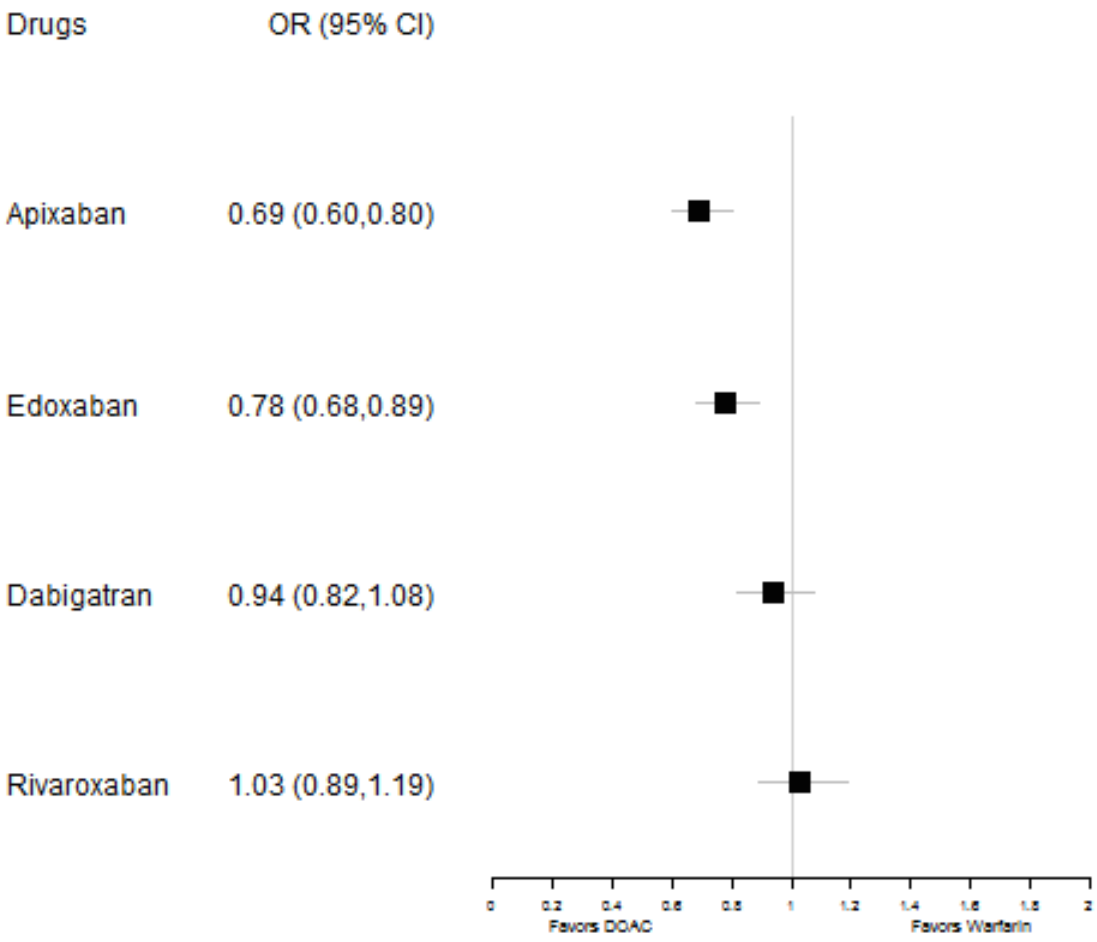
Random effects:
 Groups Name Variance Std.Dev.
 id   arm 0.01477 0.1215
Number of obs: 8, groups: id, 4

Fixed effects:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.94592   0.04901 -60.11 < 2e-16 ***
as.factor(arm)1 -0.16368   0.07060   -2.32   0.0204 *
as.factor(id)2   0.42121   0.06342   6.64 3.10e-11 ***
as.factor(id)3   0.36998   0.07007   5.28 1.29e-07 ***
as.factor(id)4   0.11146   0.07467   1.49   0.1355

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
          (Intr) as.()1 as.()2 as.()3
as.fctr(r)1 -0.165
as.fctr(d)2 -0.719 0.008
as.fctr(d)3 -0.720 -0.013 0.522
as.fctr(d)4 -0.717 -0.018 0.510 0.561

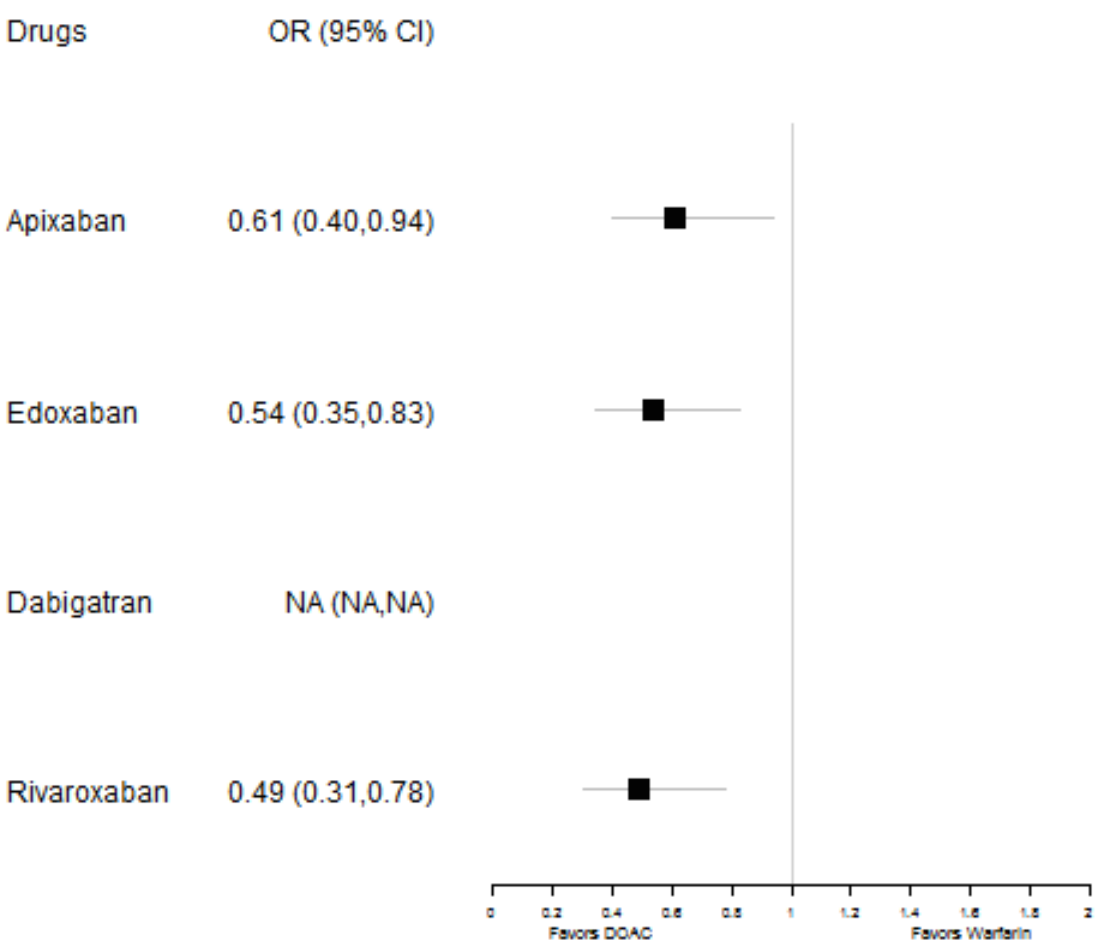
Odds Ratio of Studies for Major Bleeding



Fatal bleeding

```
Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite
Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial  ( logit )
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +      (-1 + arm | id)

    AIC      BIC   logLik deviance df.resid
   10.5      9.5     -0.3      0.5        1

Scaled residuals:
   Min     1Q  Median     3Q    Max
-0.3823 -0.2467 -0.0067  0.2225  0.4188

Random effects:
 Groups Name Variance Std.Dev.
 id     arm  0        0
Number of obs: 6, groups:  id, 3

Fixed effects:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)     -5.0552     0.1159  -43.63  < 2e-16 ***
as.factor(arm)1  -0.6014     0.1295   -4.65 3.39e-06 ***
as.factor(id)2    0.2807     0.1495    1.88   0.0605 .
as.factor(id)4    0.1605     0.1535    1.05   0.2958
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
          (Intr) as.()1 as.()2
as.fctr(r)1 -0.398
as.fctr(d)2 -0.652  0.000
as.fctr(d)4 -0.635  0.001  0.492
```

Odds Ratio of Studies for Fatal Bleeding



Intracranial bleeding

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) + (-1 + arm | id)

   AIC   BIC logLik deviance df.resid
  16.3 16.8 -2.2 4.3 2

Scaled residuals:
   Min 1Q Median 3Q Max
-1.0383 -0.5899 -0.0324 0.4117 1.4954

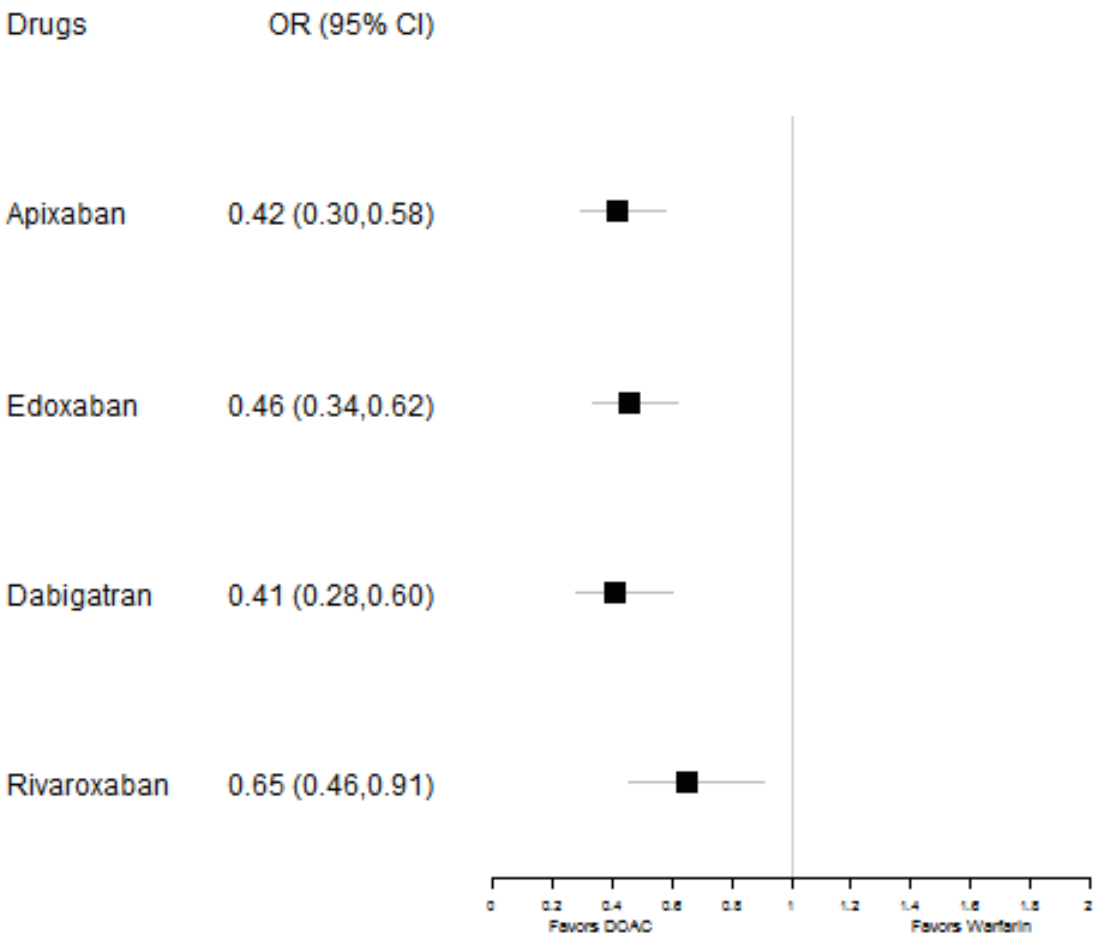
Random effects:
 Groups Name Variance Std.Dev.
 id arm 0 0
Number of obs: 8, groups: id, 4

Fixed effects:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.33169 0.08114 -53.38 < 2e-16 ***
as.factor(arm)1 -0.74160 0.08522 -8.70 < 2e-16 ***
as.factor(id)2 0.36502 0.10523 3.47 0.000522 ***
as.factor(id)3 0.10006 0.11712 0.85 0.392905
as.factor(id)4 0.01690 0.11438 0.15 0.882515

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
  (Intr) as.()1 as.()2 as.()3
as.fctr(r)1 -0.343
as.fctr(d)2 -0.680 0.000
as.fctr(d)3 -0.611 -0.001 0.471
as.fctr(d)4 -0.626 0.001 0.483 0.434

Odds Ratio of Studies for Intracranial Bleeding



Gastrointestinal bleeding

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) + (-1 + arm | id)

   AIC   BIC logLik deviance df.resid
  23.1 23.6 -5.6 11.1 2

Scaled residuals:
   Min 1Q Median 3Q Max
-1.01639 -0.49079 0.00631 0.42784 1.06326

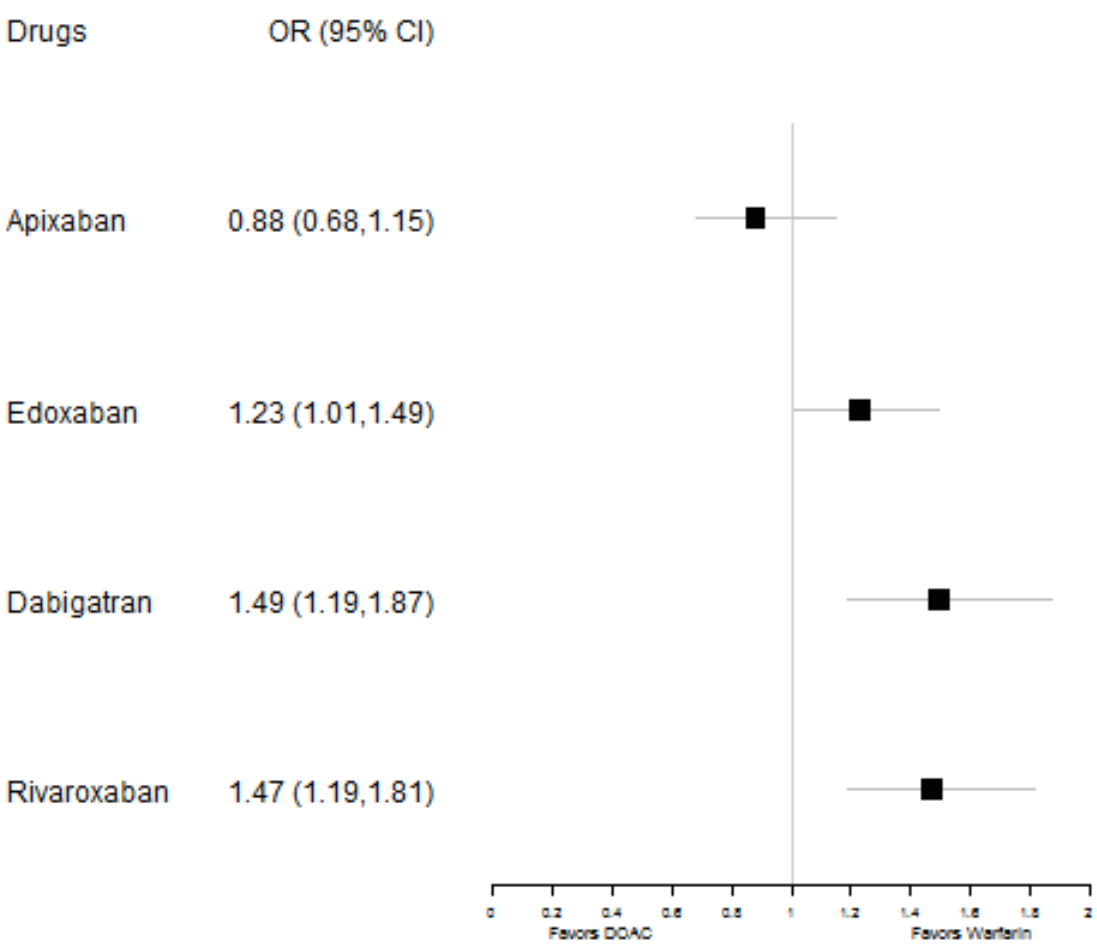
Random effects:
 Groups Name Variance Std.Dev.
 id arm 0.0149 0.1221
Number of obs: 8, groups: id, 4

Fixed effects:
  Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.41646 0.11807 -37.41 < 2e-16 ***
as.factor(arm)1 0.22908 0.08423 2.72 0.006535 **
as.factor(id)2 0.83015 0.12798 6.49 8.79e-11 ***
as.factor(id)3 0.61827 0.16332 3.79 0.000153 ***
as.factor(id)4 0.64286 0.15787 4.07 4.66e-05 ***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
  (Intr) as.()1 as.()2 as.()3
as.fctr(r)1 -0.304
as.fctr(d)2 -0.850 0.129
as.fctr(d)3 -0.856 0.118 0.742
as.fctr(d)4 -0.871 0.132 0.753 0.797

Odds Ratio of Studies for Gastrointestinal Bleeding



Results of Meta-analyses: Venous thromboembolism

Efficacy

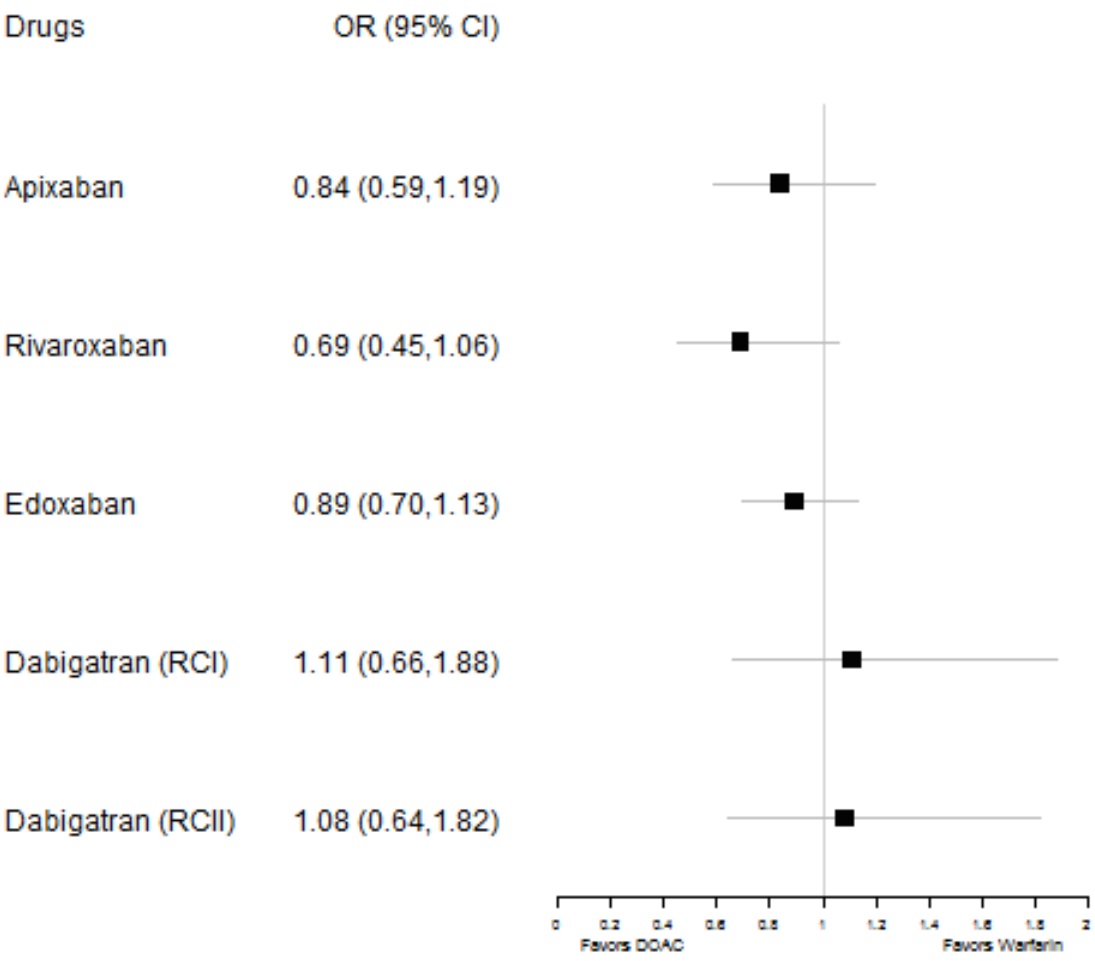
Data Used

Trial	drug	Sample size	Recurrent VTE and Related Death (PO)	Death from Any Cause	Recurrent DVT	Fatal PE
AMPLIFY	Apixaban	2609	59	41	20	1
EINSTEIN DVT	Rivaroxaban	1731	36	38	14	1
Hokusai-VTE	Edoxaban	4118	130	132	57	4
RE-COVER	Dabigatran (RCI)	1274	30	21	16	
RECOVER II	Dabigatran (RCII)	1279	30	25	25	
AMPLIFY	Warfarin	2635	71	52	33	2
EINSTEIN DVT	Warfarin	1718	51	49	28	0.5
Hokusai-VTE	Warfarin	4122	146	126	63	3
RE-COVER	Warfarin	1265	27	21	18	
RECOVER II	Warfarin	1289	28	25	17	
Trial	**drug**	**Recurrent PE (Non-Fatal)**	**Net Clinical Benefit**	**Myocardial Infarction**	**All death Sample size**	**MIss**
AMPLIFY	Apixaban	27	73	4	2676	2609
EINSTEIN DVT	Rivaroxaban	20	51	5	1731	1731
Hokusai-VTE	Edoxaban	49	120		4118	4118
RE-COVER	Dabigatran (RCI)	13		4	1274	1274
RECOVER II	Dabigatran (RCII)	7		4	1279	1280
AMPLIFY	Warfarin	23	118	2	2689	2635
EINSTEIN DVT	Warfarin	18	73	1	1718	1718
Hokusai-VTE	Warfarin	59	144		4122	4122
RE-COVER	Warfarin	7		2	1265	1265
RECOVER II	Warfarin	13		2	1289	1288

Recurrent VTE and related death

```
Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite
Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial  ( logit )
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +      (-1 + arm | id)

    AIC      BIC   logLik deviance df.resid
   16.6     18.7     -1.3      2.6        3

Scaled residuals:
   Min     1Q  Median     3Q    Max
-0.7858 -0.4514  0.0014  0.4746  0.7425

Random effects:
 Groups Name Variance Std.Dev.
 id     arm  0        0
Number of obs: 10, groups:  id, 5

Fixed effects:
             Estimate Std. Error z value Pr(>|z|)
(Intercept)    -3.61083    0.09681  -37.30  < 2e-16 ***
as.factor(arm)1 -0.12721    0.08244   -1.54  0.12284
as.factor(id)2   0.01838    0.14029    0.13  0.89579
as.factor(id)3   0.31024    0.10788    2.88  0.00403 **
as.factor(id)4  -0.10104    0.16074   -0.63  0.52963
as.factor(id)5  -0.09533    0.15978   -0.60  0.55074
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
          (Intr) as.()1 as.()2 as.()3 as.()4
as.fctr(r)1 -0.398
as.fctr(d)2 -0.580 -0.003
as.fctr(d)3 -0.754 -0.002  0.521
as.fctr(d)4 -0.506 -0.002  0.350  0.455
as.fctr(d)5 -0.510  0.000  0.352  0.458  0.307
```

Odds Ratio of Studies for Recurrent VTE and Related Death (PO)



Death from any cause

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) + (-1 + arm | id)

   AIC   BIC logLik deviance df.resid
  16.5 18.6 -1.2   2.5   3

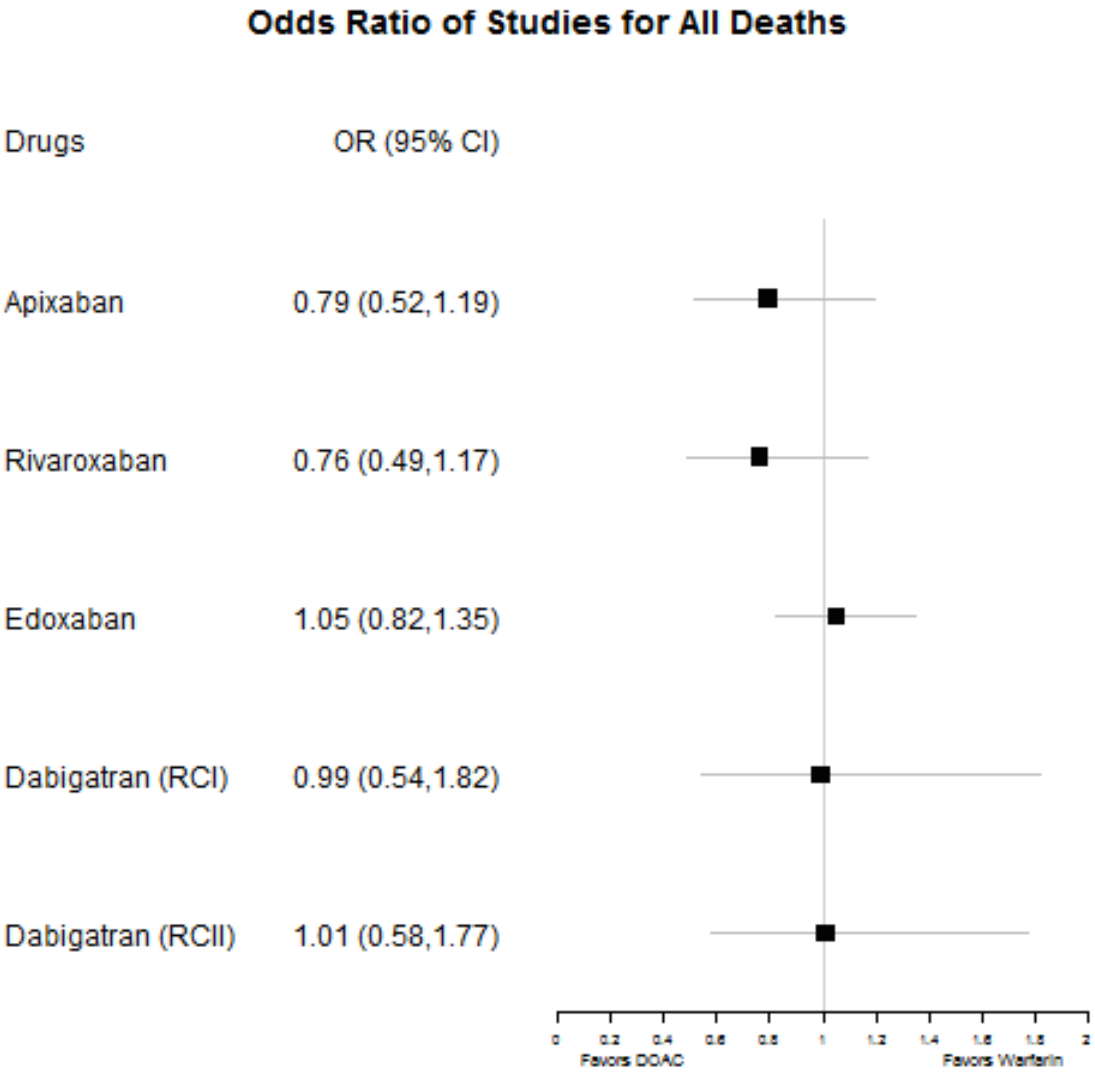
Scaled residuals:
    Min   1Q Median   3Q   Max
-0.67762 -0.49102 0.00163 0.47825 0.66054

Random effects:
 Groups Name Variance Std.Dev.
 id   arm 0   0
Number of obs: 10, groups: id, 5

Fixed effects:
                 Estimate Std. Error z value Pr(>|z|)
(Intercept)   -4.00724   0.11295 -35.48 < 2e-16 ***
as.factor(arm)1 -0.06172   0.08805   -0.70   0.483
as.factor(id)2   0.38338   0.15078   2.54   0.011 *
as.factor(id)3   0.60565   0.12225   4.95 7.25e-07 ***
as.factor(id)4 -0.04743   0.18749   -0.25   0.800
as.factor(id)5   0.11833   0.17703   0.67   0.504

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

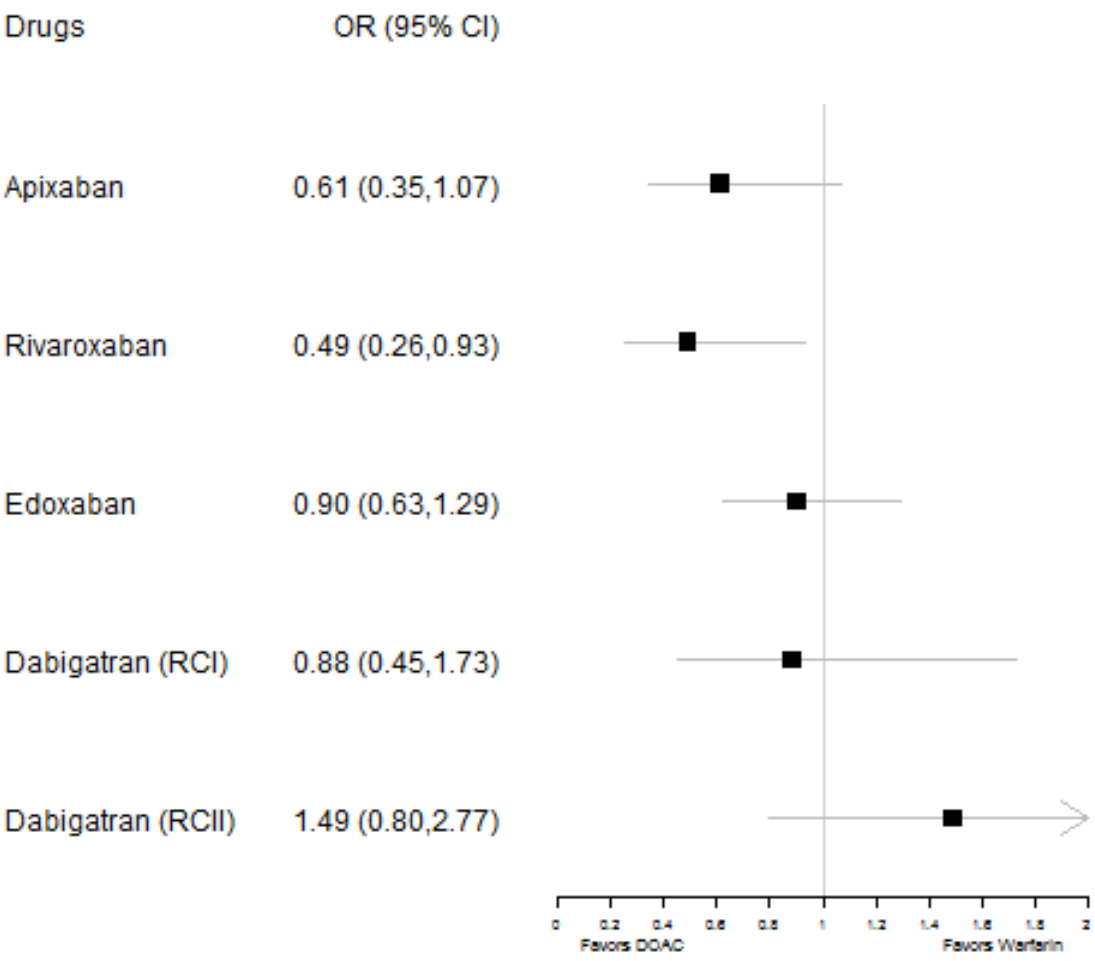
Correlation of Fixed Effects:
            (Intr) as.()1 as.()2 as.()3 as.()4
as.fctr(r)1 -0.377
as.fctr(d)2 -0.642 -0.002
as.fctr(d)3 -0.792 -0.001 0.594
as.fctr(d)4 -0.516 -0.001 0.387 0.477
as.fctr(d)5 -0.547 0.000 0.410 0.506 0.330


Odds Ratio of Studies for All Deaths
Drugs
OR (95% CI)
Apixaban
0.79 (0.52,1.19)
Rivaroxaban
0.76 (0.49,1.17)
Edoxaban
1.05 (0.82,1.35)
Dabigatran (RCI)
0.99 (0.54,1.82)
Dabigatran (RCII)
1.01 (0.58,1.77)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Favors DOAC
Favors Warfarin

Recurrent DVT

```
Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite
Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial  ( logit )
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +      (-1 + arm | id)

   AIC      BIC   logLik deviance df.resid
  21.6     23.7     -3.8      7.6        3

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.26411 -0.68339  0.00542  0.63531  1.38932

Random effects:
 Groups Name Variance  Std.Dev.
 id     arm  2.463e-18 1.569e-09
Number of obs: 10, groups:  id, 5

Fixed effects:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)     -4.4955     0.1481 -30.356   <2e-16 ***
as.factor(arm)1  -0.1872     0.1185  -1.579   0.1143
as.factor(id)2    0.1893     0.2078   0.911   0.3622
as.factor(id)3    0.3703     0.1659   2.232   0.0256 *
as.factor(id)4    0.2855     0.2211   1.292   0.1965
as.factor(id)5    0.4878     0.2080   2.345   0.0190 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
         (Intr) as.()1 as.()2 as.()3 as.()4
as.fctr(r)1 -0.362
as.fctr(d)2 -0.619 -0.003
as.fctr(d)3 -0.775 -0.002  0.553
as.fctr(d)4 -0.581 -0.002  0.415  0.520
as.fctr(d)5 -0.619 -0.001  0.441  0.552  0.415
```

Odds Ratio of Studies for Recurrent DVT



Fatal PE

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) + (-1 + arm | id)

   AIC BIC logLik deviance df.resid
  11.8 10.7 -0.9 1.8 1

Scaled residuals:
   Min 1Q Median 3Q Max
-0.67240 -0.39577 -0.00441 0.42745 0.61069

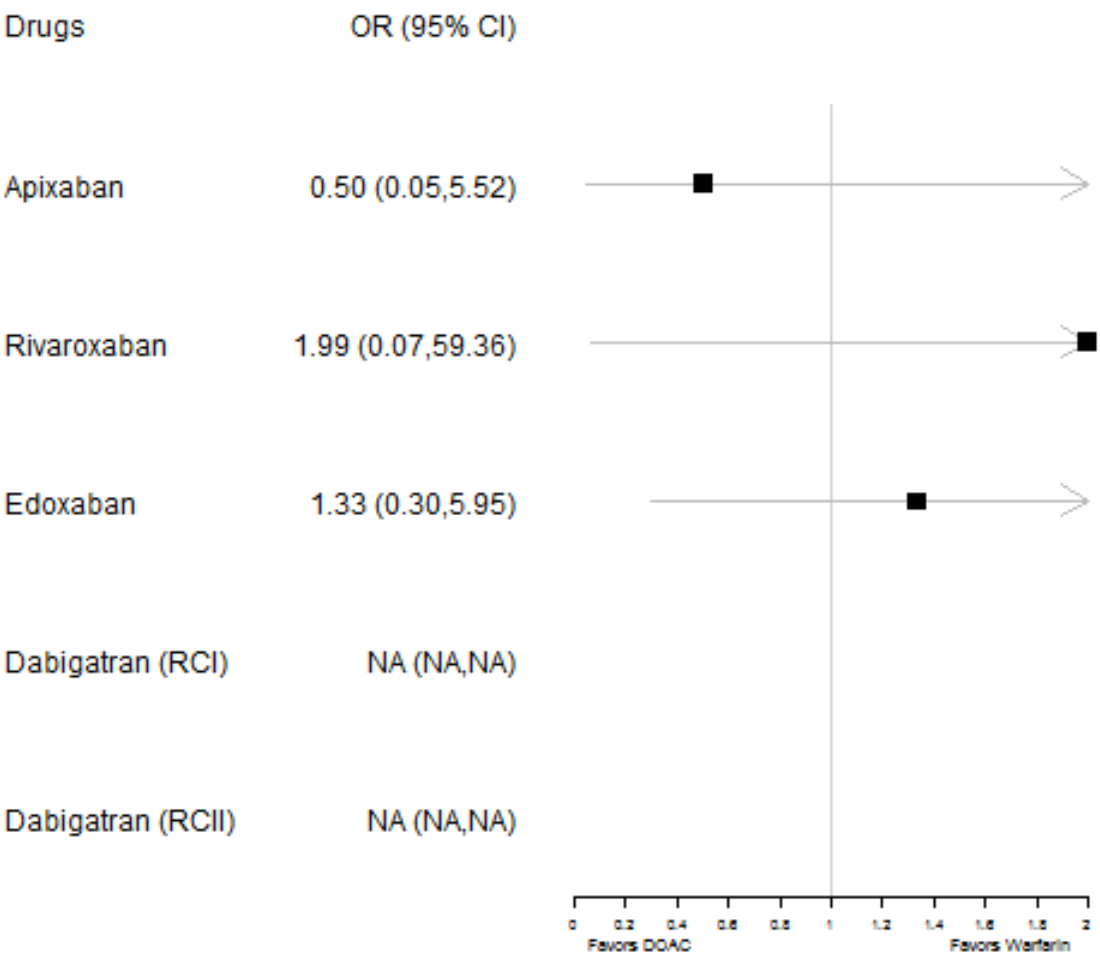
Random effects:
 Groups Name Variance Std.Dev.
 id arm 0 0
Number of obs: 6, groups: id, 3

Fixed effects:
  Estimate Std. Error z value Pr(>|z|)
(Intercept) -7.5620 0.6648 -11.375 <2e-16 ***
as.factor(arm)1 0.1851 0.6057 0.306 0.760
as.factor(id)2 -0.6807 1.1549 -0.589 0.556
as.factor(id)3 0.3952 0.6903 0.573 0.567

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
  (Intr) as.()1 as.()2
as.fctr(r)1 -0.495
as.fctr(d)2 -0.433 -0.002
as.fctr(d)3 -0.726 -0.002 0.418

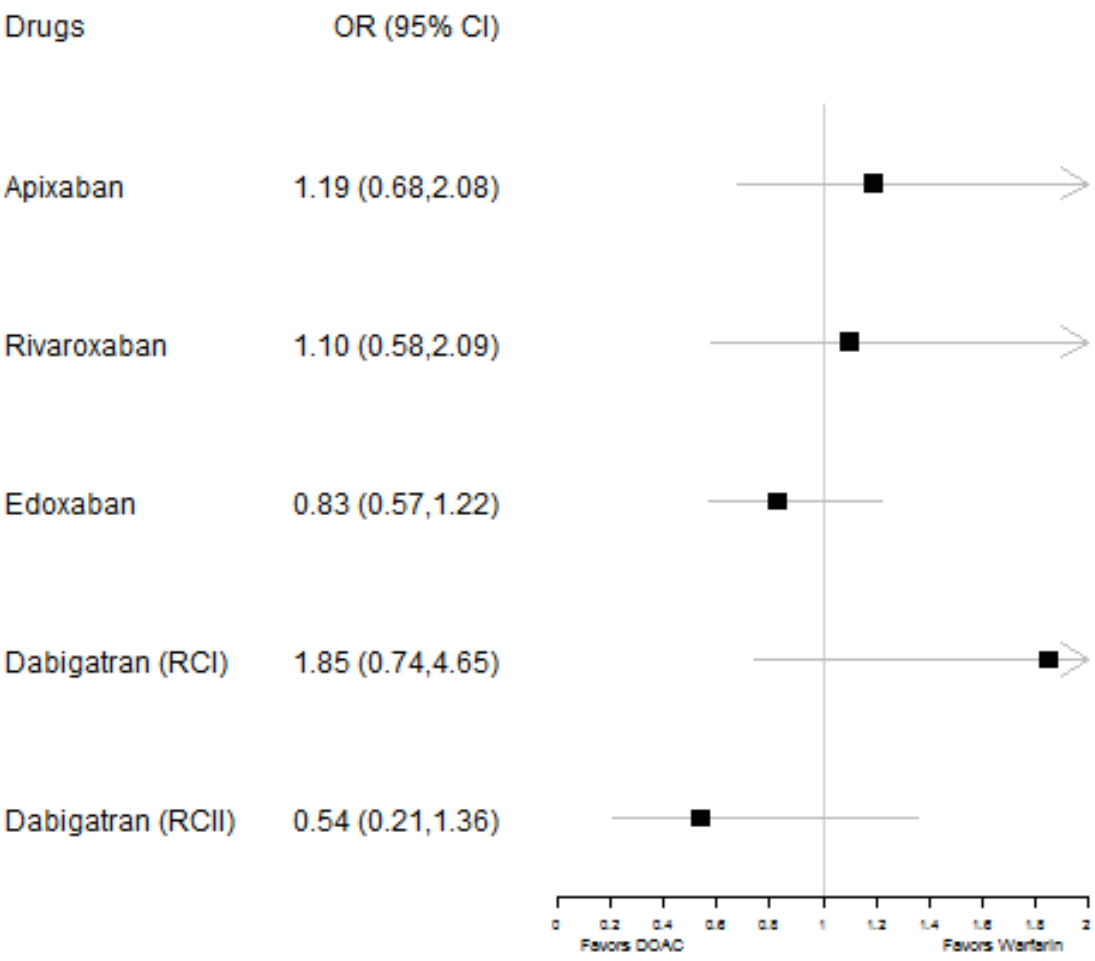
Odds Ratio of Studies for Fatal PE



Recurrent PE (non-fatal)

```
Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite
Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial  ( logit )
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +      (-1 + arm | id)

   AIC      BIC   logLik deviance df.resid
  18.9     21.0     -2.5      4.9        3

Scaled residuals:
    Min      1Q  Median      3Q     Max
-0.98675 -0.55035  0.00176  0.54609  0.99930

Random effects:
 Groups Name Variance Std.Dev.
 id     arm  0        0
Number of obs: 10, groups:  id, 5

Fixed effects:
             Estimate Std. Error z value Pr(>|z|)
(Intercept)    -4.62701    0.15588 -29.682   <2e-16 ***
as.factor(arm)1 -0.03288    0.13094  -0.251   0.8017
as.factor(id)2   0.14621    0.21634   0.676   0.4992
as.factor(id)3   0.32188    0.17197   1.872   0.0613 .
as.factor(id)4  -0.19251    0.26569  -0.725   0.4687
as.factor(id)5  -0.20408    0.26568  -0.768   0.4424
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
          (Intr) as.()1 as.()2 as.()3 as.()4
as.fctr(r)1 -0.411
as.fctr(d)2 -0.598 -0.003
as.fctr(d)3 -0.753 -0.002  0.543
as.fctr(d)4 -0.487 -0.002  0.351  0.442
as.fctr(d)5 -0.487  0.000  0.351  0.442  0.286
```

Odds Ratio of Studies for Recurrent PE (Non Fatal)



Net clinical benefit

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +   (-1 + arm | id)

    AIC   BIC   logLik deviance df.resid
   12.4   11.4   -1.2   2.4   1

Scaled residuals:
    Min   1Q Median   3Q   Max
-0.81205 -0.59411 -0.01502 0.56822 0.83814

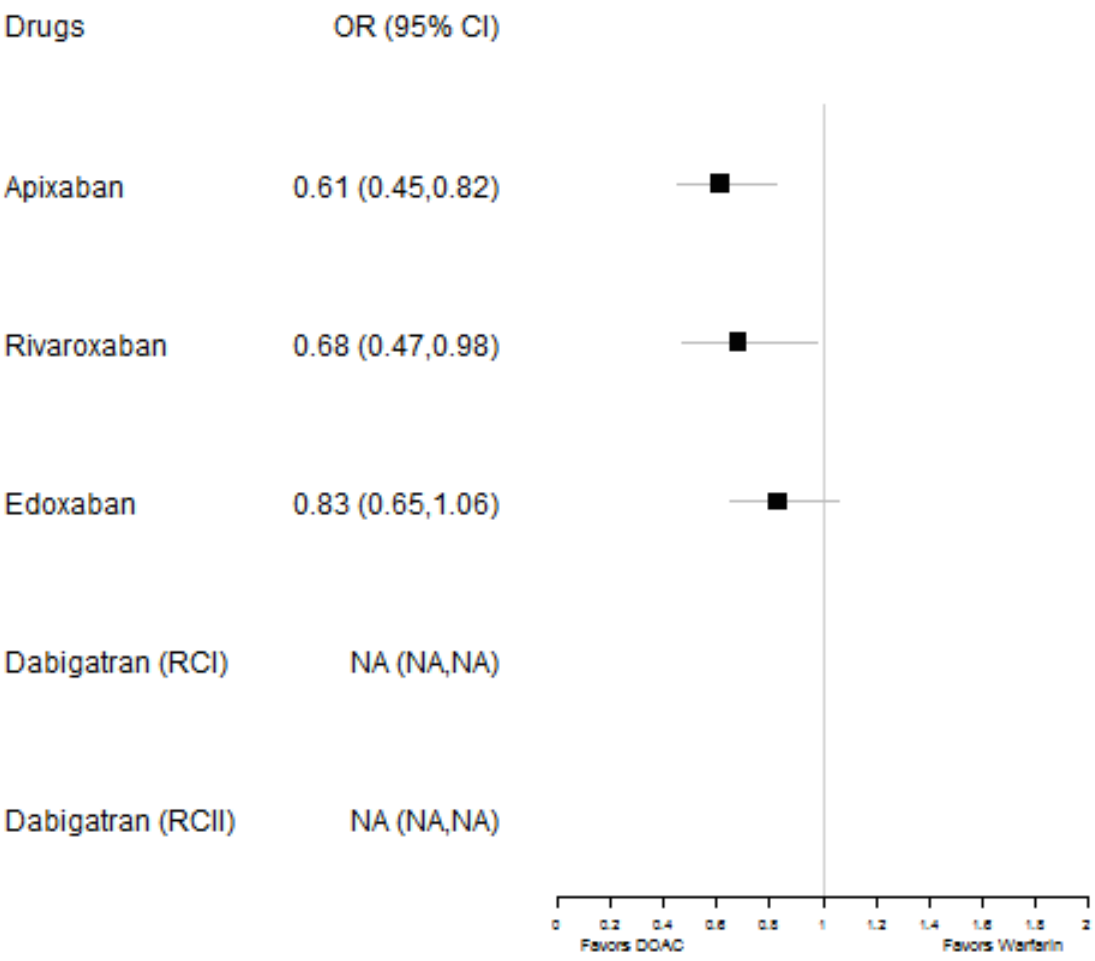
Random effects:
 Groups Name Variance Std.Dev.
 id   arm 0   0
Number of obs: 6, groups: id, 3

Fixed effects:
                 Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.12556   0.08214 -38.05 < 2e-16 ***
as.factor(arm)1 -0.32596   0.08561   -3.81 0.00014 ***
as.factor(id)2 -0.01208   0.11752   -0.10 0.91813
as.factor(id)3 -0.13217   0.09672   -1.37 0.17178

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
            (Intr) as.()1 as.()2
as.fctr(r)1 -0.440
as.fctr(d)2 -0.562 -0.003
as.fctr(d)3 -0.684 -0.001 0.478

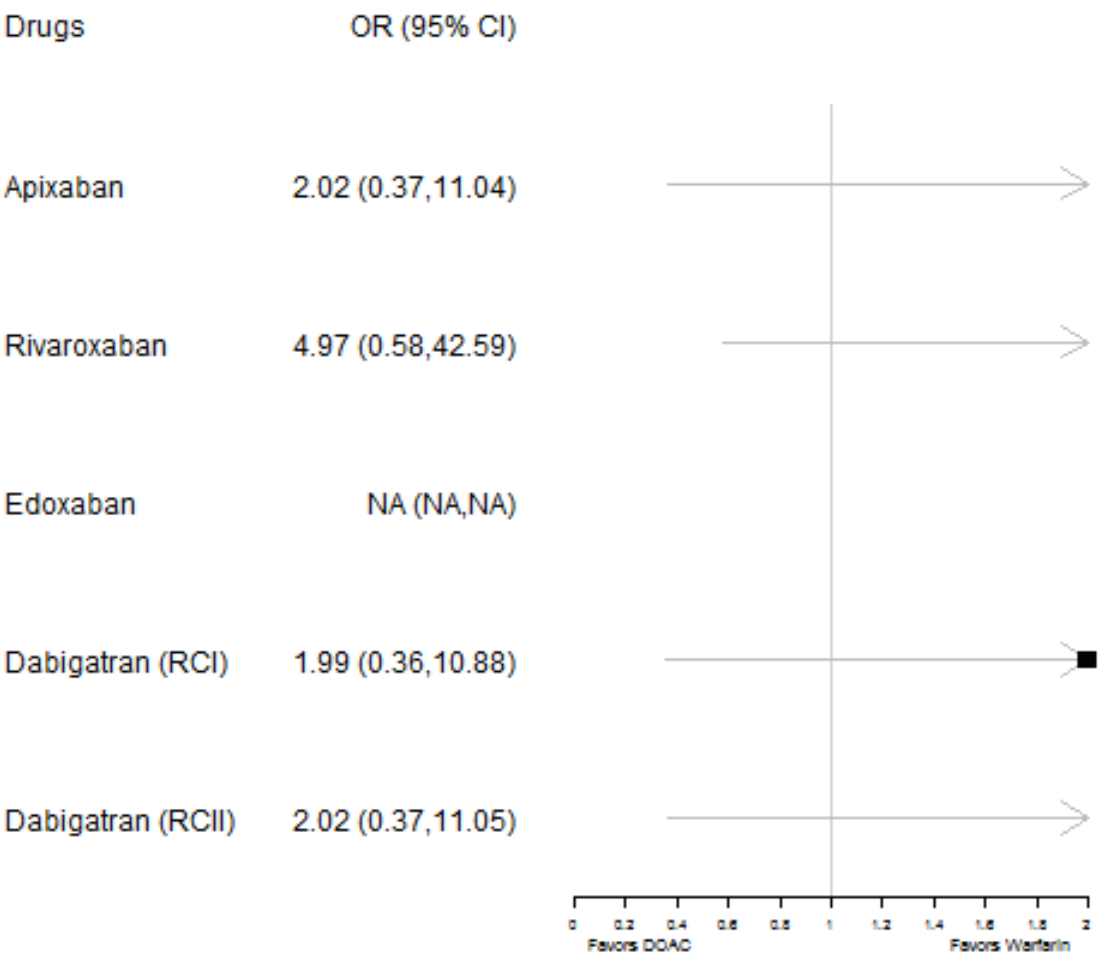
Odds Ratio of Studies for Net Clinical Benefit



Myocardial infarction

```
Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite
Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial  ( logit )
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +      (-1 + arm | id)

    AIC      BIC   logLik deviance df.resid
   12.6     13.1     -0.3      0.6        2

Scaled residuals:
    Min      1Q  Median      3Q     Max
-0.56129 -0.11978  0.03198  0.18622  0.35898

Random effects:
 Groups Name Variance Std.Dev.
 id     arm  0        0
Number of obs: 8, groups:  id, 4

Fixed effects:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)     -7.3101     0.5174 -14.130   <2e-16 ***
as.factor(arm)1   0.8893     0.4494   1.979   0.0479 *
as.factor(id)2    0.4161     0.5778   0.720   0.4715
as.factor(id)4    0.7232     0.5779   1.251   0.2108
as.factor(id)5    0.7146     0.5779   1.236   0.2163
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
          (Intr) as.()1 as.()2 as.()4
as.fctr(r)1 -0.614
as.fctr(d)2 -0.557 -0.003
as.fctr(d)4 -0.557 -0.002  0.500
as.fctr(d)5 -0.558  0.000  0.500  0.500
```

Odds Ratio of Studies for Myocardial Infarction



Safety

Data Used

STUDY	Drug	Sample Size	All-cause Mortality	Major Bleeding	Fatal Bleeding	Intracranial Bleeding	Gastrointestinal Bleeding
RE-COVER	Dabigatran (RCI)	1273	21	20	1	0	53
RE-COVER2	Dabigatran (RCII)	1280	25	15	0	2	48
EINSTEIN-DVT	Rivaroxaban	1718	38	14	1		
AMPLIFY	Apixaban	2676	41	15	1	3	7
Hokusai-VTE	Edoxaban	4118	132	56	2	5	
RE-COVER	Warfarin	1266	21	24	1	3	35
RE-COVER2	Warfarin	1288	25	22	1	2	33
EINSTEIN-DVT	Enoxaparin, Warfarin/acenocoumarol	1711	49	20	5		
AMPLIFY	Enoxaparin,Warfarin	2689	52	49	2	6	18
Hokusai-VTE	LMWH Warfarin	4122	126	66	10	18	
STUDY	Drug	ALT greater than 3xULN	Non-major Relevant Bleeding	Serious Adverse Event	Medication Stopped (ADE)	All-cause Mortality Denominator	ALT greater than 3xULN Denominator
RE-COVER	Dabigatran (RCI)	42		165	126	1273	1220
RE-COVER2	Dabigatran (RCII)			156	102	1280	
EINSTEIN-DVT	Rivaroxaban	25	126	201	85	1718	1680
AMPLIFY	Apixaban	50	103	417	150	2676	2601
Hokusai-VTE	Edoxaban	81	298	503	41	4118	3901
RE-COVER	Warfarin	46		150	102	1266	1199
RE-COVER2	Warfarin			153	101	1288	
EINSTEIN-DVT	Enoxaparin, Warfarin/acenocoumarol	62	119	233	81	1711	1649
AMPLIFY	Enoxaparin,Warfarin	145	215	410	182	2689	2598
Hokusai-VTE	LMWH Warfarin	90	368	544	51	4122	3903

Major bleeding

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) + (-1 + arm | id)

   AIC   BIC logLik deviance df.resid
  23.4 25.5 -4.7   9.4   3

Scaled residuals:
    Min   1Q Median   3Q   Max
-1.31368 -0.29020 0.02406 0.37533 0.94190

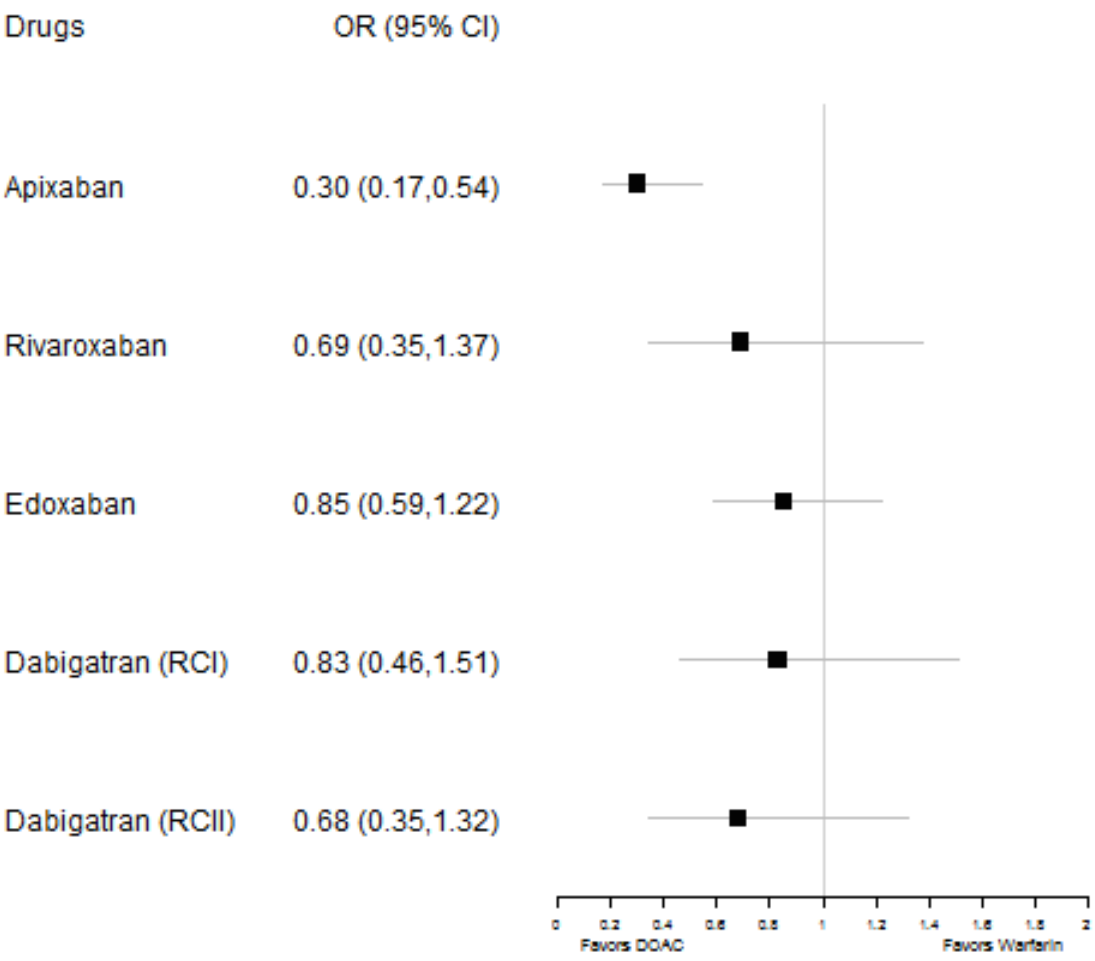
Random effects:
 Groups Name Variance Std.Dev.
 id   arm 0.04453 0.211
Number of obs: 10, groups: id, 5

Fixed effects:
                 Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.8733   0.1771 -21.867 < 2e-16 ***
as.factor(arm)1 -0.4505   0.1591 -2.832 0.00463 **
as.factor(id)2   -0.1633   0.2485 -0.657 0.51101
as.factor(id)3   -0.5424   0.2532 -2.142 0.03217 *
as.factor(id)4   -0.2491   0.2511 -0.992 0.32126
as.factor(id)5   -0.1916   0.2017 -0.950 0.34199

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

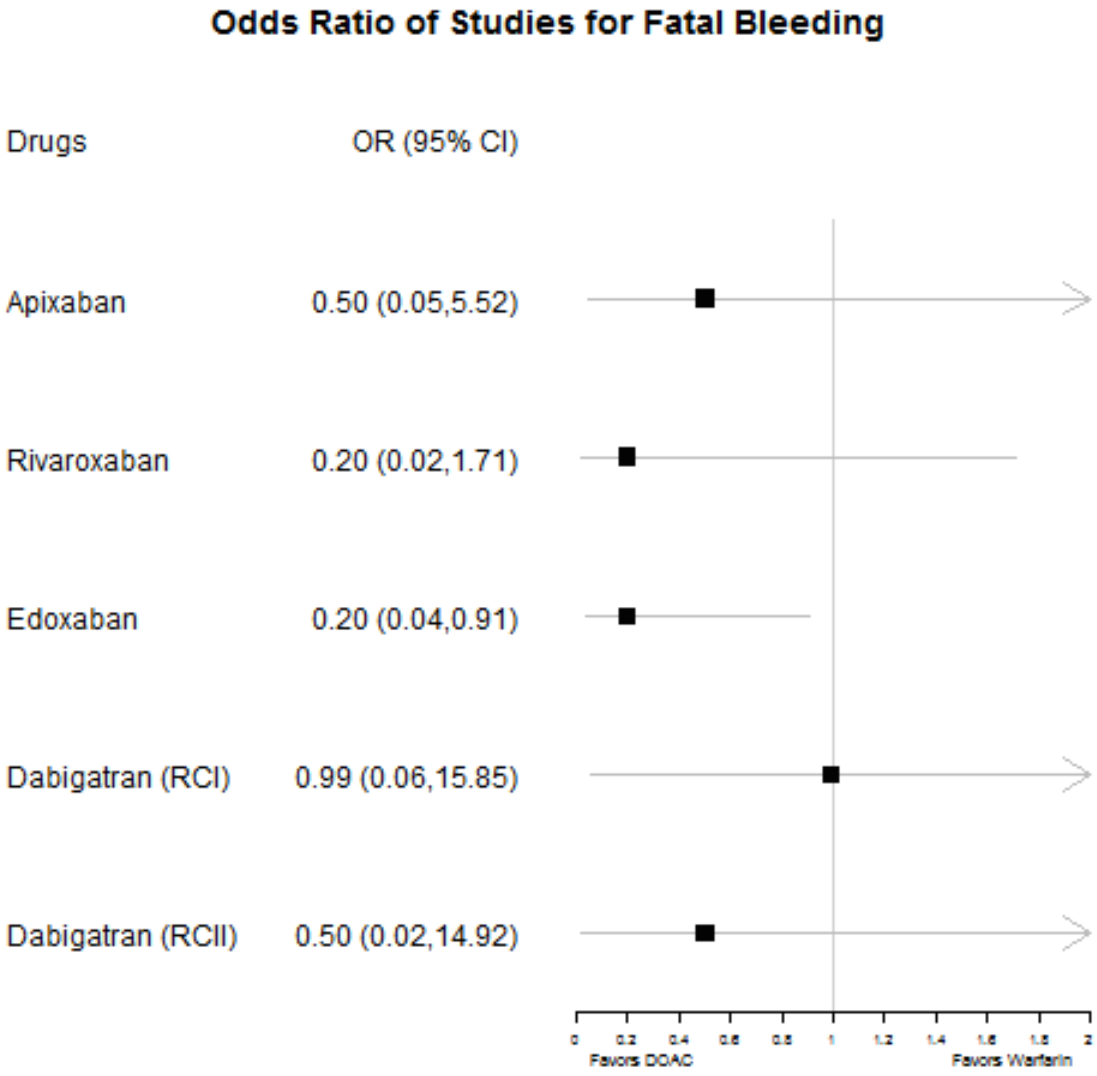
Correlation of Fixed Effects:
            (Intr) as.()1 as.()2 as.()3 as.()4
as.fctr(r)1 -0.216
as.fctr(d)2 -0.665 -0.021
as.fctr(d)3 -0.650 -0.024 0.463
as.fctr(d)4 -0.740 -0.035 0.512 0.498
as.fctr(d)5 -0.804 0.083 0.560 0.550 0.536

Odds Ratio of Studies for Major Bleeding



Fatal bleeding

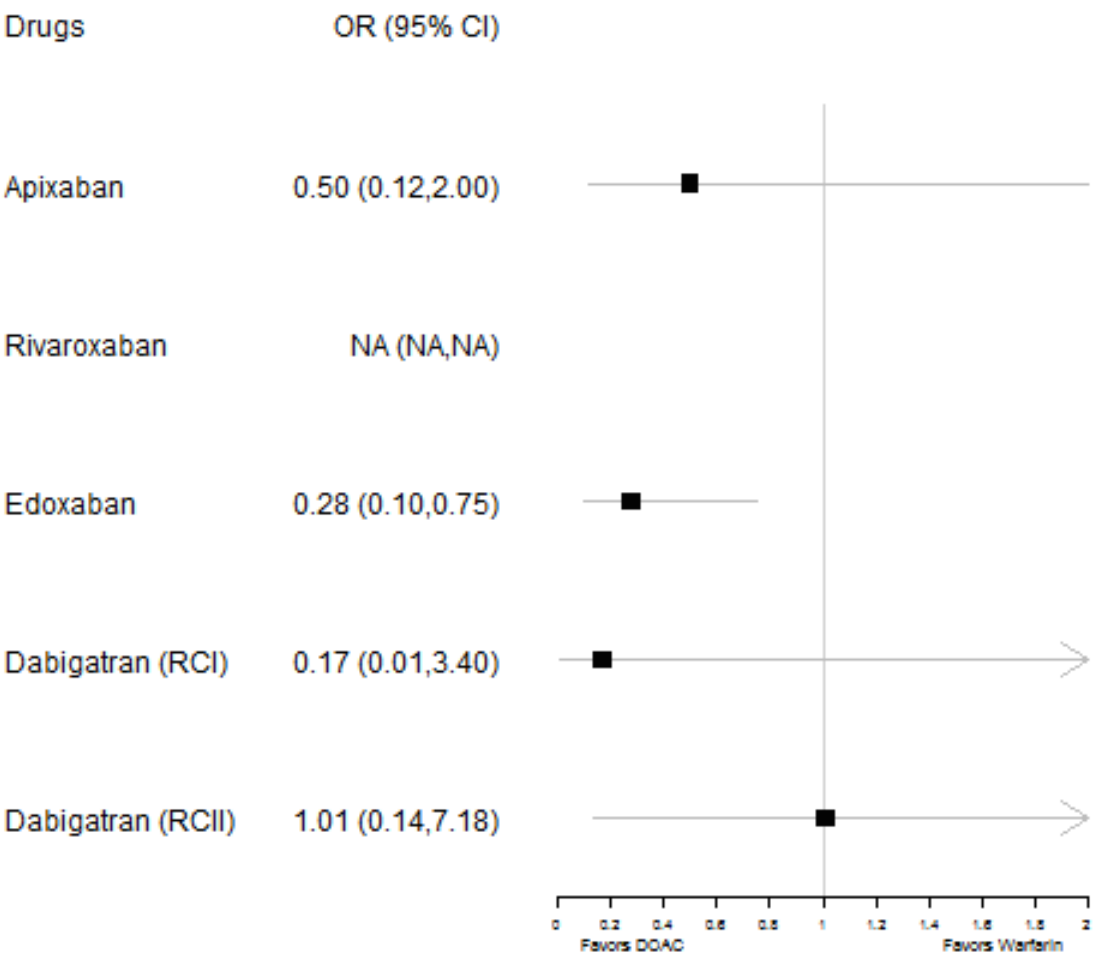
```
Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite
Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial  ( logit )
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +      (-1 + arm | id)

    AIC      BIC   logLik deviance df.resid
   15.4     17.5     -0.7      1.4        3

Scaled residuals:
    Min      1Q  Median      3Q     Max
-0.44158 -0.28097  0.00517  0.27078  0.81836

Random effects:
 Groups Name Variance Std.Dev.
 id     arm  0        0
Number of obs: 10, groups:  id, 5

Fixed effects:
                 Estimate Std. Error z value Pr(>|z|)
(Intercept)      -6.7046     0.7158  -9.366   <2e-16 ***
as.factor(arm)1  -1.2411     0.4844  -2.562   0.0104 *
as.factor(id)2   -0.3025     1.0806  -0.280   0.7795
as.factor(id)3    0.7990     0.8170   0.978   0.3281
as.factor(id)4   -0.3458     0.9132  -0.379   0.7049
as.factor(id)5    0.6136     0.7642   0.803   0.4220
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
            (Intr) as.()1 as.()2 as.()3 as.()4
as.fctr(r)1 -0.153
as.fctr(d)2 -0.647  0.001
as.fctr(d)3 -0.856  0.000  0.567
as.fctr(d)4 -0.766  0.001  0.507  0.671
as.fctr(d)5 -0.915  0.001  0.606  0.802  0.717
```


Odds Ratio of Studies for Fatal Bleeding
Drugs
OR (95% CI)
Apixaban
0.50 (0.05,5.52)
Rivaroxaban
0.20 (0.02,1.71)
Edoxaban
0.20 (0.04,0.91)
Dabigatran (RCI)
0.99 (0.06,15.85)
Dabigatran (RCII)
0.50 (0.02,14.92)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Favors DOAC
Favors Warfarin

Intracranial bleeding

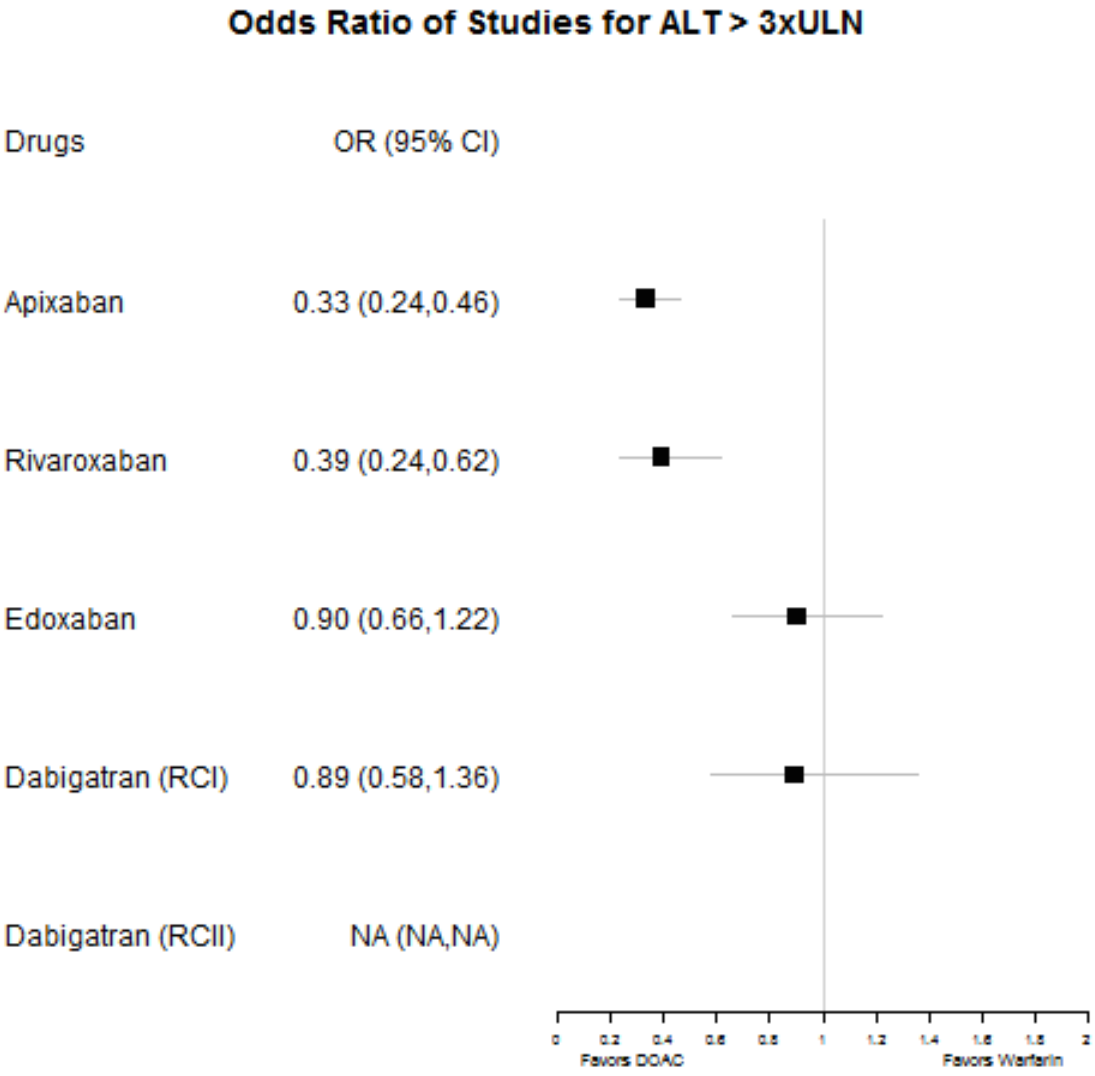
```
Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite
Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial  ( logit )
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +      (-1 + arm | id)

   AIC     BIC   logLik deviance df.resid
  13.8    14.3    -0.9     1.8       2

Scaled residuals:
    Min      1Q  Median      3Q     Max
-0.54918 -0.45066  0.01637  0.30424  0.91436

Random effects:
 Groups Name Variance Std.Dev.
 id     arm  0        0
Number of obs: 8, groups:  id, 4

Fixed effects:
                 Estimate Std. Error z value Pr(>|z|)
(Intercept)      -6.1996     0.5436 -11.405  < 2e-16 ***
as.factor(arm)1  -1.0163     0.3605  -2.819  0.00482 **
as.factor(id)2    0.1196     0.7326   0.163  0.87027
as.factor(id)4    0.1943     0.6305   0.308  0.75799
as.factor(id)5    0.7057     0.5743   1.229  0.21914
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
          (Intr) as.()1 as.()2 as.()4
as.fctr(r)1 -0.177
as.fctr(d)2 -0.719  0.001
as.fctr(d)4 -0.835  0.001  0.620
as.fctr(d)5 -0.917  0.000  0.680  0.790
```

Odds Ratio of Studies for Intracranial Bleeding



ALT > 3xULN

```
Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite
Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial  ( logit )
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +      (-1 + arm | id)

    AIC      BIC   logLik deviance df.resid
   24.8     25.3     -6.4     12.8        2

Scaled residuals:
    Min      1Q  Median      3Q     Max
-0.37833 -0.31366 -0.01216  0.24833  0.34724

Random effects:
 Groups Name Variance Std.Dev.
 id     arm  0.1674   0.4092
Number of obs: 8, groups:  id, 4

Fixed effects:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)    -3.17499    0.14458 -21.961  < 2e-16 ***
as.factor(arm)1 -0.57433    0.22651  -2.536  0.01123 *
as.factor(id)3  -0.09717    0.19455  -0.499  0.61743
as.factor(id)4   0.32629    0.16995   1.920  0.05487 .
as.factor(id)5  -0.54432    0.17355  -3.136  0.00171 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
          (Intr) as.()1 as.()3 as.()4
as.fctr(r)1 -0.155
as.fctr(d)3 -0.750  0.024
as.fctr(d)4 -0.861  0.079  0.659
as.fctr(d)5 -0.797  0.055  0.593  0.681
```


Odds Ratio of Studies for ALT > 3xULN
Drugs
OR (95% CI)
Apixaban
0.33 (0.24,0.46)
Rivaroxaban
0.39 (0.24,0.62)
Edoxaban
0.90 (0.66,1.22)
Dabigatran (RCI)
0.89 (0.58,1.36)
Dabigatran (RCII)
NA (NA,NA)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Favors DOAC
Favors Warfarin

Gastrointestinal bleeding

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +   (-1 + arm | id)

    AIC   BIC   logLik deviance df.resid
   19.3   18.2   -4.6   9.3   1

Scaled residuals:
    Min   1Q Median   3Q   Max
-1.01435 -0.29156 -0.01378 0.25732 0.88046

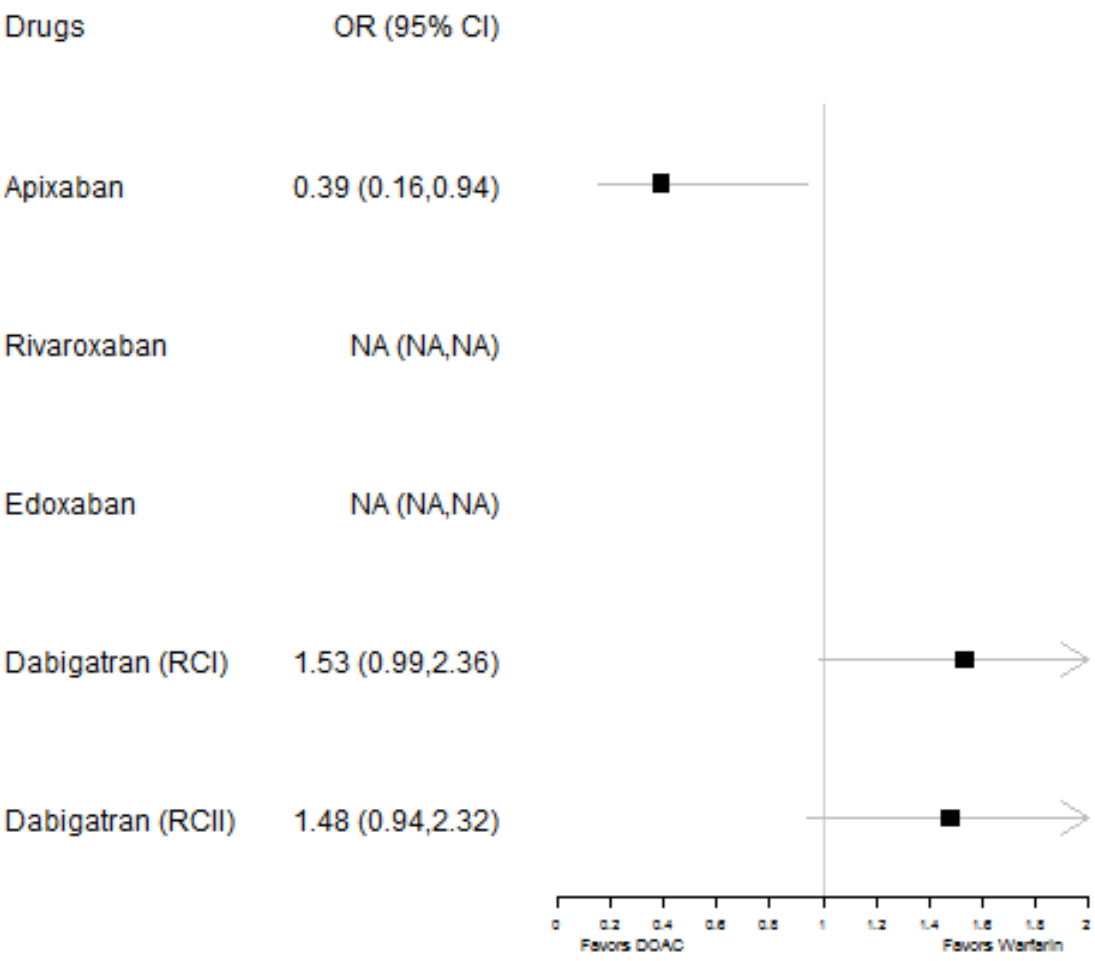
Random effects:
 Groups Name Variance Std.Dev.
 id   arm 0.1361   0.3689
Number of obs: 6, groups: id, 3

Fixed effects:
                  Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.50915   0.16817 -20.867 < 2e-16 ***
as.factor(arm)1 0.08666   0.30441   0.285   0.776
as.factor(id)2 -0.08124   0.22098 -0.368   0.713
as.factor(id)4 -1.69853   0.40471 -4.197 2.71e-05 ***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
            (Intr) as.()1 as.()2
as.fctr(r)1 -0.058
as.fctr(d)2 -0.647 -0.021
as.fctr(d)4 -0.569 -0.392 0.288

Odds Ratio of Studies for Gastrointestinal Bleeding



Non-major relevant bleeding

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) + (-1 + arm | id)

AIC	BIC	logLik	deviance	df.resid
21.4	20.3	-5.7	11.4	1

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.41013	-0.24558	0.00297	0.23940	0.31422

Random effects:

Groups	Name	Variance	Std.Dev.
id	arm	0.09464	0.3076

Number of obs: 6, groups: id, 3

Fixed effects:

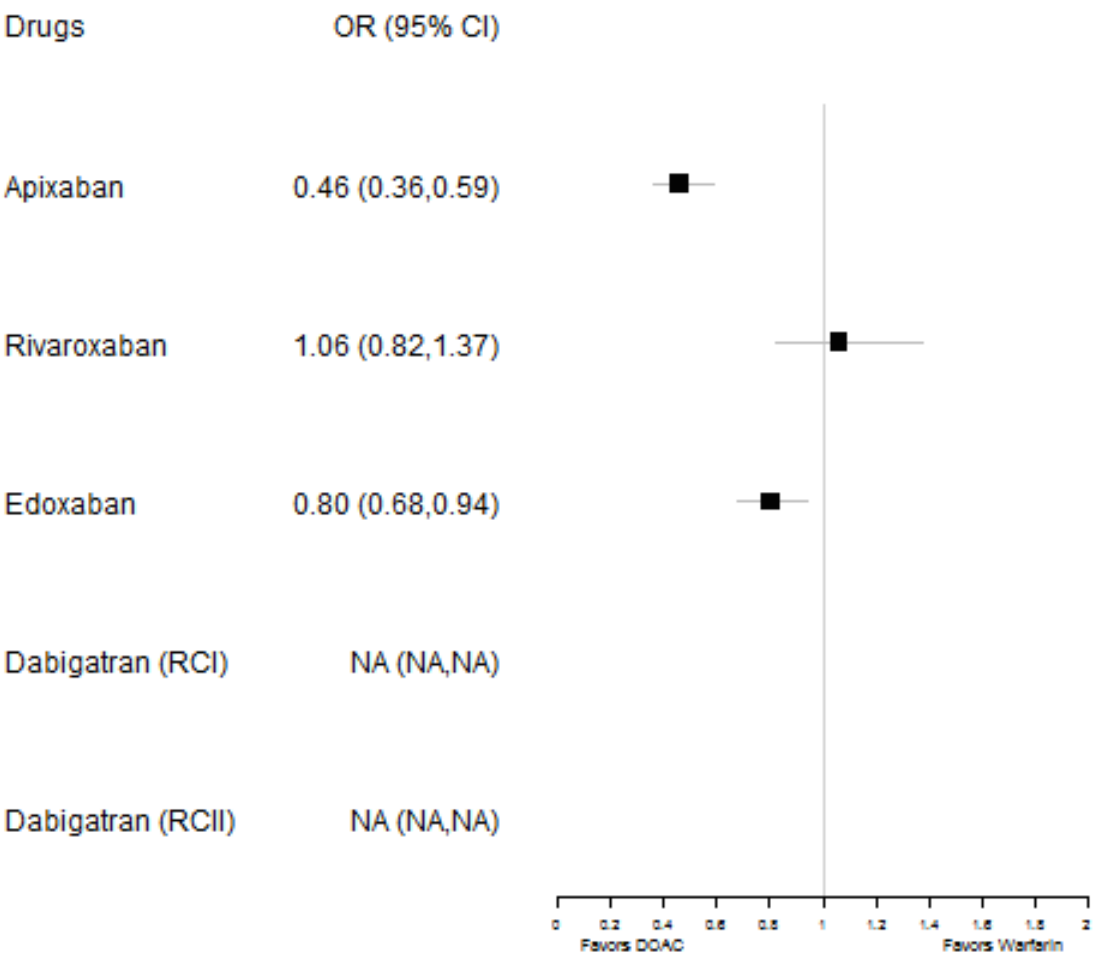
	Estimate	Std. Error	z value	Pr(>|z|)	
(Intercept)	-2.56402	0.09429	-27.193	<2e-16	***
as.factor(arm)1	-0.31886	0.18927	-1.685	0.092	.
as.factor(id)4	0.09965	0.12153	0.820	0.412	
as.factor(id)5	0.24415	0.10743	2.273	0.023	*

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:

	(Intr)	as.()1	as.()4
as.fctr(r)1	-0.157		
as.fctr(d)4	-0.801	0.049	
as.fctr(d)5	-0.864	0.086	0.693

Odds Ratio of Studies for Non-major Relevent Bleeding



Serious adverse event

Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial (logit)
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) + (-1 + arm | id)

   AIC   BIC   logLik deviance df.resid
  18.7 20.8   -2.4   4.7   3

Scaled residuals:
    Min   1Q Median   3Q   Max
-0.94906 -0.57324 0.00324 0.57783 0.93815

Random effects:
 Groups Name Variance Std.Dev.
 id   arm 0   0
Number of obs: 10, groups: id, 5

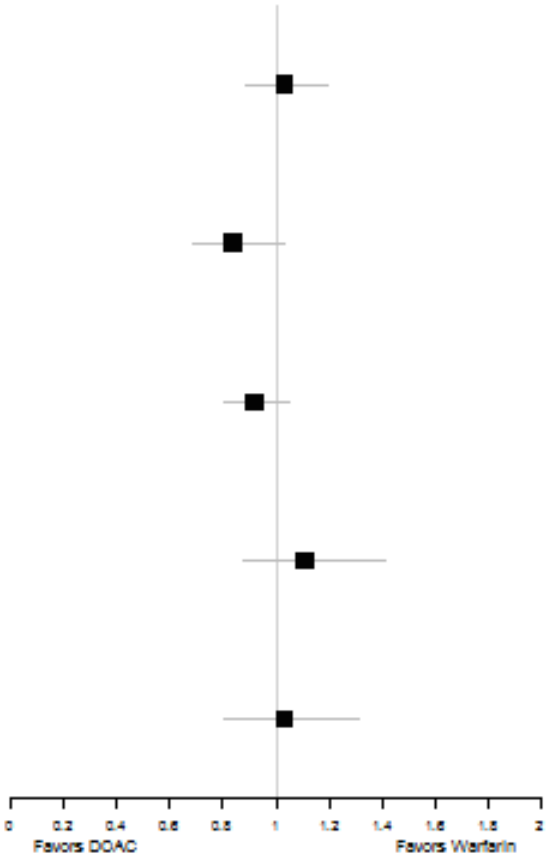
Fixed effects:
                 Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.93634   0.06332 -30.580 < 2e-16 ***
as.factor(arm)1 -0.03644   0.03969 -0.918 0.358519
as.factor(id)2 -0.03495   0.08546 -0.409 0.682529
as.factor(id)3   0.02282   0.07914   0.288 0.773041
as.factor(id)4   0.25197   0.07109   3.544 0.000394 ***
as.factor(id)5   0.02725   0.06869   0.397 0.691562

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
            (Intr) as.()1 as.()2 as.()3 as.()4
as.fctr(r)1 -0.310
as.fctr(d)2 -0.670 0.001
as.fctr(d)3 -0.723 0.000 0.536
as.fctr(d)4 -0.805 0.001 0.597 0.644
as.fctr(d)5 -0.834 0.001 0.617 0.667 0.742

Odds Ratio of Studies for Serious Adverse Event

Drugs	OR (95% CI)
Apixaban	1.03 (0.89,1.19)
Rivaroxaban	0.84 (0.69,1.03)
Edoxaban	0.92 (0.81,1.05)
Dabigatran (RCI)	1.11 (0.88,1.41)
Dabigatran (RCII)	1.03 (0.81,1.31)



Medication stopped (ADE)

```
Generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite
Quadrature, nAGQ = 7) ['glmerMod']
 Family: binomial  ( logit )
Formula: cbind(ADEs[, i], nADEs[, i]) ~ as.factor(arm) + as.factor(id) +      (-1 + arm | id)

    AIC      BIC   logLik deviance df.resid
   20.8     22.9     -3.4      6.8        3

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.27533 -0.57082  0.00149  0.56514  1.28553

Random effects:
 Groups Name Variance Std.Dev.
 id     arm  0        0
Number of obs: 10, groups:  id, 5

Fixed effects:
             Estimate Std. Error z value Pr(>|z|)
(Intercept)    -2.30305    0.07648 -30.112  < 2e-16 ***
as.factor(arm)1 -0.02615    0.06473  -0.404    0.686
as.factor(id)2  -0.13932    0.10084  -1.382    0.167
as.factor(id)3  -0.66234    0.10559  -6.273 3.55e-10 ***
as.factor(id)4  -0.40262    0.08961  -4.493 7.02e-06 ***
as.factor(id)5  -2.16771    0.12574 -17.239  < 2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Correlation of Fixed Effects:
          (Intr) as.()1 as.()2 as.()3 as.()4
as.fctr(r)1 -0.420
as.fctr(d)2 -0.626  0.002
as.fctr(d)3 -0.597  0.001  0.453
as.fctr(d)4 -0.704  0.002  0.533  0.509
as.fctr(d)5 -0.502  0.001  0.380  0.363  0.428
```

Odds Ratio of Studies for Medication Stopped (ADE)