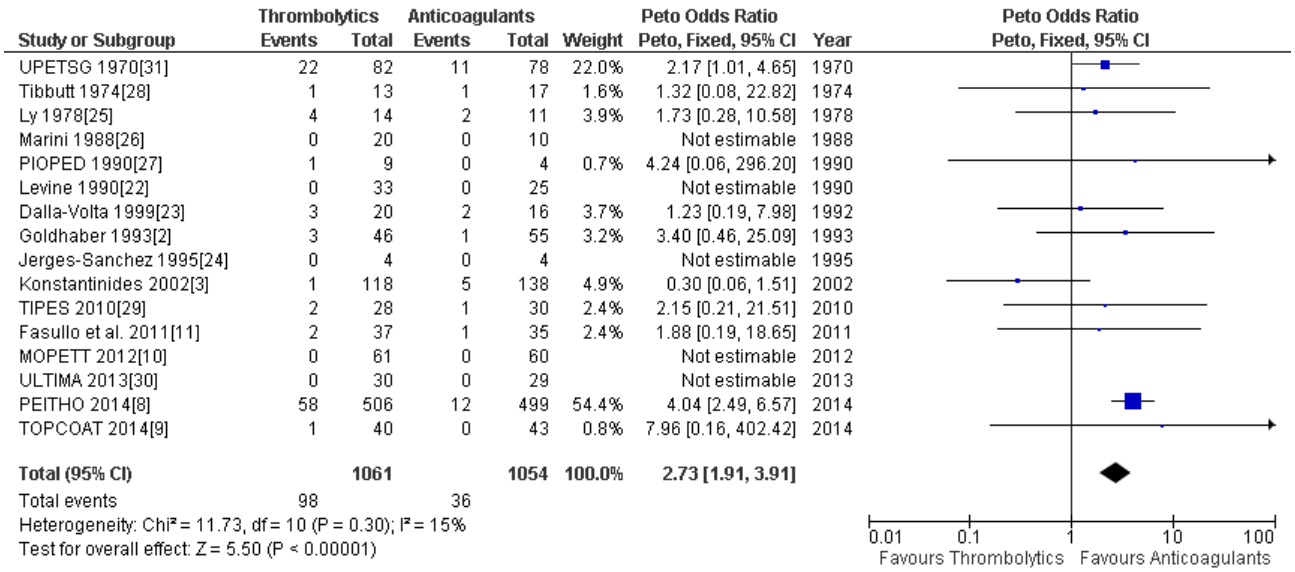
Supplementary Online Content

Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA*. doi:10.1001/jama.2014.5990.

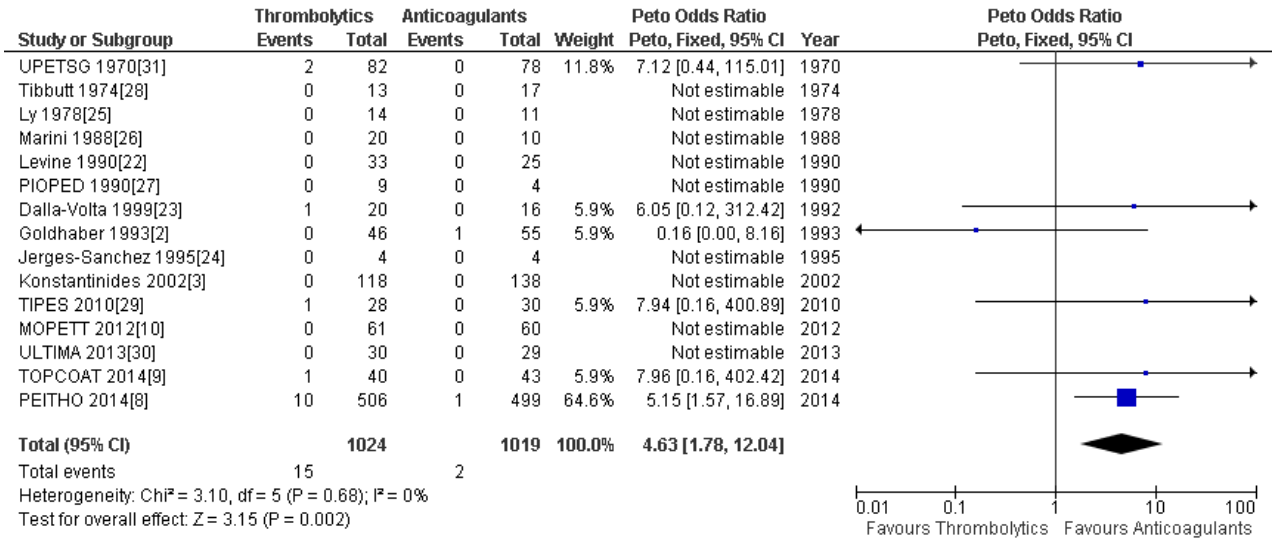
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Odds of Major Bleeding in Patients with Pulmonary Embolism treated with Thrombolytic Therapy vs Anticoagulation



MOPETT indicates Moderate Pulmonary Embolism Treated with Thrombolysis trial; PEITHO, Pulmonary Embolism Thrombolysis Trial ; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis; TIPES, Tenecteplase Italian Pulmonary Embolism Study; TOPCOAT, Tenecteplase or Placebo: Cardiopulmonary Outcomes At Three Months; ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism trial; UPETSG, Urokinase Pulmonary Embolism Trial Stage 1. Square data markers represent odds ratios (OR); horizontal lines are the 95% CIs with marker size reflecting the statistical weight of the study. A diamond data marker represents the overall OR and 95% CI for the outcome. Evaluated using Peto's method of meta-analysis. The standard practice in meta-analysis of odds ratios and risk ratios is to exclude studies from the meta-analysis where there are no events in both arms [13]. A zero-cell or continuity correction was not used based on recommendations regarding calculation of Peto Odds Ratio for studies with zero events in only one arm [13].

eFigure 2. Odds of Intracranial Hemorrhage (ICH) in Patients with Pulmonary Embolism treated with Thrombolytic Therapy vs. Anticoagulation



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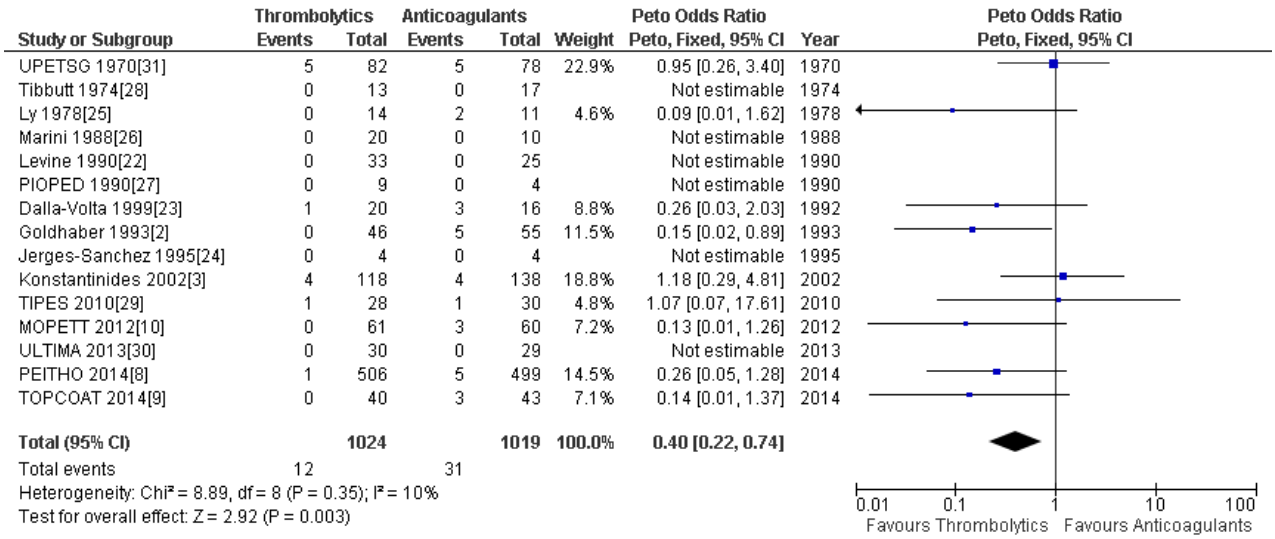
eFigure 3. Odds of Recurrent PE in Patients with Pulmonary Embolism treated with Thrombolytic Therapy vs. Anticoagulation



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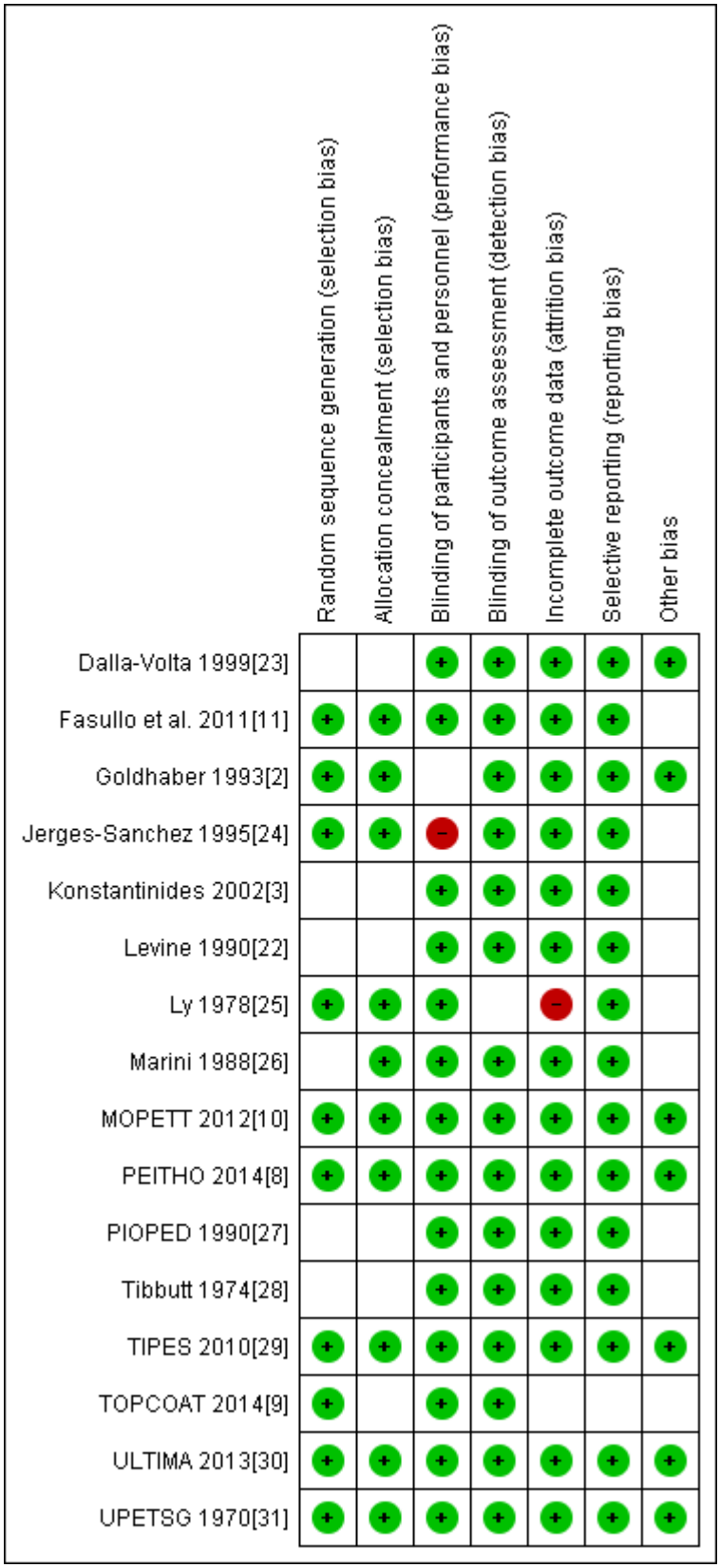
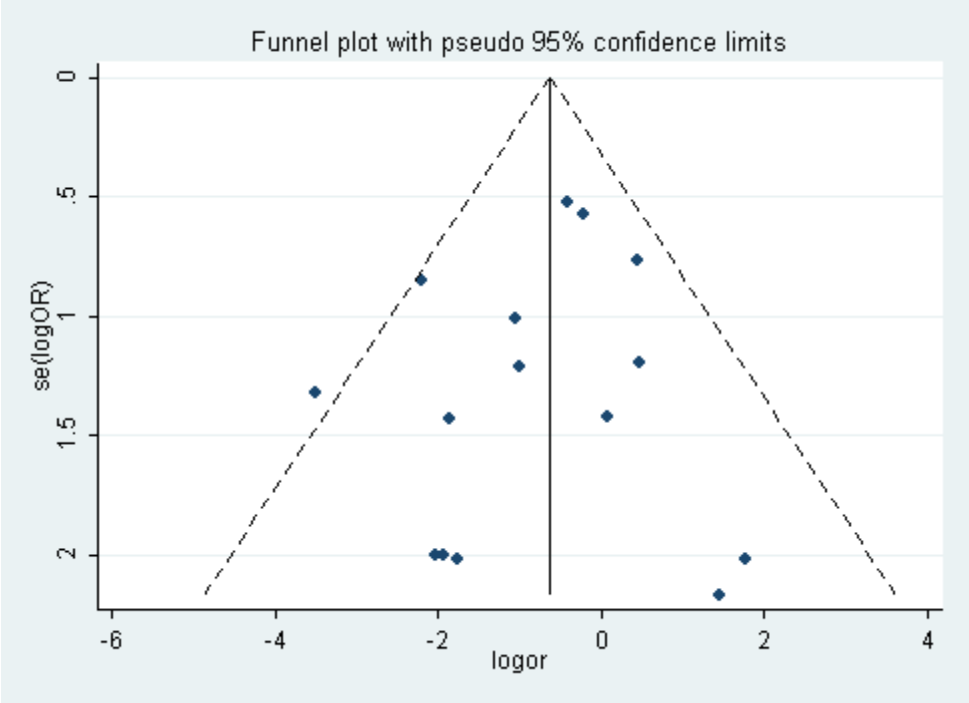
eFigure 4. Risk of Bias for Individual RCTs

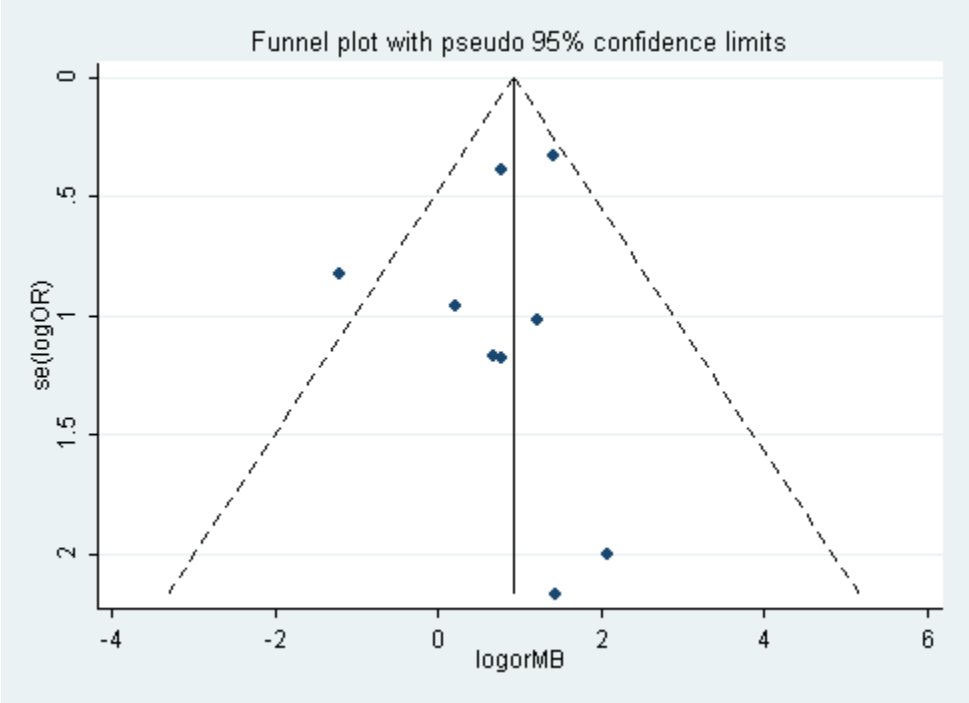


eFigure 5A. Funnel Plot for Assessment of Publication Bias for Mortality Outcome



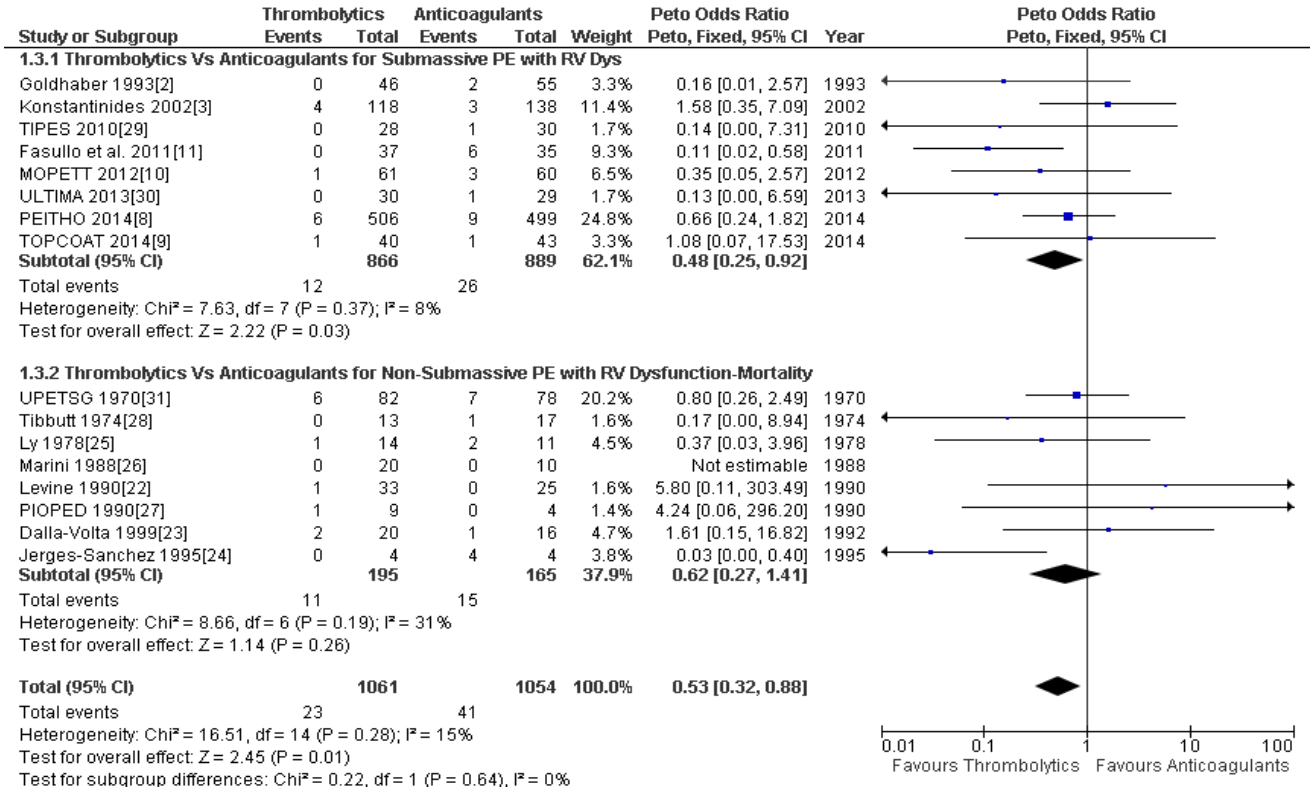
The logarithms of OR for mortality from individual trials (represented by the blue diamonds) have been plotted against the natural log of standard error of mortality for each RCT. A symmetric, inverted funnel plot indicates low risk of publication bias as is seen in the current analysis.

eFigure 5B. Funnel Plot for Assessment of Publication Bias for Major Bleeding Outcome



The logarithms of OR for major bleeding from individual trials (represented by the blue diamonds) have been plotted against the natural log of standard error of major bleeds for each RCT. A symmetric, inverted funnel plot indicates low risk of publication bias as is seen in the current analysis.

eFigure 6. Comparison of Odds of Mortality in Trials Enrolling Hemodynamically Stable Patients with Objective RV Function Assessment vs. Those Enrolling All-Comers treated with Thrombolytic Therapy vs Anticoagulation



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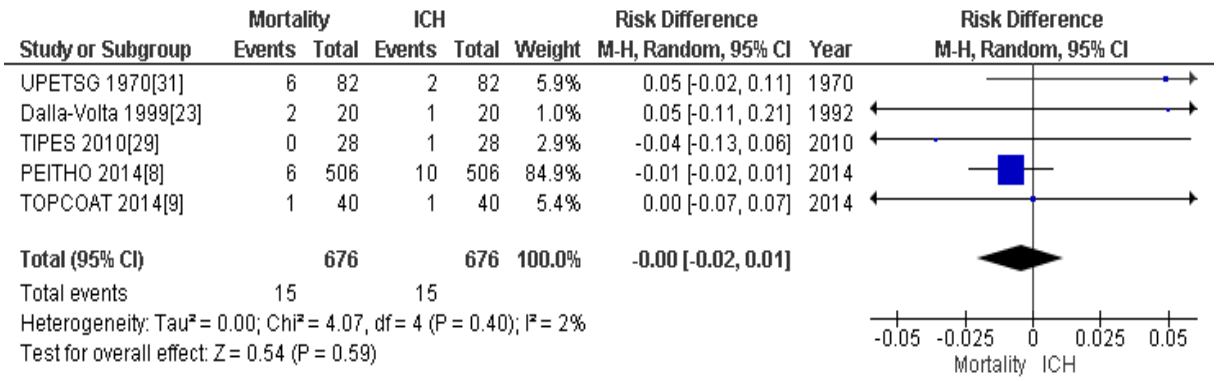
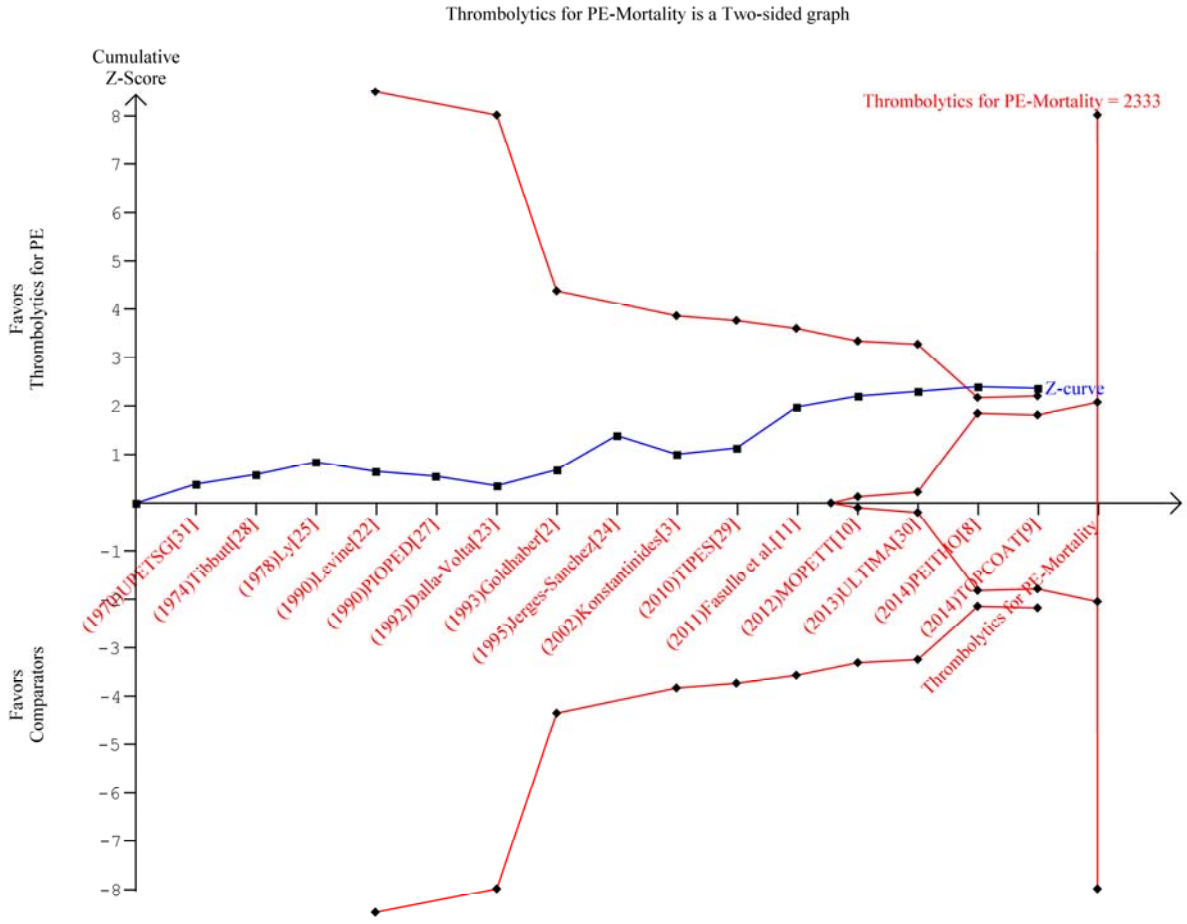
eFigure 7. Weighted Risk Difference of Mortality and ICH with Thrombolytic Therapy in PE



The figure depicts a weighted absolute risk difference analysis (as is used for assessment of benefit-harms trade-off analysis) [13] to compare the potential associations of mortality reduction with thrombolysis against the possible associations of risk of intracranial hemorrhages. PEITHO, Pulmonary Embolism Thrombolysis Trial ; TIPES, Tenecteplase Italian Pulmonary Embolism Study; TOPCOAT, Tenecteplase or Placebo: Cardiopulmonary Outcomes At Three Months; UPETSG, Urokinase Pulmonary Embolism Trial Stage 1. Square data markers represent weighted absolute risk differences for individual trials; horizontal lines are the 95% CIs with marker size reflecting the statistical weight of the study. A diamond data marker represents the overall weighted absolute risk difference, and 95% CI for the risk difference.

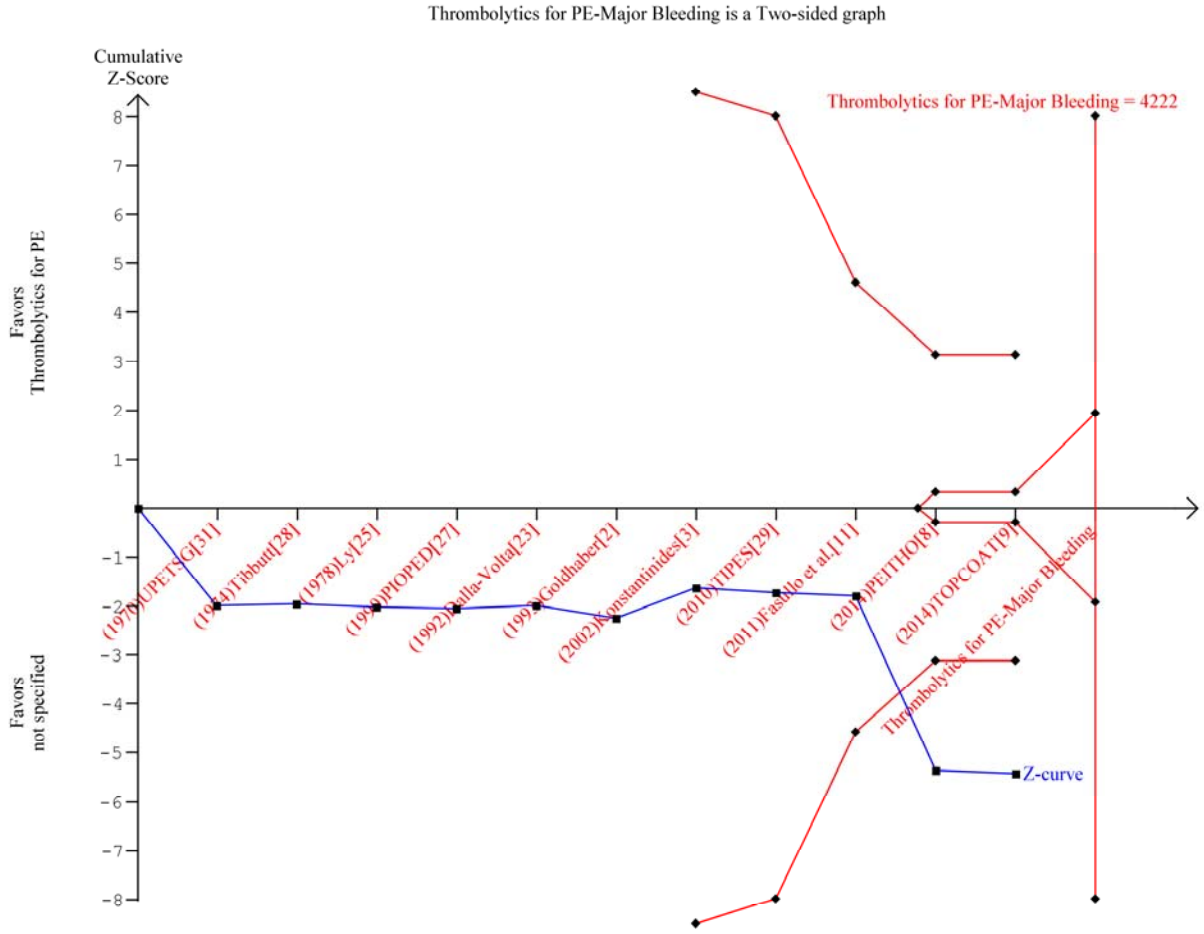
eFigure 8. Trial Sequential Analysis of Primary Mortality Endpoint (Derived from 15 RCTs)



Trial sequential analysis (TSA) for meta-analyses have been derived from the O'Brien-Fleming spending function/ 'stopping rule' for randomized trials, which provides an opportunity during interim analyses in a randomized trial to identify that further prolongation of the trial was unlikely to alter the overall outcome results. Similarly TSA for meta-analyses provides information on whether the accumulated evidence from available data maybe robust enough that it would be unlikely to be influenced by results from future trials, and the level of confidence of such; after calculating a required information size and adjusting for diversity among the individual trial population(s). The figure shows trial sequential analysis of randomized studies on all-cause mortality that tests for 12% relative mortality reduction with control event proportion of 3.89%, alpha=

.05, beta = .20, diversity (*D*2) of 0.33%, and calculated required information size of 2,333. The analysis uses a fixed-effects model with a type I error risk of 5% and a power of 80%. The blue line is the cumulative *z* score from the cumulative random-effects meta-analyses, and each black box indicates the addition of data from a new study; the red lines are the study sequential monitoring boundaries, the upper one being for positive effect and the lower one being for detrimental effects, calculated according to the O'Brien-Fleming spending function and stopping rule. The inner red lines represent 'futility boundaries', which if crossed by the cumulative z-score curve, indicates that the current available evidence from RCTs are inadequate to definitively determine superiority or inferiority of the intervention. Once the futility boundary is crossed, further trials of that intervention are likely to be futile. The red vertical line indicates the diversity-adjusted information size of 2,333 patients based on an *a priori* 12% reduction in Peto-odds of mortality. There is at present firm evidence for a 12% reduction in Peto-odds for mortality even when the cumulative meta-analysis is adjusted for sparse data and multiple testing on accumulated data, disregarding possible bias. Two-sided graph refers to the fact that two-sided hypothesis testing (for significant superiority, and inferiority in both instances) was performed for an individual outcomes (mortality) while assessing simultaneously for adequacy of sample size, and adjusting for potential diversity.

eFigure 9. Trial Sequential Analysis of Primary Bleeding Endpoint (Derived from 11 RCTs)



Trial sequential analysis (TSA) for meta-analyses have been derived from the O'Brien-Fleming spending function/ 'stopping rule' for randomized trials, which provides an opportunity during interim analyses in a randomized trial to identify that further prolongation of the trial was unlikely to alter the overall outcome results. Similarly, TSA for meta-analyses provides information on whether the accumulated evidence from available data maybe robust enough that it would be unlikely to be influenced by results from future trials, and the level of confidence of such; after calculating a required information size and adjusting for diversity among the individual trial population(s). The figure shows trial sequential analysis of randomized studies on major bleeding that tests for a 75% relative increase in bleeding with control event proportion of 2.94%, alpha=

.05, beta = .20, diversity (*D*2) of 35%, and calculated required information size of 3,983. The analysis uses a fixed-effects model with a type I error risk of 5% and a power of 80%. The blue line is the cumulative *z* score from the cumulative fixed-effects meta-analyses, and each black box indicates the addition of data from a new study; the red lines are the study sequential monitoring boundaries, the upper one being for positive effect and the lower one being for detrimental effects, calculated according to the O'Brien-Fleming spending function and stopping rule. The inner red lines represent 'futility boundaries', which if crossed by the cumulative z-score curve, indicates that the current available evidence from RCTs are inadequate to definitively determine superiority or inferiority of the intervention. Once the futility boundary is crossed, further trials of that intervention are likely to be futile. The red vertical line indicates the diversity-adjusted information size of 4,222 patients based on an *a priori* 75% Peto-odds increase in major bleeding. There is firm evidence at present for a 75% increase in Peto-odds for major bleeds even when the cumulative meta-analysis is adjusted for sparse data and multiple testing on accumulated data, disregarding possible bias. Two-sided graph refers to the fact that two-sided hypothesis testing (for significant superiority, and inferiority in both instances) was performed for an individual outcome (major bleeding) while assessing simultaneously for adequacy of sample size, and adjusting for potential diversity.

eFigure 10. WinBUGS code used for Bayesian Random-Effects Meta-analysis of Mortality with Thrombolytic Use in Pulmonary Embolism

```
# Poisson likelihood, log link
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0               # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            # LOOP THROUGH ARMS
      r[i,k] ~ dpois(theta[i,k])   # Poisson likelihood
      theta[i,k] <- lambda[i,k]*E[i,k] # failure rate * exposure
      log(lambda[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k]))          }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
  }

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}
}

# pairwise HRs and LHRs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
lhr[c,k] <- (d[k]-d[c])
log(hr[c,k]) <- lhr[c,k]
}
}

# ranking on relative scale
for (k in 1:nt) {
rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
# rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}

# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],
# and Relative Risk RR[k], for each treatment, relative to treatment 1
for (k in 2:nt) {
NNT[k] <- 1/(T[k] - T[1]) # assumes events are “good”
# NNT[k] <- 1/(T[1]- T[k]) # assumes events are “bad”
RD[k] <- T[k] - T[1]
RR[k] <- T[k]/T[1]
}
totresdev <- sum(resdev[])           #Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
```

```
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural (rate) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { log(T[k]) <- A + d[k]  }
}                              # *** PROGRAM ENDS

 Data
# ns= number of studies; nt=number of treatments
list(ns=16, nt=2, meanA=-3, precA=1.77)
```

r[,1]	r[,2]	E[,1]	E[,2]	t[,1]	t[,2]	na[]	# Trial	Max Follow-up (Days)	
2	1	20	16	2	1	2	#	Dalla-Volta 1992	30
0	6	37	35	2	1	2	#	Fasullo et al. 2011	180
0	2	46	55	2	1	2	#	Goldhaber 1993	14
0	4	4	4	2	1	2	#	Jerges-Sanchez 1995	
	30								
4	3	118	138	2	1	2	#	Konstantinides 2002	
	30								
1	0	33	25	2	1	2	#	Levine 1990	10
1	2	14	11	2	1	2	#	Ly 1978	10
0	0	20	10	2	1	2	#	Marini 1988	840
1	3	61	60	2	1	2	#	MOPETT 2012	7
12	16	506	499	2	1	2	#	PEITHO 2013	30
1	0	9	4	2	1	2	#	PIOPED 1990	7
0	1	13	17	2	1	2	#	Tibbutt 1974	7
0	1	28	30	2	1	2	#	TIPES 2010	5
1	1	40	43	2	1	2	#	TOPCOAT 2013	3
0	1	30	29	2	1	2	#	ULTIMA 2013	90
6	7	82	78	2	1	2	#	UPETSG 1970	14

END

Initial Values
#chain 1
list(d=c(NA, 0, NA, 0, NA, 0, NA, 0), sd=1, mu=c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0))
#chain 2
list(d=c(NA, -1, NA, -1, NA, -1, NA, -1), sd=4, mu=c(-3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3))
#chain 3
list(d=c(NA, 2, NA, 2, NA, 2, NA, 2), sd=2, mu=c(-3, 5, -1, -3, 7, - -3, 5, -1, -3, 7,
-3, 5, -1, -3, 7, -3, 5, -1, -3, 7, -3))

END