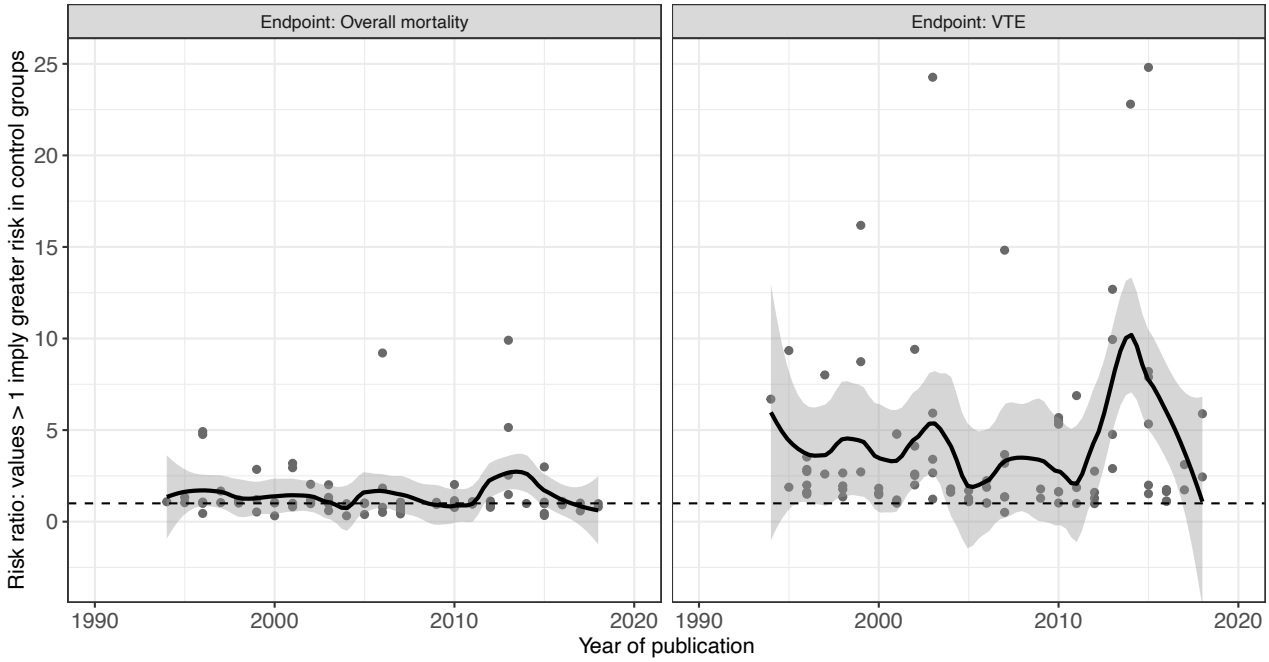
SUPPLEMENTARY APPENDIX

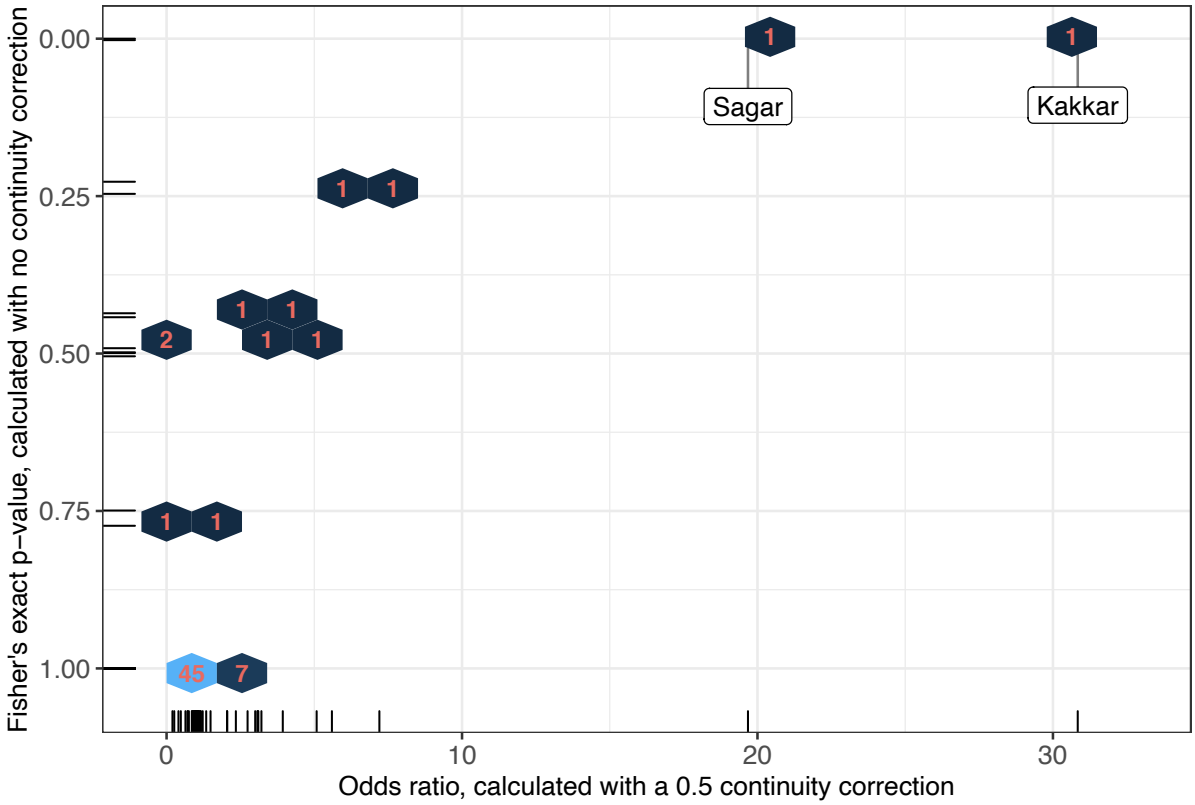
1. RISK RATIOS OF TRIALS (1993–2019) ANALYZED IN KLEMEN *et al.*

FIGURE 1. Risk ratios for overall mortality and venous thromboembolism endpoints were calculated from the original data of 86 prevention trials, with a 0.5 continuity correction, as analyzed by Klemen *et al.*[1] Regression lines are fit by locally weighted least squares,[2] as implemented by `stats::loess` in R version 4.0.2.



2. ODDS RATIOS AND FISHER'S EXACT *p*-VALUES FOR THE 70 TRIALS OF COLLINS *et al.*

FIGURE 2. The meta-analysis presented in Collins *et al*[3] is heavily influenced by two unblinded trials from 1975. We re-analyzed the 70 open-label and placebo-controlled trials listed in Table 2 of that article. Since the Peto one-step method used in the authors' meta-analysis approximates the overall odds ratio we calculated and plotted each trial's odds ratio of the treatment effect of heparin on fatal pulmonary embolism against each trial's two-sided Fisher's exact *p*-value[4] for the same effect, as implemented by `metafor::escalc`[5] and `stats::fisher.test` in `R` version 4.0.2. When calculating these odds ratios, we applied a 0.5 continuity correction to the cells of all trials in order to display every data point. The overall pattern did not appreciably differ when, in the alternative, we applied a 0.5 continuity correction only to table cells with zeroes in them, or when we applied no continuity correction. Hexagons indicate the number of trials in a plot region. The 1975 studies by Sagar *et al*[6] and Kakkar[7] are labeled, as the only two trials for which $p < 0.01$.



3. META-ANALYSIS OF THE 70 TRIALS OF COLLINS *et al.* USING THE PETO ONE-STEP METHOD

TABLE 1. Meta-analysis odds ratios, 95% confidence intervals, and *p*-values for the treatment effects of heparin using the 70 open-label and placebo-controlled trials listed in Table 2 of Collins *et al*.[8] As in Collins *et al*, odds ratio estimates are calculated by the Peto one-step method without a continuity correction: a method of fixed-effects meta-analysis based on 2×2 contingency tables.[9] Here, an odds ratio greater than 1 indicates greater risk of endpoint events in the control arm. Whereas Collins *et al* does not note which software or code the authors used, the statistics below are calculated using `metafor::rma.peto`[10] in `R` version 4.0.2. The column *N* refers to the number of trials supplying usable data for the Peto method. The number of trials is always less than 70, because the Peto method excludes the data of any trials having zero event counts in both treatment and control arms—i.e., "double-zeroes." In addition, any trials with missing endpoint data are dropped. Statistical significance is indicated by * for two-sided $p < 0.01$ and † for two-sided $p < 0.05$. The meta-analysis results of Collins *et al.* for the complete set of 70 trials are approximately replicated, for both endpoints. However, treatment effects on fatal PE and overall mortality endpoints are not statistically significant at the 5% level when the two 1975 trials are excluded. Nor are they statistically significant at the 5% level when only the placebo-controlled trials are analyzed. Identical results are obtained when a 0.5 continuity correction applied to cells with 0 in them.

Endpoint	Trials included	*N*	Odds ratio estimate	95% CI	*p*
Fatal PE	All trials	19	2.7361*	[1.7222, 4.3469]	< 0.0001
	All trials except Kakkar & Sagar *et al.*	17	1.6832	[0.9609, 2.9487]	0.0687
	Only placebo-controlled trials	5	2.1054	[0.8534, 5.1945]	0.1061
Overall mortality	All trials	30	1.2532†	[1.0419, 1.5073]	0.0166
	All trials except Kakkar & Sagar *et al.*	28	1.2032	[0.9288, 1.5585]	0.1613
	Only placebo-controlled trials	12	1.1265	[0.7772, 1.6329]	0.5293

4. META-ANALYSIS OF THE 70 TRIALS OF COLLINS *et al.* USING THE MANTEL-HAENSZEL METHOD

TABLE 2. Meta-analysis odds ratios, 95% confidence intervals, and *p*-values for the treatment effects of heparin using the 70 open-label and placebo-controlled trials analyzed in Collins *et al*.[11] Odds ratio estimates are calculated by the Mantel-Haenszel method without a continuity correction: a method of fixed-effects meta-analysis based on 2×2 contingency tables, which does not suffer the same asymptotic biases of the Peto one-step estimator.[12,13,14] Here, an odds ratio greater than 1 indicates greater risk of endpoint events in the control arm. Statistics below are calculated using `metafor::rma.mh`[15] in `R` version 4.0.2. The column *N* refers to the number of trials supplying usable data. The number of trials is always less than 70, because the method excludes trials with "double-zeroes" or missing endpoint data. Statistical significance is indicated by * for two-sided $p < 0.01$ and † for two-sided $p < 0.05$. As in Table 1 above, the effects on fatal PE and overall mortality endpoints are not statistically significant at the 5% level when the two 1975 trials are excluded. Nor are they statistically significant at the 5% level when only the placebo-controlled trials are analyzed. Identical results are obtained when a 0.5 continuity correction is applied to cells with 0 in them.

Endpoint	Trials included	*N*	Odds ratio estimate	95% CI	*p*
Fatal PE	All trials	19	3.0075*	[1.7694, 5.1118]	< 0.0001
	All trials except Kakkar & Sagar *et al.*	17	1.7081	[0.9560, 3.0519]	0.0706
	Only placebo-controlled trials	5	2.1727	[0.8260, 5.7152]	0.1158
Overall mortality	All trials	30	1.2541†	[1.0417, 1.5098]	0.0168
	All trials except Kakkar & Sagar *et al.*	28	1.2041	[0.9284, 1.5617]	0.1616
	Only placebo-controlled trials	12	1.1262	[0.7770, 1.6323]	0.5303

REFERENCES

1. Klemen ND, Feingold PL, Hashimoto B, *et al*. Mortality risk associated with venous thromboembolism: a systematic review and Bayesian meta-analysis. *Lancet Haematol*. 2020; 7: e58393.

2. Cleveland WS, Grosse E, Shyu WM. Chapter 8: Local regression models. *Statistical models in S*. Eds. Chambers JM, Hastie TJ. Boca Raton: Chapman & Hall/CRC. 1992.

3. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med*. 1988; 318: 116273.

4. Agresti A. *Categorical data analysis*. 2nd edition. New York: Wiley. 2002: 91-101.

5. Viechtbauer W. Conducting meta-analyses in R with the `metafor` package. *J Stat Soft*. 2010; 36(3): 148.

6. Sagar S, Massey J, Sanderson JM. Low-dose heparin prophylaxis against fatal pulmonary embolism. *Br Med J*. 1975; 4: 2579.

7. Kakkar VV. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. An international multicentre trial. *The Lancet*. 1975; 2: 4551.

8. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med*. 1988; 318: 116273.

9. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: An overview of the randomized trials. *Prog in Card Disease*. 1985; 27: 335-371.

10. Viechtbauer W. Conducting meta-analyses in R with the `metafor` package. *J Stat Soft*. 2010; 36(3): 148.

11. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med*. 1988; 318: 116273.

12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Nat Cancer Inst*. 1959; 22: 719-748.

13. Robins J, Breslow N, Greenland S. Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. *Biometrics*. 1986; 42: 311323.

14. Sato, T, Greenland S, Robins JM. On the variance estimator for the Mantel-Haenszel risk difference. *Biometrics*. 1989; 45: 13231324.

15. Viechtbauer W. Conducting meta-analyses in R with the `metafor` package. *J Stat Soft*. 2010; 36(3): 148.