# Supplementary Online Content

Castellucci LA, Cameron C, LeGal G, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2014.10538



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

## Appendix 1. Medline search strategy

Example of MeSH and key word terms used for the systematic search strategy. The search strategy below was used to conduct the MEDLINE review*

| |
|---|
| exp Venous Thrombosis/ |
| exp Venous Thromboembolism/ |
| Deep vein thrombosis.mp. |
| Pulmonary embolism.mp. or exp Pulmonary Embolism/ |
| exp Warfarin/ |
| expAcenocoumarol/ |
| Direct thrombin inhibitor.mp. |
| dabigatran.mp. |
| rivaroxaban.mp. |
| apixaban.mp. |
| directXa inhibitor.mp. |
| Pradax$.mp. |
| xarelto.mp. |
| eliquis.mp. |
| coumadin.mp. |
| expHeparin, low molecular weight/ |
| randomized controlled trial.pt. |
| controlled clinical trial.pt. |
| random allocation.sh. |
| double blind method.sh. |
| single-blind method.sh. |
| ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab. |
| random$.ti,ab. |
| |

*Search completed on February 28th, 2014

**Appendix 2. Summary of data on network geometry for each network**

| | **Recurrent VTE** | **Major Bleeding** |
|---|---|---|
| Total number of studies | 45 | 42 |
| Total number of studies with 2-arms | 43 | 40 |
| Total number of studies with multi-arms | 2 | 2 |
| Total number of patients | 44989 | 44434 |
| Total number of patient-years | 20842 | 20643 |
| Total number of patients who had an event | 1327 | 754 |
| Total number of treatments compared | 8 | 8 |
| Theoretical number of direct comparisons | 28 | 28 |
| Total number of comparisons with no direct comparisons | 19/28(67.9%) | 19/28(67.9%) |
| **Total number of events/patients/patient-years for each treatment** | | |
| LMWH/VKA | 533/20246/9821 | 361/20124/9760 |
| UFH/VKA | 357/7133/2134 | 169/6975/2095 |
| Fondaparinux/VKA | 85/2201/550 | 50/2201/550 |
| LMWH/dabigatran | 60/2553/1277 | 35/2553/1277 |
| LMWH/edoxaban | 66/4118/2814 | 56/4118/2814 |
| Rivaroxaban | 86/4150/2340 | 40/4150/2340 |
| Apixaban | 59/2691/1346 | 15/2691/1346 |
| LMWH alone | 81/1897/561 | 28/1622/463 |
| **Total number of studies for each comparison** | | |
| UFH/VKA vs LMWH/VKA | 22 RCTs | 22 RCTs |
| Fondaparinux/VKA vs LMWH/VKA | 1 RCT | 1 RCT |
| LMWH/dabigatran vs LMWH/VKA | 2 RCTs | 2 RCTs |
| LMWH/edoxaban vs LMWH/VKA | 1 RCT | 1 RCT |
| Rivaroxaban vs LMWH/VKA | 2 RCTs | 2 RCTs |
| Apixaban vs LMWH/VKA | 1 RCT | 1 RCT |
| LMWH alone vs LMWH/VKA | 5 RCTs | 4 RCTs |
| Fondaparinux/VKA vs UFH/VKA | 1 RCT | 1 RCT |
| LMWH/dabigatran vs UFH/VKA | 0 RCTs | 0 RCTs |
| LMWH/edoxaban vs UFH/VKA | 0 RCTs | 0 RCTs |
| Rivaroxaban vs UFH/VKA | 0 RCTs | 0 RCTs |
| Apixaban vs UFH/VKA | 0 RCTs | 0 RCTs |
| LMWH alone vs UFH/VKA | 14 RCTs | 12 RCTs |

| | **Recurrent VTE** | **Major Bleeding** |
|---|---|---|
| **Total number of studies for each comparison** | | |
| LMWH/dabigatran vs Fondaparinux/VKA | 0 RCTs | 0 RCTs |
| LMWH/edoxaban vs Fondaparinux/VKA | 0 RCTs | 0 RCTs |
| Rivaroxaban vs Fondaparinux/VKA | 0 RCTs | 0 RCTs |
| Apixaban vs Fondaparinux/VKA | 0 RCTs | 0 RCTs |
| LMWH alone vs Fondaparinux/VKA | 0 RCTs | 0 RCTs |
| LMWH/edoxaban vs LMWH/dabigatran | 0 RCTs | 0 RCTs |
| Rivaroxaban vs LMWH/dabigatran | 0 RCTs | 0 RCTs |
| Apixaban vs LMWH/dabigatran | 0 RCTs | 0 RCTs |
| LMWH alone vs LMWH/dabigatran | 0 RCTs | 0 RCTs |
| Rivaroxaban vs LMWH/edoxaban | 0 RCTs | 0 RCTs |
| Apixaban vs LMWH/edoxaban | 0 RCTs | 0 RCTs |
| LMWH alone vs LMWH/edoxaban | 0 RCTs | 0 RCTs |
| Apixaban vs Rivaroxaban | 0 RCTs | 0 RCTs |
| LMWH alone vs Rivaroxaban | 0 RCTs | 0 RCTs |
| LMWH alone vs Apixaban | 0 RCTs | 0 RCTs |

LMWH = low molecular weight heparin; RCT= randomized controlled trial; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.

| **Appendix 3. Study quality** | | | | | | |
|---|---|---|---|---|---|---|
| Study, Year (reference) | Adequate Sequence Generation | Allocation Concealment | Blinding | Incomplete Outcome Data Addressed | Free of Selective Outcome Reporting | Free of Other Bias |
| Collaborative European Study, 1991[1] | Unclear | Unclear | No | Yes | Yes | Yes |
| Hull et al, 1992[2] | Yes | Yes | Yes | Yes | Yes | Yes |
| Lopaciuk et al, 1992[3] | Yes | Yes | No | Yes | Yes | Yes |
| Prandoni et al, 1992[4] | Yes | Unclear | No | Yes | Yes | Yes |
| Simonneau et al, 1993[5] | Yes | Yes | No | Unclear | Yes | Yes |
| Fiessinger et al, 1996[6] | Unclear | Unclear | No | Yes | Yes | Yes |
| Koopman et al, 1996[7] | Unclear | Yes | No | Unclear | Yes | Yes |
| Levine et al, 1996[8] | Yes | Yes | No | Yes | Yes | Yes |
| Kirchmaier et al. 1998[9] | Unclear | Yes | No | Yes | Yes | Yes |
| Harenberg et al, 2000[10] | Unclear | Unclear | No | Yes | Yes | Yes |
| Breddin et al, 2001[11] | Unclear | Unclear | No | Yes | Yes | Yes |
| Kakkar et al, 2003[12] | Unclear | Yes | No | Yes | Yes | Yes |
| Riess et al, 2003[13] | Yes | Yes | No | Yes | Yes | Yes |
| Meyer et al, 1995[14] | Unclear | Unclear | No | Yes | Yes | Yes |
| Simonneau et al, 1997[15] | Yes | Yes | No | Unclear | Yes | Yes |
| Findik et al, 2002[16] | Unclear | Unclear | No | Yes | Yes | Yes |
| Columbus Investigators, 1997[17] | Yes | Yes | No | Yes | Yes | Yes |
| Hull et al, 2000[18] | Yes | Yes | Yes | Yes | Yes | Yes |
| Merli et al, 2001[19] | Yes | Yes | No | Yes | Yes | Yes |
| Prandoni et al, 2004[20] | Yes | Yes | No | Yes | Yes | Yes |
| Kearon et al, 2006[21] | Yes | Yes | No | Yes | Yes | Yes |
| Leizorovicz et al, 2011[22] | Yes | Yes | No | Yes | Yes | Yes |
| Bratt et al, 1990[23] | Unclear | Unclear | No | Unclear | Unclear | Yes |
| Lindmarker et al, 1994[24] | Unclear | Yes | No | Unclear | Yes | Yes |
| Pini et al, 1994[25] | Yes | Yes | No | Yes | Yes | Yes |
| Das et al, 1996[26] | Yes | Yes | No | Yes | Yes | Yes |
| Belcaro et al, 1999[27] | Unclear | Unclear | No | No | Yes | Yes |
| Gonzalez-Fajardo et al, 1999[28] | Yes | Unclear | No | Yes | Yes | Yes |
| Lopaciuk et al, 1999[29] | Unclear | Yes | No | Yes | Yes | Yes |
| Veiga et al, 2000[30] | Unclear | Yes | No | Yes | Yes | Yes |
| Ramacciotti et al, 2004[31] | Yes | No | No | Yes | Yes | Yes |
| Chong et al, 2005[32] | Unclear | Unclear | No | Yes | Yes | Yes |
| Daskalopoulos et al, 2005[33] | Yes | Yes | No | Yes | Yes | Yes |
| Romera et al, 2009[34] | Yes | Yes | No | Yes | Yes | Yes |
| Beckman et al, 2003[35] | Unclear | Unclear | No | Yes | Yes | Yes |
| Perez de Llano et al, 2003[36] | Unclear | Unclear | No | Yes | Yes | Yes |
| Hull et al, 2007[37] | Yes | Yes | No | Yes | Yes | Yes |

| | | | | | | |
|---|---|---|---|---|---|---|
| Buller et al, 2004[38] | Yes | Yes | Yes | Yes | Yes | Yes |
| Buller et al, 2003[39] | Yes | Yes | No | Yes | Yes | Yes |
| Bauersachs et al, 2010[40] | Yes | Yes | No | Yes | Yes | Yes |
| Buller et al, 2012[41] | Yes | Yes | No | Yes | Yes | Yes |

| Study, Year (reference) | Adequate Sequence Generation | Allocation Concealment | Blinding | Incomplete Outcome Data Addressed | Free of Selective Outcome Reporting | Free of Other Bias |
|---|---|---|---|---|---|---|
| Schulman et al, 2009[42] | Yes | Yes | Yes | Yes | Yes | Yes |
| Schulman et al, 2014[43] | Yes | Yes | Yes | Yes | Yes | Yes |
| Buller et al, 2013[44] | Yes | Yes | Yes | Yes | Yes | Yes |
| Agnelli et al, 2013[45] | Yes | Yes | Yes | Yes | Yes | Yes |

## Appendix 4. Probability best therapy

We assessed the probability that each treatment was the most efficacious for each outcome by calculating the hazard ratio for each drug compared with LMWH/VKA, and counting the proportion of iterations in which each drug had the most favorable hazard ratio compared with LMWH/VKA.

### eTable 4a. Probability of best therapy (%)

| Treatment | Recurrence of VTE | Major Bleeding |
|---|---|---|
| LMWH/VKA | 0.3% | 0.0% |
| UFH/VKA | 0.0% | 0.0% |
| Fondaparinux/VKA | 6.6% | 0.1% |
| LMWH/dabigatran | 5.1% | 1.0% |
| LMWH/edoxaban | 33.1% | 0.5% |
| Rivaroxaban | 16.5% | 7.4% |
| Apixaban | 31.6% | 88.9% |
| LMWH alone | 6.7% | 2.2% |

LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.

A simple numerical summary of these probabilities – the surface under the cumulative ranking (SUCRA) was calculated. The SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. SUCRA values enable the ranking of treatments overall for a particular outcome. For example, for recurrent VTE the SUCRA value for LMWH/edoxaban is 72.5%, which is better than other treatments. By contrast, UFH/VKA has a SUCRA of 5.1% for recurrent VTE meaning it is more certain to be worst for this outcome.

### eTable 4b. Surface under the cumulative ranking values (%)

| Treatment | Recurrence of VTE | Major Bleeding |
|---|---|---|
| LMWH/VKA | 48.7% | 27.8% |
| UFH/VKA | 5.1% | 9.5% |
| Fondaparinux/VKA | 48.6% | 23.2% |
| LMWH/dabigatran | 37.0% | 55.7% |
| LMWH/edoxaban | 72.5% | 45.9% |
| Rivaroxaban | 64.5% | 78.6% |
| Apixaban | 71.2% | 97.7% |
| LMWH alone | 52.5% | 61.7% |

LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.

## Appendix 5. Proportion of patients experiencing outcomes events

We report the proportion of patients expected to have a recurrent VTE or major bleeding event while using each treatment for a period of 3 and 6 months. These values were calculated, assuming a rate of 5.3 per 100 patient-years (~2.6% over 6 months) and 3.6 events per 100 patient-years (~1.8% over 6 months) for recurrent VTE and major bleeding, respectively, in the LMWH/VKA arm of the Amplify trial.[45;46] The hazard ratios were then applied to this log-rate.[47] Using this value, we calculate the difference in the proportion of patients expected to have an event relative to LMWH/VKA and number needed to treat to benefit (or harm).

## eTable 5a. Recurrent VTE

| Treatment | Proportion of patients expected to have recurrent VTE (95% CrI) | Difference in proportion of patients expected to have recurrent VTE relative to LMWH/VKA (95% CrI)* | NNTB(NNTH) relative to LMWH/VKA |
|---|---|---|---|
| **At 3 months** | | | |
| LMWH/VKA | 1.3% (1.02%, 1.62%) | Reference | Reference |
| UFH/VKA | 1.84% (1.33%, 2.51%) | **0.53% (0.19%, 1.04%)** | **(188)** |
| Fondaparinux/VKA | 1.31% (0.79%, 2.18%) | 0.01% (-0.47%, 0.79%) | (14071) |
| LMWH/dabigatran | 1.44% (0.82%, 2.43%) | 0.14% (-0.44%, 1.04%) | (733) |
| LMWH/edoxaban | 1.07% (0.57%, 1.99%) | -0.22% (-0.73%, 0.63%) | 447 |
| Rivaroxaban | 1.16% (0.7%, 1.91%) | -0.13% (-0.57%, 0.53%) | 756 |
| Apixaban | 1.08% (0.62%, 1.87%) | -0.22% (-0.78%, 0.6%) | 460 |
| LMWH alone | 1.28% (0.83%, 1.95%) | -0.02% (-0.41%, 0.54%) | 5247 |
| **At 6 months** | | | |
| LMWH/VKA | 2.58% (2.03%, 3.22%) | Reference | Reference |
| UFH/VKA | 3.64% (2.64%, 4.96%) | **1.05% (0.37%, 2.05%)** | **(95)** |
| Fondaparinux/VKA | 2.59% (1.57%, 4.32%) | 0.01% (-0.93%, 1.56%) | (7117) |
| LMWH/dabigatran | 2.85% (1.62%, 4.8%) | 0.27% (-0.87% ,2.03%) | (372) |
| LMWH/edoxaban | 2.13% (1.14%, 3.95%) | -0.44% (-1.44%, 1.23%) | 226 |
| Rivaroxaban | 2.31% (1.39%, 3.79%) | -0.26% (-1.14%, 1.03%) | 383 |
| Apixaban | 2.15% (1.23%, 3.7%) | -0.43% (-1.54%, 1.19%) | 233 |

| | | | |
|---|---|---|---|
| LMWH alone | 2.54% (1.66%, 3.86%) | -0.04% (-0.81%, 1.06%) | 2658 |

CrI= credible interval; LMWH = low molecular weight heparin; NNTB = number need to treat to benefit; NNTH = number need to treat to harm; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism
*A minus sign (-) indicates that a lower proportion of patients is expected to have an event.

Bold type font indicates significant values.

## eTable 5b. Major Bleeding

| Treatment | Proportion of patients expected to have a major bleeding event (95% CrI) | Difference in proportion of patients expected to have a major bleeding event relative to LMWH/VKA (95% CrI)* | NNTB(NNTH) relative to LMWH/VKA |
|---|---|---|---|
| **At 3 months** | | | |
| LMWH/VKA | 0.89% (0.66%, 1.16%) | Reference | Reference |
| UFH/VKA | 1.05% (0.69%, 1.56%) | 0.16% (-0.09%, 0.53%) | (609) |
| Fondaparinux/VKA | 0.94% (0.54%, 1.64%) | 0.06% (-0.32%, 0.64%) | (1779) |
| LMWH/dabigatran | 0.66% (0.37%, 1.2%) | -0.22% (-0.51%, 0.23%) | 453 |
| LMWH/edoxaban | 0.75% (0.42%, 1.32%) | -0.14% (-0.45%, 0.35%) | 732 |
| Rivaroxaban | 0.49% (0.29%, 0.85%) | **-0.39% (-0.63%, -0.1%)** | **258** |
| Apixaban | 0.28% (0.14%, 0.5%) | **-0.6% (-0.92%, -0.28%)** | **165** |
| LMWH alone | 0.63% (0.34%, 1.16%) | -0.25% (-0.55%, 0.27%) | 398 |
| **At 6 months** | | | |
| LMWH/VKA | 1.77% (1.32%, 2.31%) | Reference | Reference |
| UFH/VKA | 2.09% (1.37%, 3.09%) | 0.33% (-0.18%, 1.05%) | (307) |
| Fondaparinux/VKA | 1.87% (1.07%, 3.26%) | 0.11% (-0.63%, 1.27%) | (898) |
| LMWH/dabigatran | 1.32% (0.74%, 2.39%) | -0.44% (-1.02%, 0.45%) | 228 |
| LMWH/edoxaban | 1.49% (0.84%, 2.63%) | -0.27% (-0.9%, 0.69%) | 369 |
| Rivaroxaban | 0.98% (0.57%, 1.7%) | **-0.77% (-1.26%, -0.2%)** | **130** |
| Apixaban | 0.56% (0.29%, 0.99%) | **-1.2% (-1.82%, -0.56%)** | **83** |
| LMWH alone | 1.26% (0.67%, 2.3%) | -0.5% (-1.1%, 0.52%) | 200 |

CrI = credible interval; LMWH = low molecular weight heparin; NNTB = number need to treat to benefit; NNTH = number need to treat to harm; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism
*A minus sign (-) indicates that a lower proportion of patients is expected to have an event.

Bold type font indicates significant values.

## Appendix 6. Comparison of random-effects bayesian network meta-analysis with direct frequentist meta-analysis estimate for recurrent VTE

The effect estimates from the Bayesian network meta-analysis aligned closely with frequentist pair-wise meta-analyses. There was some heterogeneity within individual comparisons using direct frequentist meta-analysis, particularly for rivaroxaban ($I^2$=61%). However, the heterogeneity can be explained by the use of different index events among included studies. There were two rivaroxaban studies and each used a different index event (index DVT and index PE[40;41]). We stratified recurrent VTE analyses by index event in Figure 3 (main manuscript) to account for this heterogeneity.

| Treatment | NMA, Recurrent VTE HR (95% CrI) vs LMWH/VKA | | Direct estimates, Recurrent VTE Rate ratio (95% CI) vs LMWH/VKA |
|---|---|---|---|
| UFH/VKA | **1.42 (1.15, 1.80)** | | **1.40 (1.12, 1.77); $I^2$=13%** |
| Fondaparinux/VKA | 1.01 (0.65, 1.62) | | 0.96 (0.63, 1.46); $I^2$=NA |
| LMWH/dabigatran | 1.11 (0.67, 1.8) | | 1.09 (0.76, 1.57); $I^2$=0% |
| LMWH/edoxaban | 0.83 (0.46, 1.49) | | 0.83 (0.60, 1.14); $I^2$=NA |
| Rivaroxaban | 0.9 (0.57, 1.41) | | 0.90 (0.56, 1.44); $I^2$=61% |
| Apixaban | 0.84 (0.46, 1.51) | | 0.84 (0.59, 1.18); $I^2$=NA |
| LMWH alone | 0.99 (0.7, 1.42) | | 0.84 (0.41, 1.74); $I^2$=30% |

CI = confidence interval; CrI = Credible Interval; HR = hazard ratio; LMWH = low molecular weight heparin; NA = not assessable; NMA = network meta-analysis; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

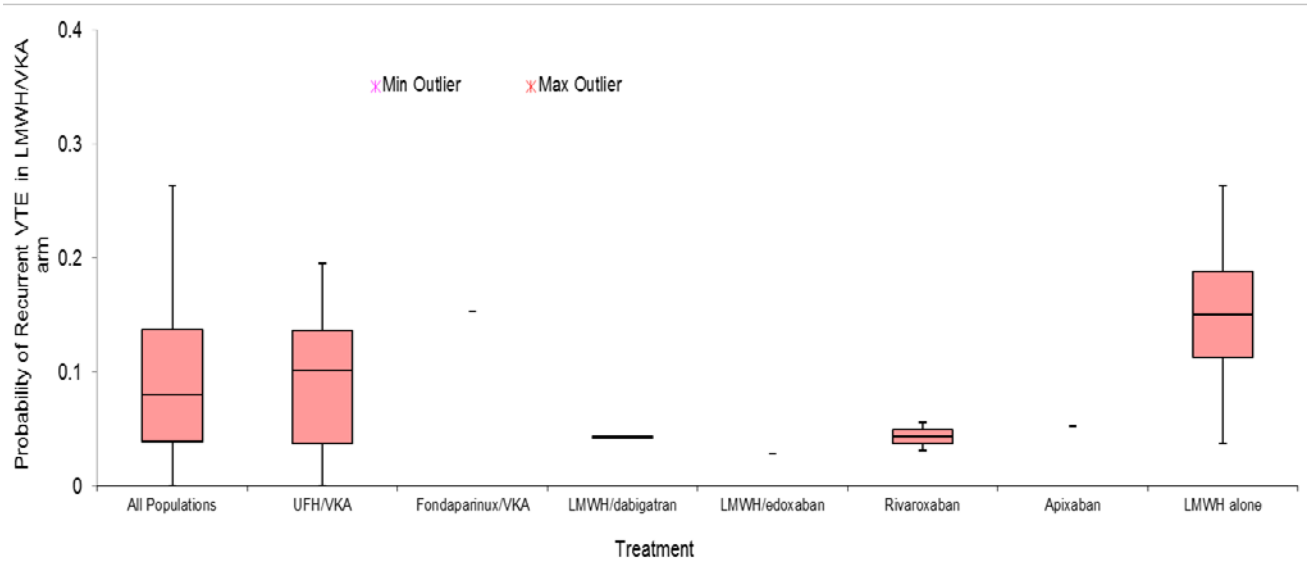
Bold type font indicates significant values.

## Appendix 7. Sensitivity analysis for duration of study

We present box plots to illustrate the rationale for the sensitivity analyses undertaken to investigate the impact of study duration. The bottom and top of the box in each box plot are the first (Q1) and third (Q3) quartiles, and the band inside the box is the median value. The ends of the whisker are set at 1.5*interquartile range (IQR) above the third quartile (Q3) and 1.5*IQR below the first quartile (Q1), where IQR = Q3 − Q1. If the minimum or maximum values are outside this range, then they are shown as outliers. The small dashes indicate one point is available (Fondaparinux/VKA, LMWH/edoxaban, apixaban) while a long bar indicates two studies with very similar findings (LMWH/dabigatran) and the IQR is not visible unless you zoom in (narrow box plot).

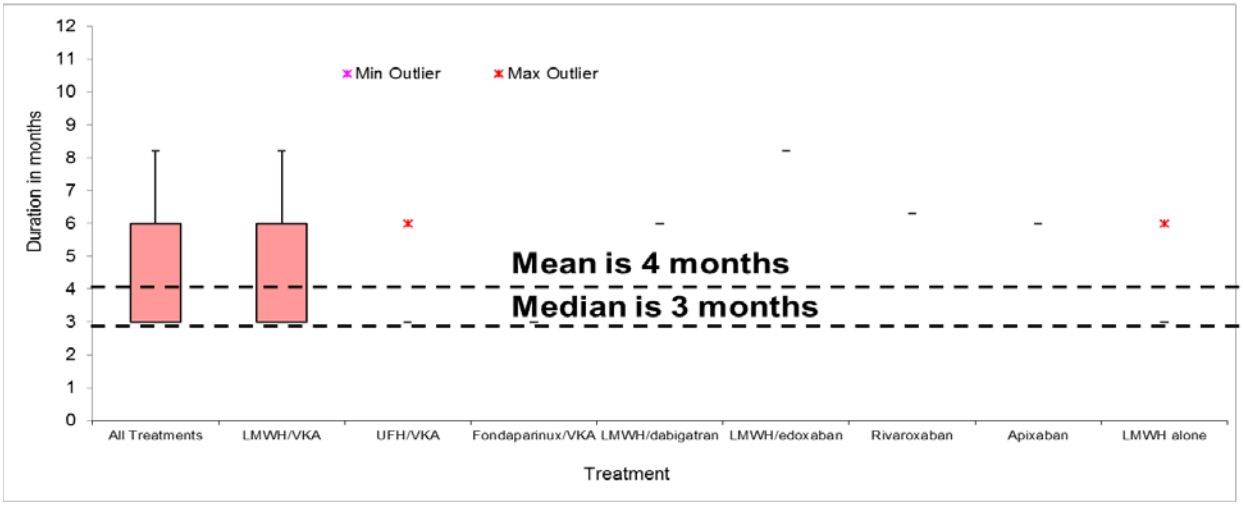
The probability of recurrent VTE is higher in the LMWH/VKA arm of patients using UFH/VKA, Fondaparinux/VKA, and LMWH alone. Probabilities are calculated using the formulas defined by Fluerence et al to convert between probabilities and rates over different time points.[46] This appears partly attributable to the variation in treatment duration, although it is also attributable to combining of index PE and index DVT outcomes in the box plot (which has been stratified in Table 2 and Figure 3 of the manuscript).

### eFigure 7a. Box plot comparing treatments in terms of probability of recurrent VTE in LMWH/VKA arm



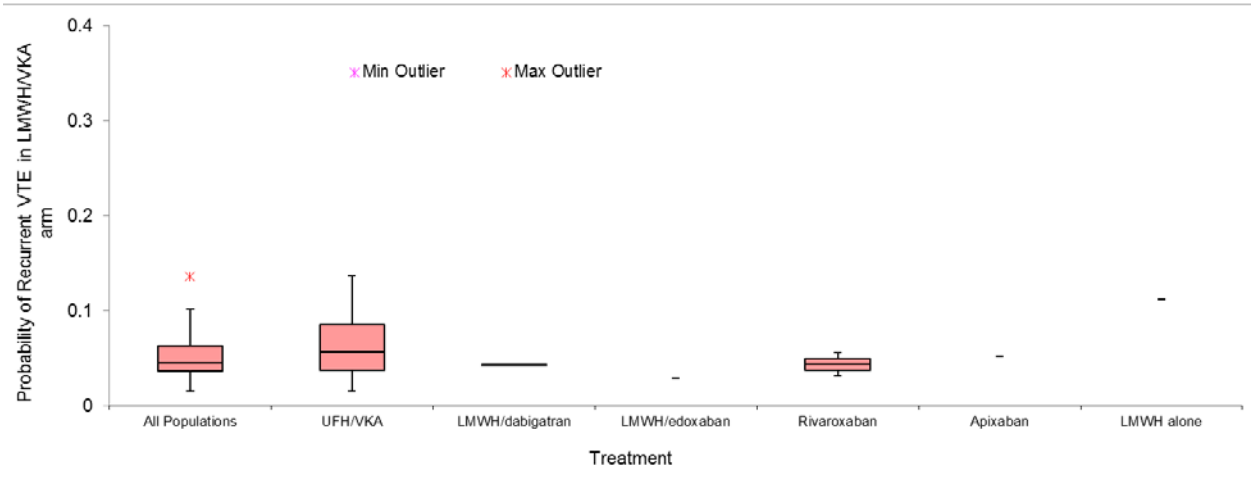

In general, the studies including direct oral anticoagulants were longer in duration than those for UFH/VKA, Fondaparinux/VKA, LMWH alone (eFigure 7b) resulting in potential variations in the probability of recurrent VTE in the LMWH/VKA arms.

## eFigure 7b. Box plot comparing treatments in terms of study treatment duration




We ran the reference case analyses using a Poisson likelihood model. However, we also conducted a sub-group analysis which investigated whether duration of treatment may have impacted results. For this analysis, we restricted studies to those that were 6 months in treatment duration or longer. This resulted in a smaller network (14 studies with 17,053 patient-years of follow-up versus 45 studies with 20,842 patient-years of follow-up). Fondaparinux/VKA was also removed from the network given all studies involving this treatment were less than 6 months in duration. Restriction of the network to studies 6 months in treatment duration or longer resulted in more homogeneous estimates of the probability of recurrent VTE in the LMWH/VKA arm compared to the reference case network (eFigure 7c versus eFigure 7a).

## eFigure 7c. Box plot comparing treatments in terms of probability of recurrent VTE in LMWH/VKA arm when restricted to trials with at least 6 months of treatment




The results for the sub-group analysis yielded similar results to the primary analysis, with the exception being that the UFH/VKA effect estimate is slightly higher in the sub-group analysis (1.88 vs 1.42) and LMWH alone is slightly lower (0.79 vs 0.99). These do not change statistical significance from the primary

analysis. The relative ordering of the SUCRAs are also similar to the primary analysis. SUCRA values enable the ranking of treatments overall for a particular outcome. The SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst.

## eTable 7. Comparison of results from primary analysis and sub-group analysis for study treatment duration

| Treatment | Primary Analysis | | Sub-group Analysis | |
|---|---|---|---|---|
| | Recurrent VTE HR (95% CrI) vs LMWH/VKA | SUCRA | Recurrent VTE HR (95% CrI) vs LMWH/VKA | SUCRA |
| LMWH/VKA | Reference | 48.7% | Reference | 45.7% |
| UFH/VKA | **1.42 (1.15, 1.80)** | 5.1% | **1.88 (1.13, 3.38)** | 3.2% |
| Fondaparinux/VKA | 1.01 (0.65, 1.62) | 48.6% | NA | NA |
| LMWH/dabigatran | 1.11 (0.67, 1.8) | 37.0% | 1.09 (0.60, 2.0) | 38.1% |
| LMWH/edoxaban | 0.83 (0.46, 1.49) | 72.5% | 0.83 (0.38, 1.77) | 67.3% |
| Rivaroxaban | 0.9 (0.57, 1.41) | 64.5% | 0.9 (0.50, 1.57) | 60.0% |
| Apixaban | 0.84 (0.46, 1.51) | 71.2% | 0.83 (0.38, 1.81) | 66.7% |
| LMWH alone | 0.99 (0.7, 1.42) | 52.5% | 0.79 (0.34, 1.83) | 69.0% |

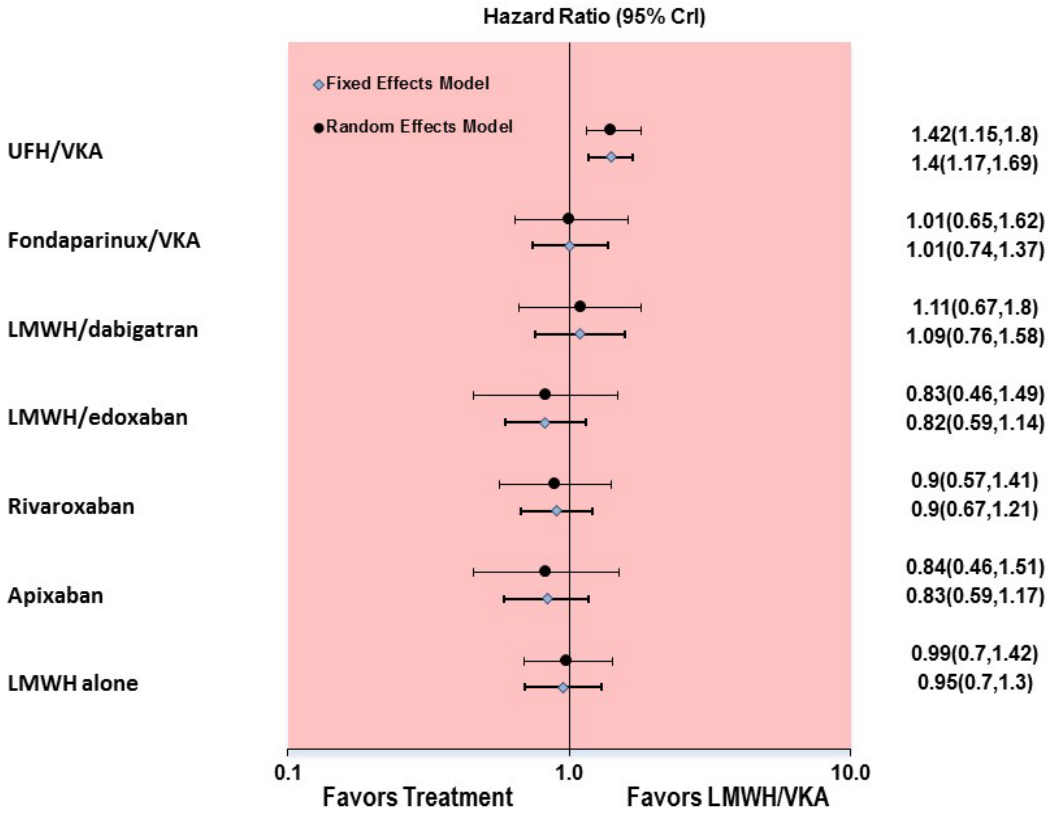
CrI = credible intervals; HR= hazard ratio; LMWH = low molecular weight heparin; NA = not available; SUCRA = Surface under the cumulative ranking curve; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Bold type font indicates significant values.

## Appendix 8. Summary of analyses to support choice of model for network meta-analyses

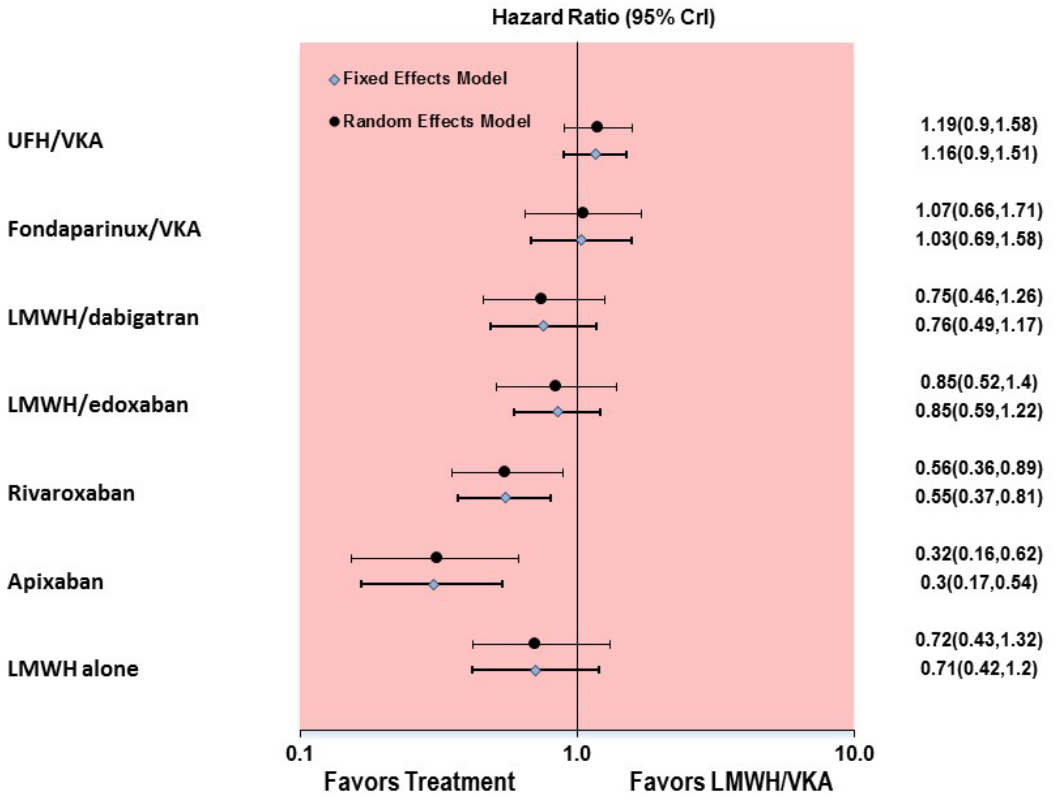
We considered a random-effects model with a vague prior and a fixed-effects model for recurrent VTE. The random-effects model was chosen because it has a lower total residual deviance (107 vs 113.1 each vs. 92 data points) and DIC (504.1 vs 503.7) and hence is a better fit to the data, although they are very similar for both models. The between study standard deviation for the random-effects model is 0.202. The total residual deviance for both random- and fixed-effects models was higher than the number of unconstrained data points (107 vs 113.1 each vs. 92 data points); however, this was largely driven by inclusion of 4 studies – Hull et al.[18], Lopaciuk et al.[3], Lindmarker et al.[24], and Leizorovicz et al.[22] (See Appendix 10). Removal of these 4 studies from the analyses improved fit but did not alter findings substantially (See Appendix 10).

### eFigure 8a. Recurrent VTE. Comparison of fixed- and random-effects models for each treatment versus LMWH/VKA




We considered a random-effects model and a fixed-effects model for major bleeding. The random-effects model was chosen because it has a lower residual deviance (71.2 vs 71.4 each vs 86 data points) and similar DIC (370.3 vs 368.3), although they are very similar for both models. The between study standard deviation for the random-effects model for major bleeding was 0.139. The total residual deviance for both random- and fixed-effects models was higher than the number of unconstrained data points (71.2 vs 71.4 each vs 86 data points) indicating good model fit; however, the some of the fit is driven by inclusion of 5 studies with multiple zero event cells.

## eFigure 8b. Major bleeding. Comparison of Fixed- and Random-Effects models for each treatment versus LMWH/VKA

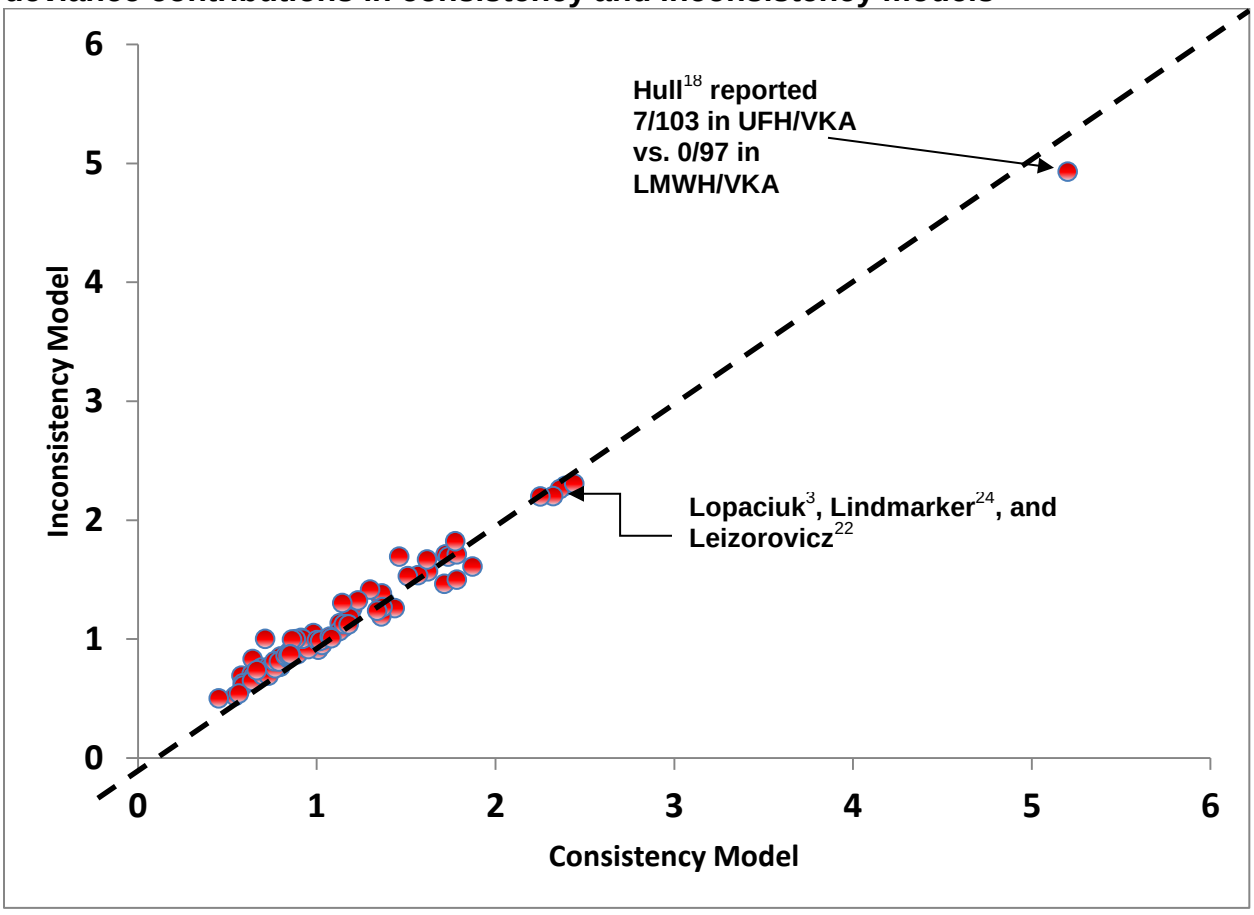



The model fit statistics for the major bleeding analysis seemed to be better than the recurrent VTE analysis. The between study standard deviation was lower (0.139 vs 0.202) and the total residual deviance was closer to the number of unconstrained data points (even if we exclude the double/multiple zero cells). Accordingly, we conducted numerous sensitivity analyses related to recurrent VTE. In particular, we conducted an analysis where we stratify by index PE/DVT (Figure 3 and Table 2 of manuscript). We also conducted an analysis where we only considered studies 6 months or longer treatment duration (Appendix 7) and another analysis removing studies that did not fit the model well (Appendix 10). The results for the latter 2 analyses did not alter findings substantially, while there were some differences when results were stratified by index event.

## Appendix 9. Assessment of inconsistency.

We plotted the posterior mean deviance of the individual data points (each arm) in the inconsistency model against their posterior mean deviance in the consistency model to help identify loops where inconsistency is present. In our analysis, the posterior mean deviance contributions are very similar and close to 1, for both models. The consistency model has a similar total residual deviance of the residual deviance (107 vs 106.3 each versus 92 data points) and DIC (504.1 vs 506.3). However, the between study standard deviation was lower for the consistency model (0.202 vs 0.250), and hence the consistency model appears to fit the data slightly better. The parameter estimates are also similar for both models and there is considerable overlap in the 95% credible intervals (see table below) suggesting no evidence of inconsistency in the network, although this should be interpreted with caution as there may not be sufficient power to detect inconsistency.

### eFigure 9. Plot of individual data points (each arm), posterior mean deviance contributions in consistency and inconsistency models




LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist

## eTable 9. Comparison of hazard ratios (95% CrI) from consistency and inconsistency models

| Treatment Comparison | Consistency Model | Inconsistency Model |
|---|---|---|
| UFH/VKA vs LMWH/VKA | **1.42 (1.15,1.80)** | **1.47 1.16,1.91)** |
| Fondaparinux/VKA vs LMWH/VKA | 1.01 (0.65,1.62) | 0.96 (0.47,1.98) |
| LMWH/dabigatran vs LMWH/VKA | 1.11 (0.67,1.8) | 1.1 (0.63,1.9) |
| LMWH/edoxaban vs LMWH/VKA | 0.83 (0.46,1.49) | 0.82 (0.42,1.62) |
| Rivaroxaban vs LMWH/VKA | 0.9 (0.57,1.41) | 0.9 (0.54,1.49) |
| Apixaban vs LMWH/VKA | 0.84 (0.46,1.51) | 0.84 (0.42,1.65) |
| LMWH alone vs LMWH/VKA | 0.99 (0.7,1.42) | 0.86 (0.46,1.53) |
| Fondaparinux/VKA vs UFH/VKA | 0.71 (0.45,1.12) | 0.76 (0.37,1.52) |
| LMWH alone vs UFH/VKA | 0.7 (0.5,0.95) | 0.75 (0.49,1.15) |
| Residual deviance | 107 vs 92 | 106.3 vs 92 |
| DIC | 504.1 | 506.3 |
| Between-study standard deviation | 0.202 | 0.250 |

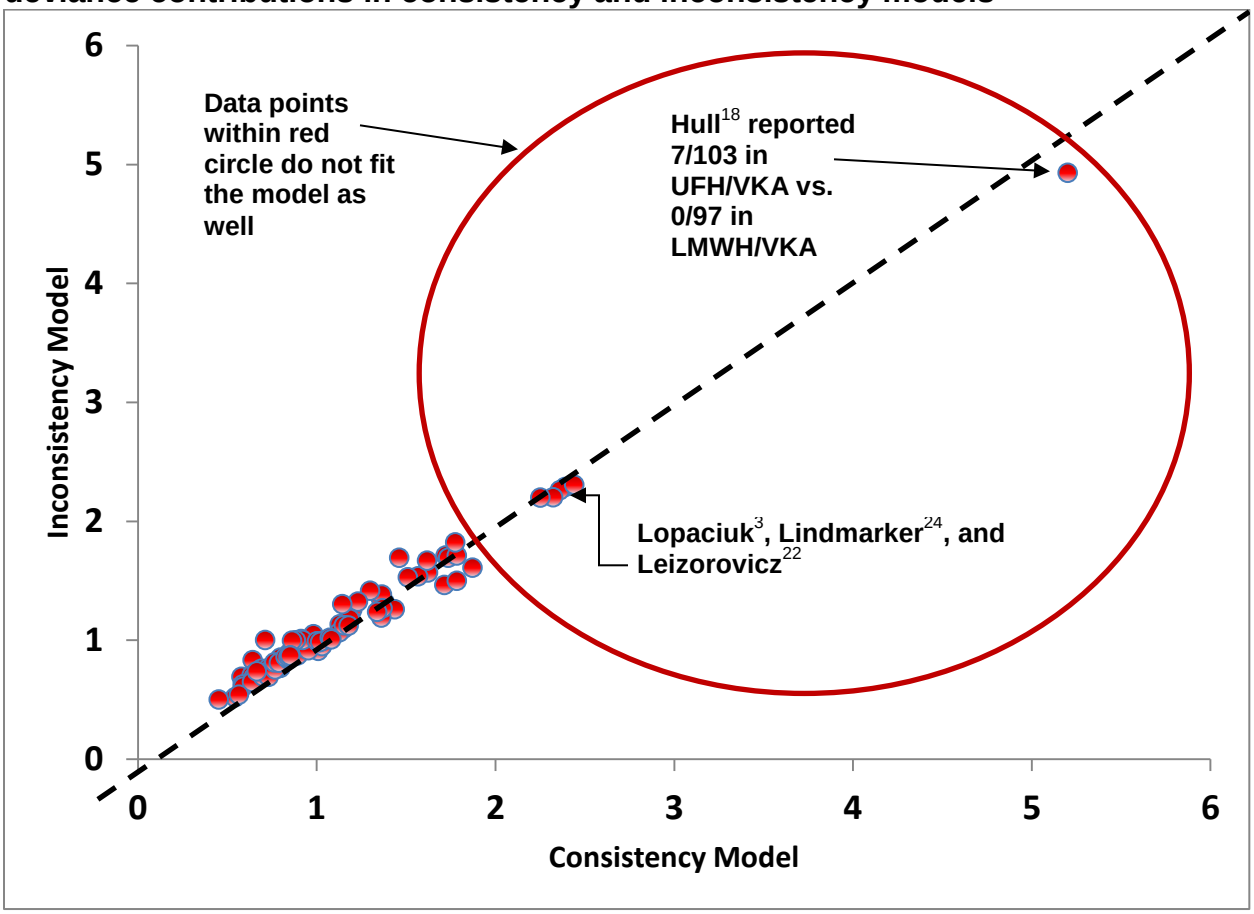
CrI = credible interval; LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Bold type font indicates significant values.

## Appendix 10. Exclusion of studies contributing to poor fit for recurrent VTE network meta-analysis

The total residual deviance for both random-effects models was higher than the number of unconstrained data points (107 vs 92 data points); however, this was largely driven by inclusion 4 studies – Hull et al.[18], Lopaciuk et al.[3], Lindmarker et al.[24], and Leizorovicz et al.[22]

### eFigure 10. Plot of individual data points (each arm), posterior mean deviance contributions in consistency and inconsistency models




Exclusion of these 4 studies improved model fit. The between study standard deviation decreased (15.00 vs. 20.02) and the total residual deviance is closer to the number of unconstrained data points (88.22 vs 84 vs 113.1 vs 92). However, the findings did not change substantially. Despite this improvement in model fit, these 4 studies remained in the primary analysis for analytic completeness and because it did not alter findings/conclusions.

**eTable 10. Comparison of results for recurrent VTE from primary analysis and sub-group analysis based on study duration.**

| Treatment | Primary Analysis | | Sensitivity analysis removing 4 studies with poor fit to the model | |
|---|---|---|---|---|
| | Recurrent VTE HR (95% CrI) vs LMWH/VKA | SUCRA | Recurrent VTE HR (95% CrI) vs LMWH/VKA | SUCRA |
| LMWH/VKA | Reference | 48.7% | Reference | 48.6% |
| UFH/VKA | **1.42 (1.15,1.80)** | 5.1% | **1.43 (1.15,1.73)** | 4.2% |
| Fondaparinux/VKA | 1.01 (0.65,1.62) | 48.6% | 1.04 (0.68,1.63) | 44.6% |
| LMWH/dabigatran | 1.11 (0.67,1.8) | 37.0% | 1.12 (0.69,1.72) | 36.3% |
| LMWH/edoxaban | 0.83 (0.46,1.49) | 72.5% | 0.81 (0.5,1.37) | 75.7% |
| Rivaroxaban | 0.9 (0.57,1.41) | 64.5% | 0.92 (0.61,1.33) | 63.1% |
| Apixaban | 0.84 (0.46,1.51) | 71.2% | 0.84 (0.5,1.4) | 72.8% |
| LMWH alone | 0.99 (0.7,1.42) | 52.5% | 0.96 (0.67,1.46) | 54.9% |
| Total residual deviance versus number of unconstrained data points | 113.1 vs 92 | | 88.22 vs 84 | |
| DIC | 504.1 | | 463.1 | |
| Between study standard deviation | 0.202 | | 0.150 | |

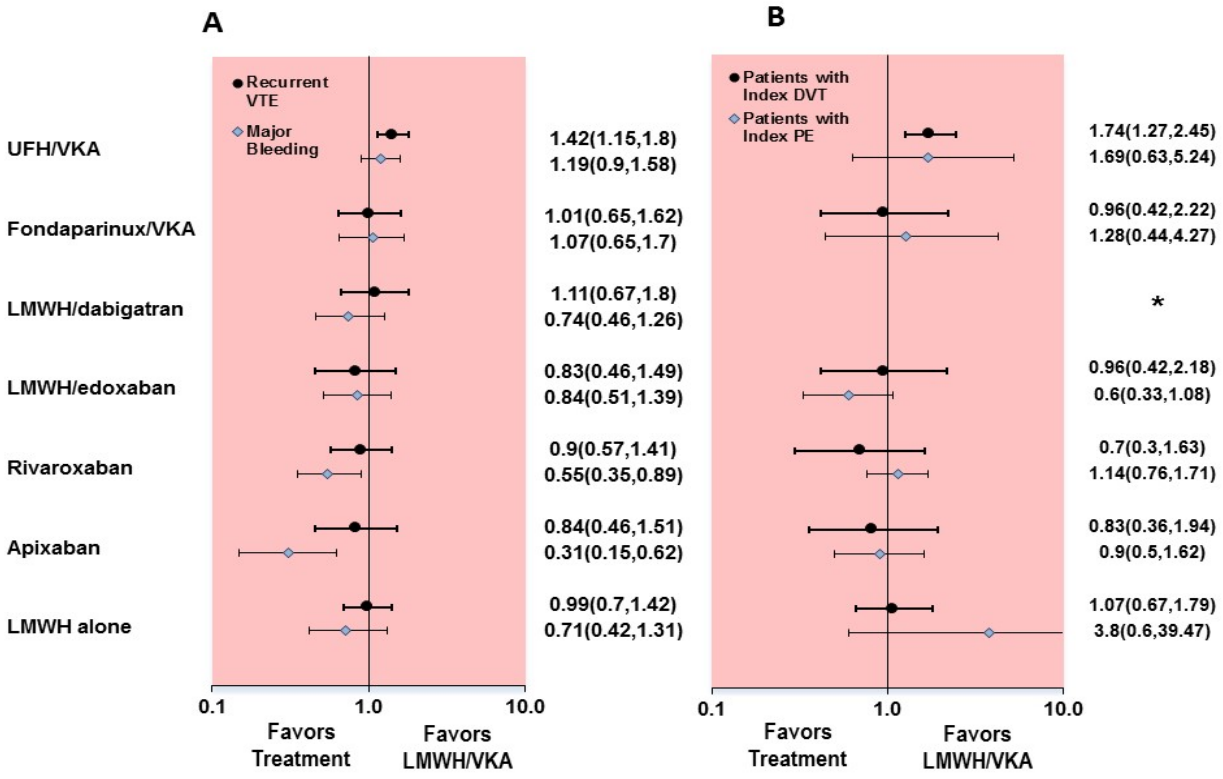
CrI = credible intervals; HR= hazard ratio; LMWH = low molecular weight heparin; SUCRA. Surface under the cumulative ranking curve; UFH = unfractionated heparin; VKA = vitamin K antagonist

Bold type font indicates significant values.

## Appendix 11. Summary of network meta-analysis odds ratios using a binomial likelihood model – random-effects model with informative priors

We conducted an analysis using a binomial likelihood model which accounts for multi-arm trials. The primary analysis using this model was a random-effects model with informative priors.[48;49] The findings for the odds ratios from the binomial likelihood model aligned closely with hazard ratios from the Poisson likelihood model used in the primary analysis.

## eFigure 11. Summary of network meta-analysis odds ratios (95% CrI) using a binomial likelihood model (compared to LMWH/VKA)




* Data not stratified by Index DVT/PE
CrI = credible interval; DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

## Reference Section


(1) Duroux P, Beclere A. A randomised trial of subcutaneous low molecular weight heparin (CY216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. A Collaborative European Multicentre Study. *Thromb Haemost* 1991;65(3):251-256.

(2) Hull RD, Raskob GE, Pineo GF et al. Subcutaneous low-molecular-weight Heparin compared with continuous intravenous Heparin in the treatment of proximal vein thrombosis. *N Engl J Med* 1992;326(15):975-982.

(3) Lopaciuk S, Meissner AJ, Filipecki S et al. Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: a Polish multicenter trial. *Thromb Haemost* 1992;68(1):14-18.

(4) Prandoni P, Lensing AWA, Buller HR et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. *Lancet* 1992;339(8791):441-445.

(5) Simonneau G, Charbonnier B, Decousus H et al. Subcutaneous low molecular weight Heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. *Arch Intern Med* 1993;153:1541-1546.

(6) Fiessinger JN, Lopez-Fernandez M, Gatterer E et al. Once-daily subcutaneous Dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. *Thromb Haemost* 1996;76(2):195-199.

(7) Koopman MMW, Prandoni P, Piovella F et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low molecular weight heparin administered at home. *N Engl J Med* 1996;334(11):682-687.

(8) Levine MN, Gent M, Hirsh J et al. A comparison of low molecular weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep vein thrombosis. *N Engl J Med* 1996;334(11):677-681.

(9) Kirchmaier CM, Wolf H, Schäfer H, Ehlers B, Breddin HK. Efficacy of a low molecular weight heparin administered intravenously or subcutaneously in comparison with intravenous unfractionated heparin in the treatment of deep venous thrombosis. *Int Angiol* 1998;17(3):135-145.

(10) Harenberg J, Schmidt JA, Koppenhagen K, Tolle A, Huisman MV, Buller HR. Fixed-dose, body-weight-independent subcutaneous LMW Heparin versus adjusted dose unfractionated intravenous Heparin in the initial treatment of proximal venous thrombosis. *Thromb Haemost* 2000;83(5):652-656.

(11) Breddin HK, Hach-Wunderle V, Nakov R, Kakkar VV. Effects of a low molecular weight heparin on thrombus regression and recurrent thromboembolism in patients with deep vein thrombosis. *N Engl J Med* 2001;344(9):626-631.

(12) Kakkar VV, Gebska M, Kadziola Z, Saba N, Carrasco P. Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis. *Thromb Haemost* 2003;89(4):674-680.

(13) Riess H, Koppenhagen K, Tolle A et al. Fixed-dose, body weight-independent subcutaneous low molecular weight heparin certoparin compared with adjusted-dose intravenous unfractionated heparin in patients with proximal deep venous thrombosis. *Thromb Haemost* 2003;90(2):252-259.

(14) Meyer G, Brenot F, Pacouret G et al. Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. *Thromb Haemost* 1995;74(6):1432-1435.

(15) Simonneau G, Sors H, Charbonnier B et al. A Comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med* 1997;337(10):663-669.

(16) Findik S, Erkan ML, Selcuk MB, Albayrak S, Atici AG, Doru F. Low-molecular-weight heparin versus unfractionated heparin in the treatment of patients with acute pulmonary thromboembolism. *Respiration* 2002;69(5):440-444.

(17) Columbus Investigators, ten Cate JW. Low molecular weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997;337(10):657-662.

(18) Hull RD, Raskob GE, Brant RF et al. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. *Arch Intern Med* 2000;160(2):229-236.

(19) Merli G, Spiro TE, Olsson CG et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001;134(3):191-202.

(20) Prandoni P, Carnovali M, Marchiori A. Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism. *Arch Intern Med* 2004;164(10):1077-1083.

(21) Kearon C, Ginsberg JS, Julian JA et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA* 2006;296:935-942.

(22) Leizorovicz A, Siguret V, Mottier D et al. Safety profile of tinzaparin versus subcutaneous unfractionated heparin in elderly patients with impaired renal function treated for acute deep vein thrombosis: the Innohep(R) in Renal Insufficiency Study (IRIS). *Thromb Res* 2011;128(1):27-34.

(23) Bratt G, Aberg W, Johansson M, Tornebohm E, Granqvist S, Lockner D. Two daily subcutaneous injections of Fragmin as compared with intravenous standard heparin in the treatment of deep venous thrombosis (DVT). *Thromb Haemost* 1990;64(4):506-510.

(24) Lindmarker P, Holmstrom H, Granqvist S, Johnsson H, Lockner D. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated Heparin in the treatment of deep vein thrombosis. *Thromb Haemost* 1994;72(2):186-190.

(25) Pini M, Aiello S, Manotti C et al. Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. *Thromb Haemost* 1994;72(2):191-197.

(26) Das SK, Cohen AT, Edmondson RA, Melissari E, Kakkar VV. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. *World J Surg* 1996;20(5):521-526.

(27) Belcaro G, Barsotti A, Nicolaides AN et al. Comparison of low-molecular-weight Heparin, administered primarily at home, with unfractionated Heparin, administered in hospital, and subcutaneous Heparin, administered at home for deep-vein thrombosis. *Angiology* 1999;50(10):781-787.

(28) Gonzalez-Fajardo JA, Arreba E, Castrodeza J et al. Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. *J Vasc Surg* 1999;30(2):283-292.

(29) Lopaciuk S, Bielska-Falda H, Noszczyk W et al. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. *Thromb Haemost* 1999;81(1):26-31.

(30) Veiga F, Escriba A, Maluenda MP et al. Low molecular weight Heparin (Enoxaparin) versus oral anticoagulant therapy (Acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. *Thromb Haemost* 2000;84:559-564.

(31) Ramacciotti E, Araujo GR, Lastoria S et al. An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis. *Thromb Res* 2004;114:149-153.

(32) Chong BH, Brighton TA, Baker RI, Thurlow P, Lee CH. Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis. *J Thromb Thrombolysis* 2005;19(3):173-181.

(33) Daskalopoulos ME, Daskalopoulou SS, Tzortzis E et al. Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. *Eur J Vasc Endovasc Surg* 2005;29(6):638-650.

(34) Romera A, Cairols MA, Vila-Coll R et al. A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. *Eur J Vasc Endovasc Surg* 2009;37(3):349-356.

(35) Beckman JA, Dunn K, Sasahara AA, Goldhaber SZ. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. *Thromb Haemost* 2003;89(6):953-958.

(36) Perez de Llano LA, Baloira VA, Veres RA, Veiga F, Golpe GR, Pajuelo FF. [Multicenter, prospective study comparing enoxaparin with unfractionated heparin in the treatment of submassive pulmonary thromboembolism]. *Arch Bronconeumol* 2003;39(8):341-345.

(37) Hull RD, Pineo GF, Brant RF et al. Self-managed long-term low-molecular-weight heparin therapy: the balance of benefits and harms. *Am J Med* 2007;120:72-82.

(38) Buller HR, Davidson BL, Decousus H et al. Fondaparinux or Enoxaparin for the initial treatment of symptomatic deep venous thrombosis. A randomized trial. *Ann Intern Med* 2004;140:867-873.

(39) Buller HR, Davidson BL, Decousus H et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003;349:1695-1702.

(40) Einstein Investigators, Bauersachs R, Berkowitz SD et al. Oral Rivaroxaban for Symptomatic Venous Thromboembolism. *N Engl J Med* 2010;363(26):2499-2510.

(41) Buller HR, Prins MH, Lensin AW et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366(14):1287-1297.

(42) Schulman S, Kearon C, Kakkar AK et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361(24):2342-2352.

(43) Schulman S, Kakkar AK, Goldhaber SZ et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014;129(7):764-772.

(44) Buller HR, Decousus H, Grosso MA et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369(15):1406-1415.

(45) Agnelli G, Buller HR, Cohen A et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369(9):799-808.

(46) Fleurence RL, Hollenbeak CS. Rates and probabilities in economic modelling: transformation, translation and appropriate application. *Pharmacoeconomics* 2007;25(1):3-6.

(47) Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU technical support document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.

(48) Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012;41(3):818-827.

(49) Thorlund K, Thabane L, Mills EJ. Modelling heterogeneity variances in multiple treatment comparison meta-analysis--are informative priors the better solution? *BMC Med Res Methodol* 2013;13:2.