Supplemental Online Content

CRISTAL Study Group. Effect of aspirin vs enoxaparin on symptomatic venous thromboembolism in patients undergoing hip or knee arthroplasty: the CRISTAL randomized trial. *JAMA*. Published August 23, 2022. doi:10.1001/jama.2022.13416

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

eAppendix1. Collaborators and Participating Institutions

Study Investigators

In addition to the authors listed in the writing group, the following authors were a part of the study investigators' group: Justine Maree Naylor, Ilana Ackerman, Beng Hock Cheng, Richard de Steiger, Anthony Harris, Michelle Lorimer, Elizabeth C. Griffith, Steve Webb, Durga Bastiras, Maggie Cripps, Amber Hansen and Ornella Clavisi.

Site investigators

In addition to the authors listed in the writing group and the study investigators, the following authors were site investigators (sites are listed in italics): *Prince of Wales Hospital, Randwick, Sydney, New South Wales, Australia* – Michael Solomon, *Fairfield Hospital, Fairfield, Sydney, New South Wales, Australia* – David Lieu, *Canterbury Hospital, Canterbury, Sydney, New South Wales, Australia* – Leonard Kuo, *Nepean Hospital, Nepean, Sydney, New South Wales, Australia* – Rami Sorial, *Coffs Harbour Base Hospital, Coffs Harbour, New South Wales, Australia* – Peter Summersell, *Lakeview Private Hospital, Baulkam Hills, Sydney, New South Wales, Australia and Westmead Private Hospital, Westmead, Sydney, New South Wales, Australia* – Roger Brighton, *The Institute of Rheumatology and Orthoapedics, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia* – Mark Horsley, *St George Private Hospital, St George, Sydney, New South Wales, Australia* – Samuel Macdessi, *Kareena Private Hospital, Sutherland, Sydney, New South Wales, Australia* – Michael Dixon, *Hornsby Hospital, Hornsby, Sydney, New South Wales, Australia* – David Hale, *North Shore Public Hospital, St Leonards, Sydney, New South Wales, Australia* – Bill Walter, *North Shore Private Hospital, St Leonards, Sydney, New South Wales, Australia* – Andrew Ellis, *Calvary John James Hospital, Deakin, Canberra, Australian Capital Territory, Australia* – Alexander Burns, *Greenslopes Private Hospital, Greenslopes, Brisbane, Queensland, Australia* – Mark Dekkers, *Mater Hospital Brisbane, Raymond Terrace, Brisbane, Queensland, Australia* – John Radavanovic, *Prince Charles Hospital, Chermside, Brisbane, Queensland, Australia* – Catherine McDougall, *Calvary Adelaide Hospital, Adelaide, South Australia, Australia* – Peter Lewis, *Flinders Medical Centre, Bedford Park, Adelaide, South Australia, Australia* – Chris Wilson, *Launceston General Hospital, Launceston, Tasmania, Australia* – Jonathan Mulford, *Bendigo Hospital, Bendigo, Victoria, Australia* – Dugal James, *Epworth Eastern Hospital, Box Hill, Melbourne, Victoria, Australia* – Raphael Hau, *Footscray Hospital, Footscray, Melbourne, Victoria, Australia and Williamstown Hospital, Williamstown, Melbourne, Victoria, Australia* – Phong Tran, *Frankston Hospital, Frankston, Melbourne, Victoria, Australia* – Peter McCombe, *St John of God Hospital Geelong, Geelong, Victoria, Australia and University Hospital Geelong (Barwon Hospital), Geelong, Victoria, Australia* – Richard Page, *Fremantle Hospital, Fremantle, Perth, Western Australia, Australia* – Omar Khorshid, *Sir Charles Gardiner Hospital, Nedlands, Perth, Western Australia, Australia and Osborn Park Hospital, Stirling, Perth, Western Australia, Australia* – David Wysocki.

Steering Committee:

I.A. Harris (Chair), the writing group and all investigators listed in section 1 of this appendix. Responsible for final protocol approval, study oversight and principal publication approval

Writing Group:
V.S. Sidhu, TL Kelly, N. Pratt, K. Cashman, S.E. Graves, R. Buchbinder, S. Adie, I.A. Harris. Responsible for protocol development and preparation of principal publication

Trial Management Committee:
I.A. Harris, S.E. Graves, V.S. Sidhu, S. Adie, D. Bastiras, C. Turner, E.C. Griffith, R. de Steiger, M. Lorimer, N. Pratt. Responsible for integration with AOANJRR patient reported outcome measures program, ethics approval and ethics issues that arose during the trial and site liaison (recruitment, auditing and maintenance).

Data Quality Committee:
I.A. Harris, D. Bastiras, M. Lorimer, R. de Steiger. Responsible for data management.

Outcome Verification Committee
J.M. Naylor, I.A. Harris, B.H. Cheng, D. Bastiras. Responsible for process of validation verification of venous thromboembolic events during follow-up

Data Safety Monitoring Board:
L. Billot (senior statistician), A. Tuckfield (hematologist) and C. Vertullo (orthopedic surgeon). Responsible for blinded interim analyses.

eAppendix 2. Letter Recommending Early Trial Cessation

The George Institute for Global Health Australia

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16 December 2020

Re: CRISTAL DSMB Recommendations

Dear Professor Harris,

The DSMB met on 9 December 2020 to review the Interim report. The report included primary outcome data (VTE within 90 days) related to 8,296 procedures undertaken before 31 July 2020 with follow-up until 30 October 2020.

The primary analysis comparing the proportion of patients experiencing VTE showed a strongly significant difference between the two arms with the 99.90% confidence interval around this difference excluding zero. This interim finding therefore crosses the pre-specified boundary which corresponds to a level of significance of 0.1%. This excess of harm in one arm appears to be consistent across sites as reviewed in a subsequent report.

There was no evidence of a difference for any of the other outcomes including major bleeding, death and further surgery. Baseline characteristics were well balanced between the two randomised arms.

Given the strong sign of harm, as indicated by a significant difference in the proportion of patients experiencing VTE (p-value < 0.001) and the absence of any noticeable differences in other outcomes, we recommend that the trial be stopped. In parallel, we strongly recommend that patients with a prior history of VTE be completely excluded from future enrolment in the trial given the additional risk in this subgroup.

We acknowledge that the results might change slightly as more hospitals cross over to the other arm; however, we are concerned that delaying the decision might put further participants at risk. We also believe that there is sufficient evidence to suggest that the primary non-inferiority hypothesis is now very unlikely.

We understand that the final decision rests with the study management committee and remain at your disposal to provide further guidance and / or discuss the findings in more details.

Sincerely,

A/Prof Laurent Billot, on behalf of the CRISTAL DSMB
Membership of the CRISTAL DSMB: Laurent Billot (Chair), Annabel Tuckfield, Chris Vertullo

Affiliated with

UNSW SYDNEY

eAppendix 3. Results of Second Interim Analysis

CRISTAL - Interim Analysis
Second Interim Analysis
25th November 2020

Background:

The primary objective of the study is to determine whether aspirin is non-inferior to low molecular weight heparin (LMWH) in the prevention of symptomatic venous thromboembolism (VTE) occurring within 90-days in patients undergoing primary elective total hip arthroplasty (THA) or total knee arthroplasty (TKA) for osteoarthritis (OA). CRISTAL has been designed as a pragmatic, non-inferiority, cluster randomised crossover trial. Thirty-one hospitals across Australia are participating.

This interim analysis includes procedures up to and including 31 July 2020, giving 90-days follow-up to 31 October 2020. As of 31/7/2020, there were 12 hospitals that have crossed over to the second treatment arm. Of these, nine hospitals are in the 'AB' sequence and three are in the 'BA' sequence.

The following interim analysis was undertaken in response to a single death of one participant following a suspected VTE at one hospital. For the purposes of this interim analysis, the treatments were labelled A and B to preserve blinding. All analyses were performed for primary THA and TKA for OA.

The outcomes considered for analysis are:

- VTE occurring within 90-days among patients enrolled in CRISTAL
- VTE occurring within 90 days among patients enrolled in CRISTAL with a patient reported history of VTE
- Death within 90 days among patients enrolled in CRISTAL
- Death within 90 days among patients enrolled in CRISTAL with a patient reported history of VTE
- Major bleeding within 90-days among patients enrolled in CRISTAL
- Further surgery (any recorded) among patients enrolled in CRISTAL
- Readmission to hospital (any recorded) among patients enrolled in CRISTAL
- Death within 90-days for all procedures undertaken at CRISTAL hospitals by participating surgeons
- Revision surgery within 90-days for all procedures undertaken at CRISTAL hospitals by participating surgeons

Note that for the outcome of further surgery, no date of surgery is recorded, and this question is asked at both three- and six-months post operation. Therefore, this outcome is reporting any recorded and validated further surgery. The outcome of readmission to hospital is a combined outcome incorporating both further surgery

and readmission to hospital due to bleeding. This outcome is also reporting any recorded readmission to hospital, regardless of time since operation.

Method of Analysis:

For each outcome, a summary proportion for each cluster was determined. For those hospitals that have crossed over, a linear regression of treatment differences on treatment sequence, weighted for cluster size, was performed as per Turner et. al. (2007). For those hospitals that have not crossed over, a linear regression was performed using the summary proportions. Results from the two models were combined using inverse variance weights and group differences (A -B) were calculated (Andrew Forbes, private communication, 25/8/2020). A significance level of 0.1% was chosen. Confidence Intervals presented are based on the Haybittle-Peto boundary.

Reference

Turner RM, White IR, Croudace, T. 2007. Analysis of cluster randomized cross-over trial data: A comparison of methods. Statistics in Medicine. 26: 274-289

Procedures enrolled in CRISTAL

Baseline Demographic Summaries

Table 1: Baseline Characteristics of Procedures Enrolled in CRISTAL

Characteristic		A~(n=3858)	B~(n=4438)
Age	n	3855	4424
	mean (SD)	67.2 (10.4)	66.4 (10.4)
	median (min, max)	68.0 (18.0, 95.0)	67.0 (18.0, 96.0)
	median (Q1, Q3)	68.0 (61.0, 74.0)	67.0 (60.0, 74.0)
BMI	n	3797	4371
	mean (SD)	31.0 (6.6)	31.2 (6.4)
	median (min, max)	30.4 (15.7, 82.4)	30.5 (14.6, 85.8)
	median (Q1, Q3)	30.4 (26.5, 34.5)	30.5 (26.8, 34.7)
Sex	Male	1676 (43%)	1900 (43%)
	Female	2179 (57%)	2524 (57%)
	Missing	3	14
ASA	1	213 (5.5%)	255 (5.8%)
	2	2136 (55%)	2512 (57%)
	3	1472 (38%)	1602 (36%)
	4	32 (0.8%)	39 (0.9%)
	Missing	5	30
Approach*	Anterior	145 (9.8%)	328 (20%)
	Lateral	247 (17%)	186 (12%)
	Posterior	1085 (73%)	1096 (68%)
	Missing	1	1

*Approach applies only to THA procedures

Table 2: Baseline Characteristics of Primary Elective (THA and TKA for OA) Procedures Enrolled in CRISTAL

Characteristic		A~(n=3394)	B~(n=3922)
Age	n	3394	3922
	mean (SD)	67.6 (9.7)	67.0 (9.7)
	median (min, max)	68.0 (18.0, 95.0)	67.0 (23.0, 96.0)
	median (Q1, Q3)	68.0 (61.0, 74.0)	67.0 (60.0, 74.0)
BMI	n	3366	3879
	mean (SD)	31.2 (6.5)	31.4 (6.4)
	median (min, max)	30.5 (15.7, 82.4)	30.6 (15.2, 85.8)
	median (Q1, Q3)	30.5 (26.8, 34.6)	30.6 (27.0, 35.0)
Sex	Male	1450 (43%)	1671 (43%)
	Female	1944 (57%)	2251 (57%)
ASA	1	183 (5.4%)	217 (5.6%)
	2	1902 (56%)	2248 (58%)
	3	1284 (38%)	1411 (36%)
	4	23 (0.7%)	33 (0.8%)
	Missing	2	13
Approach*	Anterior	134 (10%)	303 (21%)
	Lateral	213 (16%)	159 (11%)
	Posterior	979 (74%)	1008 (69%)
	Missing	1	0

*Approach applies only to THA procedures

Group Comparison Results

Table 3: VTE occurring within 90-days among patients enrolled in CRISTAL: Observed Means

Group	Number of Clusters	N Procedures	N 90-day VTE	Mean	Std Error
A	18	3394	47	0.013848	.001971349
B	25	3922	121	0.030852	.004583925

Table 4: VTE occurring within 90-days among patients enrolled in CRISTAL: Estimate of Group Difference

Group Difference	Cross Over Estimate	Cross Over SE	Parallel Estimate	Parallel SE	Combined Estimate	Combined Standard Error	Lower 99.99% CI	Upper 99.99% CI
A - B	-0.01892	0.006325	-0.02239	0.01226	-0.019652	.005620773	-0.038145	-.001159889

Table 5: VTE occurring within 90 days among patients enrolled in CRISTAL with a patient reported history of VTE: Observed Means

Group	Number of Clusters	N Procedures	N 90-day VTE	Mean	Std Error
A	18	208	3	0.014423	0.006576
B	25	203	17	0.083744	0.015520

Table 6: VTE occurring within 90 days among patients enrolled in CRISTAL with a patient reported history of VTE: Estimate of Group Difference

Group Difference	Cross Over Estimate	Cross Over SE	Parallel Estimate	Parallel SE	Combined Estimate	Combined Standard Error	Lower 99.95% CI	Upper 99.95% CI
A - B	-0.06853	0.03019	-0.08791	0.03461	-0.076904	0.022751	-0.15175	-.002053776

Table 7: Death within 90 days among patients enrolled in CRISTAL: Observed Means

Group	Number of Clusters	N Procedures	N 90-day Mortality	Mean	Std Error
A	18	3394	3	.000883913	.000424352
B	25	3922	4	.001019888	.000406459

Table 8: Death within 90 days among patients enrolled in CRISTAL: Estimate of Group Difference

Group Difference	Cross Over Estimate	Cross Over SE	Parallel Estimate	Parallel SE	Combined Estimate	Combined Standard Error	Lower 99.95% CI	Upper 99.95% CI
A - B	-0.00135	0.001250	0.000704	0.000967	-.000064834	.000764864	-.002581236	.002451567

Table 9: Death within 90 days among patients enrolled in CRISTAL with a patient reported history of VTE: Observed Means

Group	Number of Clusters	N Procedures	N 90-day Mortality	Mean	Std Error
A	18	208	.	0	0
B	25	203	1	.004926108	.004668506

Group differences not calculated due to there being only 1 death in total.

Table 10: Major bleeding within 90-days among patients enrolled in CRISTAL: Observed Means

Group	Number of Clusters	N Procedures	N 90-day Major Bleed	Mean	Std Error
A	18	3394	15	.004419564	.001244191
B	25	3922	11	.002804691	.000867022

Table 11: Major bleeding within 90-days among patients enrolled in CRISTAL: Estimate of Group Difference

Group Difference	Cross Over Estimate	Cross Over SE	Parallel Estimate	Parallel SE	Combined Estimate	Combined Standard Error	Lower 99.95% CI	Upper 99.95% CI
A - B	0.002330	0.003464	0.001073	0.002455	.001493261	.002003180	-.0050972	.008083722

Table 12: Further surgery (any recorded) among patients enrolled in CRISTAL : Observed Means

Group	Number of Clusters	N Procedures	N Further Surgery	Mean	Std Error
A	18	3394	76	0.022392	.003028544
B	25	3922	81	0.020653	.003108415

Table 13: Further surgery (any recorded) among patients enrolled in CRISTAL : Estimate of Group Difference

Group Difference	Cross Over Estimate	Cross Over SE	Parallel Estimate	Parallel SE	Combined Estimate	Combined Standard Error	Lower 99.95% CI	Upper 99.95% CI
A - B	0.004835	0.007575	-0.01372	0.007680	-.004315893	.005393175	-0.022059	0.013428

Table 14: Readmission to hospital (any recorded) among patients enrolled in CRISTAL : Observed Means

Group	Number of Clusters	N Procedures	N Readmission to Hospital	Mean	Std Error
A	18	3394	81	0.023866	.003121787
B	25	3922	85	0.021673	.003198854

Table 15: Readmission to hospital (any recorded) among patients enrolled in CRISTAL : Estimate of Group Difference

Group Difference	Cross Over Estimate	Cross Over SE	Parallel Estimate	Parallel SE	Combined Estimate	Combined Standard Error	Lower 99.95% CI	Upper 99.95% CI
A - B	0.004616	0.008358	-0.01354	0.007816	-.005069116	.005708836	-0.023851	0.013713

All Procedures Undertaken at CRISTAL Hospitals by Participating Surgeons

Table 16: Baseline Characteristics of all Procedures Undertaken at CRISTAL Hospitals by Participating Surgeons

Characteristic		A~(n=7599)	B~(n=9988)
Age	n	7599	9988
	mean (SD)	69.4 (11.2)	69.0 (11.4)
	median (min, max)	70.0 (13.0, 104.0)	69.0 (11.0, 108.0)
	median (Q1, Q3)	70.0 (62.0, 77.0)	69.0 (62.0, 77.0)
BMI	n	7172	9528
	mean (SD)	30.6 (6.7)	30.8 (6.7)
	median (min, max)	29.9 (12.0, 82.4)	30.0 (10.6, 85.8)
	median (Q1, Q3)	29.9 (26.0, 34.3)	30.0 (26.2, 34.5)
Sex	Male	3305 (43%)	4312 (43%)
	Female	4294 (57%)	5676 (57%)
ASA	1	329 (4.3%)	438 (4.4%)
	2	3494 (46%)	4643 (47%)
	3	3437 (45%)	4484 (45%)
	4	329 (4.3%)	387 (3.9%)
	5	3 (0.0%)	3 (0.0%)
	Missing	7	33
Approach*	Anterior	240 (9.2%)	599 (18%)
	Lateral	443 (17%)	377 (11%)
	Posterior	1912 (74%)	2417 (71%)
	Missing	5	5

*Approach applies only to THA procedures

eAppendix 4. Second Interim Analysis – Update on Patients With a Reported History of VTE

CRISTAL - Interim Analysis
Second Interim Analysis - Update
17 December 2020

Background:

The primary objective of the study is to determine whether aspirin is non-inferior to low molecular weight heparin (LMWH) in the prevention of symptomatic venous thromboembolism (VTE) occurring within 90-days in patients undergoing primary elective total hip arthroplasty (THA) or total knee arthroplasty (TKA) for osteoarthritis (OA). CRISTAL has been designed as a pragmatic, non-inferiority, cluster randomised crossover trial. Thirty-one hospitals across Australia are participating.

This interim analysis includes procedures up to and including 31 July 2020, giving 90-days follow-up to 31 October 2020. As of 31/7/2020, there were 12 hospitals that have crossed over to the second treatment arm. Of these, nine hospitals are in the 'AB' sequence and three are in the 'BA' sequence.

The following interim analysis was undertaken in response to a single death of one participant following a suspected VTE at one hospital. For the purposes of this interim analysis, the treatments were labelled A and B to preserve blinding. All analyses were performed for primary THA and TKA for OA.

The outcomes considered for analysis are:

- VTE occurring within 90-days among patients enrolled in CRISTAL
- VTE occurring within 90 days among patients enrolled in CRISTAL with a patient reported history of VTE
- VTE occurring within 90 days among patients enrolled in CRISTAL with no patient reported history of VTE
- Death within 90 days among patients enrolled in CRISTAL
- Death within 90 days among patients enrolled in CRISTAL with a patient reported history of VTE
- Death within 90 days among patients enrolled in CRISTAL with no patient reported history of VTE

Note that for the outcome of further surgery, no date of surgery is recorded, and this question is asked at both three- and six-months post operation. Therefore, this outcome is reporting any recorded and validated further surgery. The outcome of readmission to hospital is a combined outcome incorporating both further surgery

and readmission to hospital due to bleeding. This outcome is also reporting any recorded readmission to hospital, regardless of time since operation.

Method of Analysis:

For each outcome, a summary proportion for each cluster was determined. For those hospitals that have crossed over, a linear regression of treatment differences on treatment sequence, weighted for cluster size, was performed as per Turner et. al. (2007). For those hospitals that have not crossed over, a linear regression was performed using the summary proportions. Results from the two models were combined using inverse variance weights and group differences (A -B) were calculated (Andrew Forbes, private communication, 25/8/2020). A significance level of 0.1% was chosen. Confidence Intervals presented are based on the Haybittle-Peto boundary.

Reference

Turner RM, White IR, Croudace, T. 2007. Analysis of cluster randomized cross-over trial data: A comparison of methods. Statistics in Medicine. 26: 274-289

Note: there are 538 patients for whom history of VTE data is missing

Table 1: VTE occurring within 90-days among patients enrolled in CRISTAL by Patient Reported History of VTE

		VTE within 90 days	
		0	1
		N	N
Treatment Group	History of VTE		
A	.	213	2
	0	2929	42
	1	205	3
B	.	319	4
	0	3296	100
	1	186	17

Table 2: Death within 90 days among patients enrolled in CRISTAL by Patient Reported History of VTE

		Died within 90 days	
		0	1
		N	N
Treatment Group	History of VTE		
A	.	214	1
	0	2969	2
	1	208	.
B	.	323	.
	0	3393	3
	1	202	1

Table 1: VTE occurring within 90-days among patients enrolled in CRISTAL: Observed Means

Group	Number of Clusters	N Procedures	N 90-day VTE	Mean	Std Error
A	18	3394	47	0.013848	.001971349
B	25	3922	121	0.030852	.004583925

Table 2: VTE occurring within 90-days among patients enrolled in CRISTAL: Estimate of Group Difference

Group Difference	Cross Over Estimate	Cross Over SE	Parallel Estimate	Parallel SE	Combined Estimate	Combined Standard Error	Lower 99.99% CI	Upper 99.99% CI
A - B	-0.01892	0.006325	-0.02239	0.01226	-0.019652	.005620773	-0.038145	-.001159889

Table 3: VTE occurring within 90 days among patients enrolled in CRISTAL with a patient reported history of VTE: Observed Means

Group	Number of Clusters	N Procedures	N 90-day VTE	Mean	Std Error
A	18	208	3	0.014423	0.006576
B	25	203	17	0.083744	0.015520

Table 4: VTE occurring within 90 days among patients enrolled in CRISTAL with a patient reported history of VTE: Estimate of Group Difference

Group Difference	Cross Over Estimate	Cross Over SE	Parallel Estimate	Parallel SE	Combined Estimate	Combined Standard Error	Lower 99.95% CI	Upper 99.95% CI
A - B	-0.06853	0.03019	-0.08791	0.03461	-0.076904	0.022751	-0.15175	-.002053776

Table 5: VTE occurring within 90 days among patients enrolled in CRISTAL with no patient reported history of VTE: Observed Means

Group	Number of Clusters	N Procedures	N 90 Day VTE	Mean	Std Error
A	18	2971	42	0.014137	.001936287
B	25	3396	100	0.029446	.004836909

Table 6: VTE occurring within 90 days among patients enrolled in CRISTAL with no patient reported history of VTE: Estimate of Group Difference

Group Difference	Cross Over Estimate	Cross Over SE	Parallel Estimate	Parallel SE	Combined Estimate	Combined Standard Error	Lower 99.95% CI	Upper 99.95% CI
A - B	-0.01510	0.007212	-0.02128	0.01228	-0.016683	.006219203	-0.037144	.003778277

Table 7: Death within 90 days among patients enrolled in CRISTAL: Observed Means

Group	Number of Clusters	N Procedures	N 90-day Mortality	Mean	Std Error
A	18	3394	3	.000883913	.000424352
B	25	3922	4	.001019888	.000406459

Table 8: Death within 90 days among patients enrolled in CRISTAL: Estimate of Group Difference

Group Difference	Cross Over Estimate	Cross Over SE	Parallel Estimate	Parallel SE	Combined Estimate	Combined Standard Error	Lower 99.95% CI	Upper 99.95% CI
A - B	-0.00135	0.001250	0.000704	0.000967	-.000064834	.000764864	-.002581236	.002451567

Table 9: Death within 90 days among patients enrolled in CRISTAL with a patient reported history of VTE: Observed Means

Group	Number of Clusters	N Procedures	N 90-day Mortality	Mean	Std Error
A	18	208	.	0	0
B	25	203	1	.004926108	.004668506

Group differences not calculated due to there being only 1 death in total.

Table 10: Death within 90 days among patients enrolled in CRISTAL with no patient reported history of VTE: Observed Means

Group	Number of Clusters	N Procedures	N 90 Day Mortality	Mean	Std Error
A	18	2971	2	.000673174	.000417778
B	25	3396	3	.000883392	.000390125

Table 11: Death within 90 days among patients enrolled in CRISTAL with no patient reported history of VTE: Estimate of Group Difference

Group Difference	Cross Over Estimate	Cross Over SE	Parallel Estimate	Parallel SE	Combined Estimate	Combined Standard Error	Lower 99.95% CI	Upper 99.95% CI
A - B	-0.00127	0.000633	0.000737	0.001066	-.00075059	.000543934	-.002540134	.001038955

eAppendix 5. Minutes From Meeting to Unblind Investigators

CRISTAL Writing Group Meeting
9th November 2020, Tuesday 1900 (AEST)
Minutes

Attendees: Chair: Ian Harris (IH), Verinder Sidhu (VS), Stephen Graves (SEG), Nicole Pratt (NP), Kara Cashman (KC), Rachelle Buchbinder (RB), Sam Adie (SA), Durga Bastiras (DB)

1. **Introduction/Agenda**
   Group was greeted and agenda items were announced.
   Agenda
   a. Readiness for unblinding to be established
   b. Unblinding of results (if appropriate)
   c. Updating manuscript with unblinded results
   d. Any other changes to manuscript required for finalisation
   e. Decision on communicating results to other investigators

2. **Readiness for unblinding**
   IH informed group that Lan Kelly (Statistician) will not be unblinded as she is currently working on the analyses for other populations. IH is happy for both KC and NP to be present in this meeting and to be unblinded to the results as they are not involved in the analyses. Group agreed.
   IH informed group that all investigators had approved the blinded manuscript and asked members to raise any concerns prior to unblinding. No concerns were raised and therefore the group proceeded with unblinding.

3. **Unblinding of results**
   Group was informed of the process where the allocations (GROUP A and B) were checked prior to unblinding:
   a. Read-only access to the original spreadsheet containing the allocation details for Group A and B used for the randomisation was provided to the following staff
      - CRISTAL Project Coordinator
      - AOANJRR SAHMRI Statistician
      - AOANJRR SAHMRI Project Manager
   b. Allocation details were checked by the three staff.
   c. Participating sites treatment allocation (first and second treatment arm) were also cross checked with this original spreadsheet.

   Following these checks, all 3 staff confirmed that the allocation details listed in the original spreadsheet were correct. This spreadsheet was then shown to the writing group for unblinding, showing that Group A was low molecular weight heparin and Group B was aspirin.

4. **Updating manuscript following unblinding**
   Details of Group A and B were labelled accordingly on the manuscript.

   Group then discussed the conclusion and the following amendments were made on the manuscript.

Original Manuscript (version 3.2)

In conclusion, we found that A was superior to B in the prevention of symptomatic venous thromboembolism within 90 days of primary total hip or knee arthroplasty by a clinically important margin, without a difference in secondary outcomes. This trial provides strong evidence for clinical practice guidelines for the future prevention of thromboembolic events following hip and knee arthroplasty.

Amended Manuscript (Version 4.1) – For Submission

In conclusion, we found that ~~A~~ low-molecular weight heparin was superior to ~~B~~ aspirin in the prevention of symptomatic venous thromboembolism within 90 days of primary total hip or knee arthroplasty ~~by a clinically important margin, without a difference~~ . There were no between-group differences in secondary outcomes, including complications. This trial provides strong evidence for the need to update clinical practice guidelines that recommend aspirin for the ~~future~~ prevention of thromboembolic events following hip and knee arthroplasty.

The group agreed on the submission of the amended manuscript version 4.1 and minutes of this meeting will be submitted as a supplementary document.

5. Decision on communicating results to investigators

The group agreed to distribute the final, unblinded manuscript to all Investigators at the time of submission. However, prior to distribution, IH will email all investigators emphasising that the manuscript has not undergone external peer review (and therefore, that the final paper will likely be different to this version) and that results cannot be communicated until publication and lifting of any embargo on reporting of results. Surgeons are free to change practice if they wish, but they cannot use the results of the CRISTAL trial in any official capacity until they have been externally reviewed and published.

eAppendix 6. Audit Process for Inpatient Adherence

Methods

Inpatient adherence during the acute care period was monitored by an audit of all sites over the first 2 weeks after commencing patient enrolment. The aim was to audit the first 20 patients of each treatment group to determine if patients had been given the correct drug and dose, prescribed once daily, commencing within 24 hours of surgery and that all patients were supplied with a discharge prescription of the allocated study drug. Hospitals were considered adherent for each patient if all of these aspects were achieved.

Additional aspects of the audit assessed the number of missed doses, whether patients were contraindicated to receive the study drug, were given calf compressors, if mobilization was achieved by day 1 postoperatively and whether a tourniquet was used. These aspects were not required to be achieved in order for a patient to be considered adherent.

If hospitals had less than 80% of patients adherent after the initial audit, a repeat audit was performed after one month.

The audit was conducted by research assistants at each participating hospital for hospitals outside Sydney (New South Wales). For hospitals within Sydney, a researcher independent to each hospital performed the audit.

Data collection form used for audit:

CRISTAL IN-HOSPITAL COMPLIANCE AUDIT FORM

Hospital:	**Patient surname:**
Date of audit:	**Patient DOB:**
Drug: Aspirin Clexane	**Age:**

Joint	Tourniquet Use?	Calf compressors worn?	Hours between leaving OR and time of 1st dose
Hip Knee	Yes No NA (hip)	Yes No	
Correct Drug?	**Contraindication to correct drug?*** (describe)	**Correct Dose? ***	**Administered daily?**
Yes No		Yes No	Yes No
Mobilisation by end of day 1?	**Length of Stay (days)**	**Missed Doses? (Number)**	**Discharge supply/script?**
Yes No			Yes No

*NB: 1. Dose for aspirin – 85-150mg
2. Dose for clexane – 40mg (20mg if Weight<50kg or Creatinine Clearance <30mL/min)
3. Drug contraindicated if patient is on dual antiplatelet, warfarin, NOAC or has allergy/other reason

Notes:

Results of Inpatient Audit:

For the first treatment group, all 31 hospitals provided patients who were audited for inpatient adherence. There were 10 hospitals that required a second audit (three aspirin and seven enoxaparin) and three hospitals that required a third audit (one aspirin and two enoxaparin). In total, there were 770 patients audited, who were eligible to receive the study drug for the first treatment group (404 aspirin patients and 366 enoxaparin patients). Of these, complete inpatient drug adherence was achieved in 669 patients (87%), 343 aspirin patients (85%) and 326 enoxaparin patients (89%).

For the second treatment group, 14 of 16 hospitals that crossed over prior to trial cessation provided patients who were audited. One hospital that was allocated to aspirin for this treatment group required a second audit. There were 235 patients audited who were eligible to receive the study drug for this treatment group (139 aspirin patients and 96 enoxaparin patients). Of these, complete inpatient drug adherence was achieved in 214 patients (91%), 124 aspirin patients (89%) and 90 enoxaparin patients (94%).

Data was collected on The compliance rate averaged 86% for patients in the first audit of the first arm and 90% for those in the first audit of the second arm. Thirteen hospitals required multiple audits for the first arm and one hospital for the second arm.

eAppendix 7. Audit Process for Post-discharge Adherence

Methods

This audit administered a telephone questionnaire after hospital discharge to a subset of patients enrolled in the CRISTAL study. Eligible patients for this audit included those who consented to participate in the CRISTAL trial undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) for a diagnosis of osteoarthritis, who were eligible to receive either study drug. Patients who were excluded if they were on preoperative single antiplatelet therapy and if they had not been discharged from hospital (including inpatient rehabilitation) prior to the end of their prophylaxis period.

Eligible patients were selected from each participating hospital by trial co-ordinators at the AOANJRR, who were aware of the treatment allocation for each hospital and not involved in the statistical analysis for CRISTAL. Four consecutive patients were selected at the commencement of each treatment group. The aim was to select an equal number of patients from each arm of the study and 248 patients in total.

Prior to the commencement of the audit, a questionnaire was developed by seven trial investigators. The questions aimed to investigate adherence, the number of missed doses in each group and reasons underlying non-adherence to treatment. To minimise the effect of recall bias, the questionnaire was administered between 15-20 days after TKA and between 36-41 days after THA by the same person for all patients. The conversation was scripted to reduce the effect of interviewer bias.

The primary outcome of the audit was non-adherence, which was defined as any missed doses after discharge. The secondary outcome was the number of missed doses.

Phone Questionnaire for Post-Discharge Adherence Audit

PHONE QUESTIONNAIRE POST DISCHARGE VTE PROPHYLAXIS COMPLIANCE

Patient Surname and DOB:

Type of Joint Replacement:

Type of Anticoagulant:

Please note, standard script for each patient contacted is denoted by text in inverted commas (" and ").

Introduction

"Good Morning (Patient Name), [redacted] calling from the Australian Orthopaedic Association National Joint Replacement Registry and the University of New South Wales regarding a trial you agreed to participate in – the CRISTAL trial.

Am I speaking with <<patient name>>? If **YES** → Continue

If patient deceased and answered by relative → "I am sorry to hear about your loss. You will not be contacted regarding this trial again and I will inform the Joint Registry team."

In relation to this trial, we are conducting a telephone questionnaire to investigate if patients took take their medication to prevent leg or lung clots following their joint replacement and to understand reasons why patients might not take this medication. The questionnaire will take approximately 10 minutes to complete. All data collected will be confidential and will be stored on the University of New South Wales secure RedCap database."

Consent to Participate:

"Would you like to participate in this questionnaire? (Wait for response)

If you do not participate, it will not affect the care you will receive from your treating surgeon or hospital."

Yes → Proceed to next paragraph (Timing of Questionnaire)

No → "Thank you for your time, you will not be contacted regarding this questionnaire any further. You will be contacted at 90 days after your surgery to complete the online questionnaire for the CRISTAL trial. Have a pleasant day."

Timing of Questionnaire:

If Yes, "Would you have time to complete the questionnaire with me now?"

Yes → Proceed with Questionnaire on Page 2

No → "Can I call you at a more convenient time to complete the questionnaire?"

Record preferred time, thank patient for their time and re-contact patient at preferred later date.

QUESTIONNAIRE

1. Did you take post-surgery blood thinning medication (to avoid blood clots) after leaving hospital following your joint replacement operation?
   If **Yes**, proceed to Q2
   If **No**:
   a. What was the main reason for not taking medication to prevent clots in your legs or lung after leaving hospital?

      _____

      _____

2. How many days were you advised to take the blood thinning medication after you left hospital?

   _____

3. Did you miss any doses after discharge from hospital?
   If **No,** questionnaire is complete
   If **Yes or Unsure,** proceed to question 4

4. Did you stop taking the medication before the duration recommended to you?
   If **No,** proceed to question 5
   If **Yes,**
   a. How many days before the recommended duration did you stop taking the medication?

      _____

   b. What was the main reason you stopped taking the medication early?

      _____

      _____

   c. While taking the medication, did you miss any doses?

      _____

      _____

5. How many doses did you miss while taking the medication?

   _____

   _____

   a. What was the main reason for missing these doses?

      _____

      _____

Results of the Post-Discharge Adherence Audit

Due to the early trial cessation, 178 patients out of the intended 248 were enrolled into this audit: 71 in the aspirin group and 107 in the enoxaparin group. Non-adherence in the aspirin group was 24% (17/71) and was 30% (32/107) in the enoxaparin group, a difference that was not significant (OR = 1.4, 95% CI 0.7 to 2.9, p=0.4).

The mean number of missed doses in the aspirin group was 2.5 (standard deviation = 6.9) and in the enoxaparin group was 3.4 (standard deviation = 7.4), a difference that was not significant (difference in means = 0.9, 95% CI -1.2 to 3.1, p=0.4).

The results of the inpatient and outpatient audits were combined and are provided in the manuscript.

eAppendix 8. Audit Process for "Absence" of VTE Audit

Methods

All positive VTE events recorded by patients at 90-day follow-up were verified through contacting treating physicians and surgeons.

To provide assurance that no VTE events were missed and whether patients were accurately reporting that they did not experience a VTE within 90 days, an "Absence of VTE" audit was conducted.

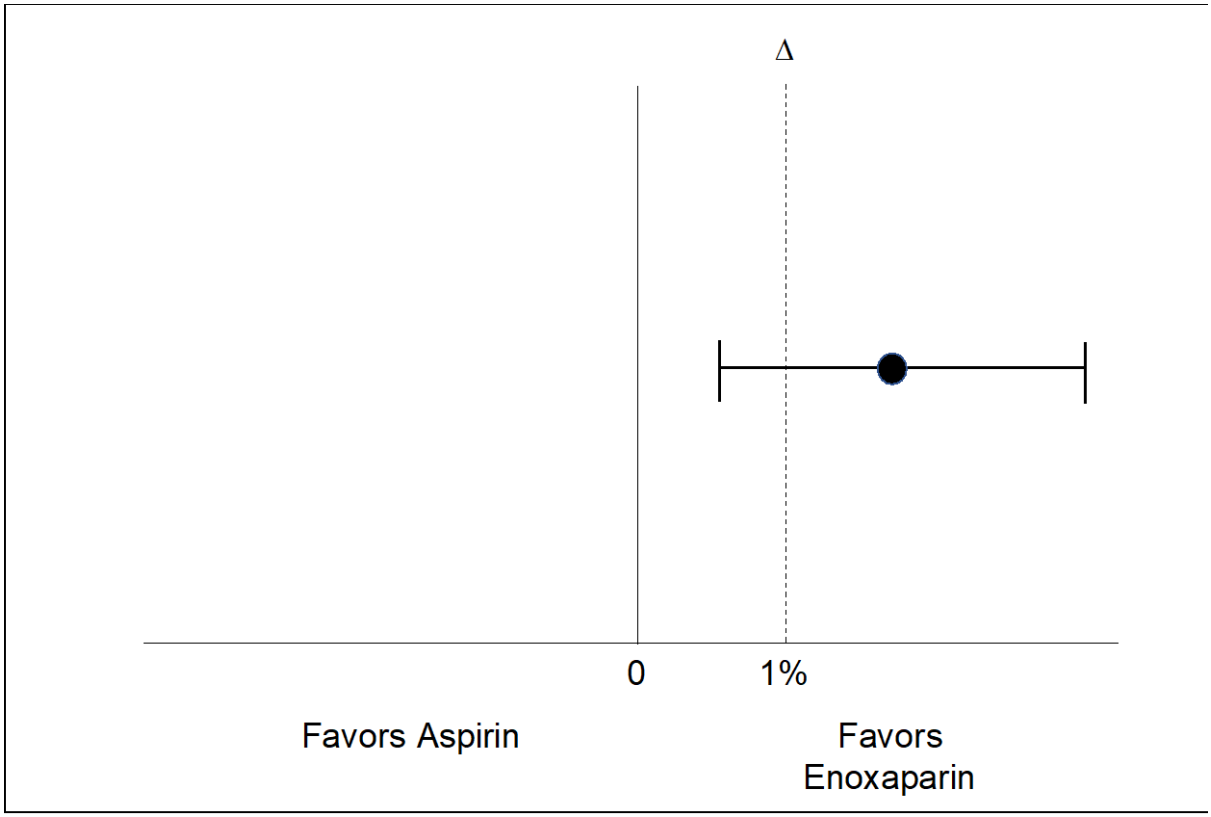
200 patients were selected randomly who recorded that they did not experience a VTE on the 90-day data collection form. To verify this result and to ensure there were no false negative events (i.e. patients who experienced a VTE, but reported that they had not), treating physicians, surgeons and general practitioners were contacted via telephone to ensure that these patients did not experience a VTE.

Results

Of the 200 patients audited, there was 1 patient who had a false negative event and who had experienced a VTE, yet had reported they did not on the 90-day data collection form. The remaining 199 patients were verified as not having a VTE. The false negative rate found was therefore 1/200 (0.5%).

eFigure. Non-inferiority Diagram for Primary Outcome

Between group change for the primary outcome and non-inferiority margin. The dotted line represents the non-inferiority margin.



eTable 1. **Baseline Features of Participating Clusters**

Number of enrolled patients and enrolment rate by treatment allocation for patients undergoing primary total hip or knee arthroplasty for a diagnosis of osteoarthritis, for each participating hospital

Hospital	Number of HA and KA procedures performed (2018)	Insurance status[a]	Initial treatment allocation	Crossover achieved	Aspirin	Aspirin Enrolment Rate	Enoxaparin	Enoxaparin Enrolment Rate	Overall enrolment rate (combined for both groups)
1	277	PUBLIC	Enoxaparin	No			290	91.9%	91.9%
2	768	PUBLIC	Enoxaparin	Yes	192	75.7%	266	71.1%	72.9%
3	655	PUBLIC	Aspirin	Yes	237	53.4%	152	44.7%	49.8%
4	580	PUBLIC	Aspirin	Yes	184	61.9%	182	90.9%	73.3%
5	337	PUBLIC	Aspirin	No	243	79.8%			79.8%
6	1,009	PUBLIC	Enoxaparin	Yes	383	73.4%	269	57.6%	65.9%
7	500	PUBLIC	Aspirin	Yes	251	68.7%	33	60.3%	67.6%
8	448	PRIVATE	Aspirin	Yes	318	59.0%	54	78.7%	61.1%
9	568	PUBLIC	Aspirin	No	102	24.9%			24.9%
10	542	PUBLIC	Enoxaparin	No			292	70.0%	70.0%
11	1,617	PRIVATE	Enoxaparin	Yes	292	56.3%	246	56.6%	56.4%
12	620	PUBLIC	Enoxaparin	Yes	137	81.4%	257	77.7%	79.0%
13	849	PRIVATE	Enoxaparin	Yes	226	56.1%	263	49.3%	52.1%
14	606	PUBLIC	Aspirin	Yes	225	69.6%	104	65.7%	68.4%
15	559	PUBLIC	Enoxaparin	Yes	311	90.7%	239	75.5%	83.9%
16	313	PUBLIC	Enoxaparin	No			74	33.7%	33.7%
17	275	PUBLIC	Enoxaparin	No			148	82.1%	82.1%
18	580	PUBLIC	Aspirin	No	139	59.8%			59.8%
19	295	PUBLIC	Aspirin	No	203	62.0%			62.0%
20	1,056	PRIVATE	Enoxaparin	Yes	338	36.1%	277	60.5%	43.9%
21	310	PUBLIC	Enoxaparin	Yes	20	66.7%	56	53.6%	56.1%
22	250	PUBLIC	Aspirin	No	206	67.4%			67.4%
23	532	PUBLIC	Aspirin	No	146	34.3%			34.3%
24	852	PRIVATE	Enoxaparin	Yes	32	62.9%	296	65.4%	65.1%
25	340	PUBLIC	Aspirin	No	177	73.7%			73.7%
26	1,170	PRIVATE	Enoxaparin	Yes	186	78.8%	249	78.8%	78.8%
27	585	PRIVATE	Aspirin	No	285	49.4%			49.4%
28	1,062	PRIVATE	Enoxaparin	Yes	331	86.7%	289	85.5%	86.2%
29	255	PRIVATE	Aspirin	No	127	58.3%			58.3%
30	688	PRIVATE	Aspirin	No	243	71.0%			71.0%
31	761	PUBLIC	Aspirin	No	141	35.3%			35.3%
Totals	**19259**	**Private – 10 Public – 21**	**15 – enoxaparin 16 – aspirin**	**16 Crossed Over**	**5675**	**Median 60%**	**4036**	**66% (median)**	**66.0% (median)**

[a]Private hospitals are owned by private corporations and patients are funded by private health insurance companies. Medicare hospitals are funded by the Australian and State Governments

eTable 2. Comparison of Enrolled and Non-enrolled Patients

Comparative demographic information of enrolled patients and non-enrolled patients undergoing primary total hip or knee arthroplasty for a diagnosis of osteoarthritis, by treatment allocation at participating hospitals

	Enrolled (n = 10965)		**Not Enrolled (n = 6650)**	
	Enoxaparin (N=4534)	**Aspirin (N=6420)**	**Enoxaparin (N=2319)**	**Aspirin (N=4331)**
Age				
N	4537	6428	2319	4331
Median (Q1, Q3)	69.0 (62.0, 75.0)	68.0 (61.0, 74.0)	70.0 (63.0, 76.0)	69.0 (62.0, 76.0)
BMI				
N	4506	6360	2291	4286
Median (Q1, Q3)	30.6 (27.0, 34.9)	30.7 (27.0, 35.2)	30.5 (26.9, 35.2)	30.7 (26.8, 35.0)
Sex				
N	4537	6428	2319	4331
Female	2559 (56.4%)	3579 (55.7%)	1338 (57.7%)	2490 (57.5%)
Male	1978 (43.6%)	2849 (44.3%)	981 (42.3%)	1841 (42.5%)
ASA Grading				
N	4534	6405	2318	4322
1	204 (4.5%)	320 (5.0%)	97 (4.2%)	186 (4.3%)
2	2375 (52.4%)	3425 (53.5%)	1139 (49.1%)	2133 (49.4%)
3	1916 (42.3%)	2586 (40.4%)	1048 (45.2%)	1943 (45.0%)
4	39 (0.9%)	74 (1.2%)	33 (1.4%)	60 (1.4%)
5	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
Joint replacement				
N	4537	6428	2319	4331
THA	1719 (37.9%)	2409 (37.5%)	856 (36.9%)	1764 (40.7%)
TKA	2818 (62.1%)	4019 (62.5%)	1463 (63.1%)	2567 (59.3%)

eTable 3. Sensitivity Analyses

Sensitivity analyses for the primary outcome, symptomatic venous thromboembolism within 90 days

	Aspirin n (%)	Enoxaparin n (%)	Estimated Absolute Risk Difference (%)	95% Confidence Interval (%)	p-value	Interaction p-value
Volume						
≥ 820 procedures (n = 6715)	135/3752 (3.60)	59/2963 (1.99)	-1.61	-2.99 to -0.23	0.02	0.83
< 820 procedures (n = 2488)	52/1664 (3.12)	10/824 (1.21)	-1.91	-4.27 to 0.43	0.11	
Enrolment rate						
≥ 66% (n = 5394)	106/2924 (3.63)	44/2470 (1.78)	-2.39	-4.23 to -0.54	0.01	0.81
< 66% (n = 3809)	81/2492 (3.25)	25/1317 (1.90)	-2.00	-4.60 to 0.06	0.13	
Multiple (≥2) compliance audits						
Yes (n = 2433)	44/1219 (3.61)	26/1214 (2.14)	-1.63	-4.27 to 1.01	0.20	0.78
No (n = 6760)	143/4197 (3.41)	43/2573 (1.67)	-2.11	-4.15 to -0.07	0.04	

eTable 4. Comparison of Complete Case and Imputed Analyses for Primary Outcome

N	Observed, Aspirin	Observed, Enoxaparin	Outcome	Estimated Difference %, (95 % CI)	Non-inferiority p-value	Superiority p-value
9,203	187/5416 (3.45%)	69/3787 (1.82%)	Complete Case	-1.97 (-3.41 to -0.54)	0.91	0.007
9,706			Imputed (excluding deaths)	-1.88 (-.3.31 to -0.46)	0.89	0.01
9,711			Imputed (including deaths)	-1.87 (-3.28 to -0.45)	0.89	0.01
9,711			Inverse probability weighting	-1.97 (-3.40 to -0.54)	0.91	0.007

eTable 5. Comparison of Complete Case and Imputed Analyses for Secondary Outcomes

Outcome	Observed, Aspirin	Observed, Enoxaparin	Estimated Difference Aspirin-Enoxaparin, (95 % CI)	p-value	Imputed Difference Aspirin-Enoxaparin, (95 % CI)	Imputed p-value
PE at 90 days	58/5416 (1.07%)	21/3787 (0.55%)	-0.44 (-1.08 to 0.19)	0.17	-0.41 (-1.07 to 0.25)	0.22
DVT at 90 days	140/5416 (2.58%)	50/3787 (1.32%)	-1.61 (-2.68 to -0.54)	0.003	-1.53 (-2.61 to -0.45)	0.005
DVT above knee at 90 days	12/5415 (0.22%)	6/3787 (0.16%)	-0.06 (-0.23 to 0.11)	0.49	-0.06 (-0.24 to 0.13)	0.55
DVT below knee at 90 days	129/5415 (2.38%)	45/3787 (1.19%)	-1.49 (-2.50 to -0.48)	0.004	-1.43 (-2.42 to -0.43)	0.005
Both PE and DVT at 90 days	11/5416 (0.2%)	2/3787 (0.05%)	-0.1 (-0.30 to 0.10)	0.32	-0.07 (-0.36 to 0.22)	0.65
Bleeding at 90 days	17/5401 (0.31%)	15/3779 (0.4%)	0.05 (-0.25 to 0.35)	0.75	0.08 (-0.30 to 0.46)	0.68
Death at 90 days	4/5675 (0.07%)	2/4036 (0.05%)	-0.05 (-0.15 to 0.05)	0.36		
Readmission at 90 days	130/5403 (2.41%)	85/3782 (2.25%)	-0.60 (-1.39 to 0.19)	0.13	-0.55 (-1.40 to 0.30)	0.21
Re-operation at 90 days	116/5412 (2.14%)	73/3787 (1.93%)	-0.67 (-1.46 to 0.12)	0.01	-0.63 (-1.46 to 0.21)	0.14
Re-operation at 6 months	175/5086 (3.44%)	120/3535 (3.39%)	-0.16 (-1.14 to 0.82)	0.75	-0.12 (-1.17 to 0.94)	0.83

eTable 6. Comparison of Complete Case and Imputed Analyses for Subgroup Analyses

Subgroup	Category	Observed, Aspirin	Observed, Enoxaparin	Estimated Difference Aspirin-Enoxaparin, (95 % CI)	Superiority p-value	Interaction p-value	Imputed Difference Aspirin-Enoxaparin, (95 % CI)	Imputed superiority p-value	Imputed interaction p-value
Joint	Hip	42/2068 (2.03%)	7/1430 (0.49%)	-1.94 (-3.93 to 0.04)	0.06	0.92	-1.82 (-3.8 to 0.16)	0.072	0.89
	Knee	145/3348 (4.33%)	62/2357 (2.63%)	-2.07 (-3.50 to -0.63)	0.005		-1.99 (-3.45 to -0.54)	0.0073	
History of VTE	Yes	23/270 (8.52%)	6/228 (2.63%)	-6.00 (-11.53 to -0.45)	0.03	0.14	-5.97 (-11.55 to -0.40)	0.036	0.14
	No	155/4826 (3.21%)	60/3379 (1.78%)	-1.71 (-3.03 to -0.39)	0.01		-1.65 (-2.98 to -0.32)	0.015	
Bilateral	Yes	26/614 (4.23%)	13/409 (3.18%)	-2.04 (-5.64 to 1.56)	0.27	0.99	-1.93 (-5.56 to 1.69)	0.3	1.0
	No	161/4802 (3.35%)	56/3378 (1.66%)	-2.01 (-3.38 to -0.64)	0.004		-1.93 (-3.32 to -0.55)	0.0062	
Anticoagulants	Yes	47/1031 (4.56%)	21/725 (2.9%)	-1.88 (-3.30 to -0.45)	0.08	0.69	-2.39 (-5.11 to 0.33)	0.085	0.68
	No	132/4070 (3.24%)	45/2882 (1.56%)	-2.51 (-5.29 to 0.27)	0.01		-1.74 (-3.13 to -0.36)	0.014	