Supplementary Online Content

Hood BR, Cowen ME, Zheng H, Hughes RE, Singal B, Hallstrom BR. Association of aspirin with prevention of venous thromboembolism in patients after total knee arthroplasty compared with other anticoagulants. *JAMA Surg*. Published online October 17, 2018. doi:10.1001/jamasurg.2018.3858

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

eMethods

For the analytical dataset 33,796 (81.36%) cases are complete without missing any value and 4,756 (11.45%) are missing only one data element resulting in 38,550 (92.81%) cases that are complete or only missing 1 value. The data point with the most missing values is creatinine with 7.2% missing, followed by assistive device usage at 4.2% missing.

The natural log transformation was applied to operation time and frequency of screening for VTE. Four variables, including age, BMI, pre-surgical hemoglobin and creatinine were centered at mean zero. Kruskal-Wallis Test is used to compare age , BMI, pre-surgical hemoglobin and creatinine and operation times between prophylaxis sub-groups (None, Anticoagulation Only, Aspirin Only, Both Anticoagulation and Aspirin). Chi-square test is used to test the association between categorical variables and prophylaxis sub-groups (None, Anticoagulation Only, Aspirin Only, Both Anticoagulation and Aspirin).

To minimize the loss of power and decrease bias due to exclusion of cases that were missing one or more covariates, missing covariates were imputed 10 times using multivariate sequential regression approach using SAS procedure proc MI and proc MIANALYZE.[1,2] To minimize the potential for bias by indication between patient groups and to enhance causal inference, we derived inverse probability of treatment weights (IPTW) using multinomial logistic regression to determine the probability of patients being in each of four potential prophylactic regimen categories.[3-6] The following explanatory variables were used to derive the probability of a given treatment: age, age^2, BMI, BMI^2, preoperative hemoglobin, preoperative creatinine, sex, ASA score, race, smoking status, insurance type, marital status, preoperative narcotic, steroid, or antiplatelet use, bleeding disorder, history of DVT or PE, use of assistive devices, Elixhauser comorbidities, foot pumps, tranexamic acid, general anesthesia, time period and VTE testing. Stabilized weights were calculated with consideration of marginal propensity score in each treatment group. To further account for overly influential cases (~1% of total cases), the stabilized weights were trimmed at 99th percentiles, with weights beyond 99th percentile replaced by the 99th percentile value. [7-9]

T-test was used to calculate the P values for inferiority.[10,11]

Table 1 in the manuscript is a shortened version for the manuscript. Appendix Table A includes the complete list of unadjusted data elements.

Appendix Table B reports the results of a sensitivity analysis performed by excluding patients with a prior history of VTE, rebuilding the propensity score model and recalculating the OR and P values. While the absolute values of the OR (95%) and p values change slightly when excluding the 2320 cases with a history of VTE, the significance conclusion remains the same. This sensitivity analysis suggests that the fundamental conclusions of the non-inferiority of aspirin compared with other anticoagulants are still established, with p for inferiority = 0.0177 for VTE/PE and p for inferiority = 0.0085 for bleeding, respectively.

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eTable 1

Raw Baseline Data of Study Population

Variable		Population N = 41537	None N = 668		Aspirin Only N =12831		Anticoagulant Only N = 22620		Both N = 5418		Tests
Continuous Variables	N	Mean (SD*)	N	Mean (SD*)	N	Mean (SD*)	N	Mean (SD*)	N	Mean (SD*)	Kruskal-Wallis Test+
Age_at_Case	41537	65.8 (9.8)	668	65.7 (10.2)	12831	65.6 (9.8)	22620	65.5 (9.8)	5418	67.4 (9.4)	p<.0001
BMI	41369	33.1 (6.9)	664	32.6 (6.6)	12783	32.7 (6.7)	22523	33.4 (7.1)	5399	33.1 (6.8)	p<.0001
Pre-op creatinine	37412	0.9 (0.4)	592	0.9 (0.5)	11824	0.9 (0.4)	20166	0.9 (0.4)	4830	0.9 (0.4)	p<.0001
Pre-op hemoglobin	40631	13.7 (1.4)	641	13.5 (1.5)	12511	13.7 (1.4)	22152	13.6 (1.3)	5327	13.7 (1.4)	p<.0001
Operative time (15 min increments)	41518	5.7 (2)	667	6 (2.5)	12817	5.4 (1.8)	22617	5.9 (2.1)	5417	5.6 (1.7)	p<.0001
Categorical Variables		n (n/N %)	Den †	Num‡	Den†	Num‡	Den†	Num‡	Den †	Num‡	Pearson Chi-square tests++
African-American		3230 (7.78%)	668	54 (8.08%)	12831	855 (6.66%)	22620	1840 (8.13%)	5418	481 (8.88%)	p <.0001
Gender (Male)		14966 (36.1%)	668	261 (39.1%)	12822	4882 (38.1%)	22605	7499 (33.2%)	5418	2324 (42.9%)	p <.0001
Marital status(Married)		27462 (66.2%)	667	453 (67.9%)	12795	8658 (67.7%)	22595	14652 (64.8%)	5415	3699 (68.3%)	p <.0001
Smoking status											p <.0001
Never		20818 (50.9%)	654	317 (48.5%)	12626	6458 (51.1%)	22355	11540 (51.6%)	5300	2503 (47.2%)	
Former		16192 (39.6%)	654	276 (42.2%)	12626	4990 (39.5%)	22355	8607 (38.5%)	5300	2319 (43.8%)	
Current		3925 (9.59%)	654	61 (9.33%)	12626	1178 (9.33%)	22355	2208 (9.88%)	5300	478 (9.02%)	
Time period											p <.0001
Apr. 1, 2013-Sep 30, 2013		5226 (12.6%)	667	108 (16.2%)	12819	676 (5.27%)	22617	3656 (16.2%)	5418	786 (14.5%)	
Oct. 1, 2013-Mar 30, 2014		7656 (18.4%)	667	109 (16.3%)	12819	1447 (11.3%)	22617	5038 (22.3%)	5418	1062 (19.6%)	

Apr. 1, 2014-Sep 30, 2014		8429 (20.3%)	667	107 (16.0%)	12819	2318 (18.1%)	22617	4878 (21.6%)	5418	1126 (20.8%)	
Oct. 1, 2014-Mar 30, 2015		9070 (21.8%)	667	154 (23.1%)	12819	3094 (24.1%)	22617	4613 (20.4%)	5418	1209 (22.3%)	
Apr. 1, 2015-Oct 31, 2015		11140 (26.8%)	667	189 (28.3%)	12819	5284 (41.2%)	22617	4432 (19.6%)	5418	1235 (22.8%)	
Surgical approach											p <.0001
Medial parapatellar		34185 (82.3%)	668	542 (81.1%)	12831	10424 (81.2%)	22620	19158 (84.7%)	5418	4061 (75.0%)	
Lateral parapatellar		181 (.44%)	668	< 10	12831	96 (.748%)	22620	52 (.230%)	5418	27 (.498%)	
Midvastus		5814 (14.0%)	668	90 (13.5%)	12831	1774 (13.8%)	22620	2800 (12.4%)	5418	1150 (21.2%)	
Subvastus		1016 (2.45%)	668	15 (2.25%)	12831	420 (3.27%)	22620	479 (2.12%)	5418	102 (1.88%)	
Other		341 (.82%)	668	15 (2.25%)	12831	117 (.912%)	22620	131 (.579%)	5418	78 (1.44%)	
General anesthesia		13383 (32.2%)	667	265 (39.7%)	12819	4211 (32.8%)	22617	7021 (31.0%)	5418	1886 (34.8%)	p <.0001
Steroids		966 (2.33%)	667	22 (3.30%)	12819	268 (2.09%)	22617	572 (2.53%)	5418	104 (1.92%)	p <.0001
Narcotic use prior to surgery		10588 (25.5%)	667	187 (28.0%)	12819	2963 (23.1%)	22617	6222 (27.5%)	5418	1216 (22.4%)	p <.0001
ASA status											p <.0001
I		702 (1.69%)	667	< 10	12806	250 (1.95%)	22599	338 (1.50%)	5416	107 (1.98%)	
II		21837 (52.6%)	667	322 (48.3%)	12806	6986 (54.6%)	22599	11873 (52.5%)	5416	2656 (49.0%)	
III		18480 (44.5%)	667	323 (48.4%)	12806	5438 (42.5%)	22599	10130 (44.8%)	5416	2589 (47.8%)	
IV		469 (1.13%)	667	15 (2.25%)	12806	132 (1.03%)	22599	258 (1.14%)	5416	64 (1.18%)	
Insurance											p <.0001
Commercial		15128 (36.4%)	668	233 (34.9%)	12831	4868 (37.9%)	22620	8335 (36.8%)	5418	1692 (31.2%)	
Federal		19826 (47.7%)	668	307 (46.0%)	12831	5887 (45.9%)	22620	10785 (47.7%)	5418	2847 (52.5%)	
State, Local		1278 (3.08%)	668	21 (3.14%)	12831	455 (3.55%)	22620	691 (3.05%)	5418	111 (2.05%)	
self/unknown/other		5305 (12.8%)	668	107 (16.0%)	12831	1621 (12.6%)	22620	2809 (12.4%)	5418	768 (14.2%)	

On antiplatelet agent before admission		17393 (41.9%)	667	280 (42.0%)	12819	5485 (42.8%)	22617	7837 (34.7%)	5418	3791 (70.0%)	p <.0001
History of bleeding disorder		472 (1.14%)	667	36 (5.40%)	12799	136 (1.06%)	22596	232 (1.03%)	5414	68 (1.26%)	p <.0001
History of VTE		2320 (5.59%)	667	39 (5.85%)	12803	399 (3.12%)	22589	1532 (6.78%)	5409	350 (6.47%)	p <.0001
Use of cane or walker prior to surgery		11911 (30.1%)	617	196 (31.8%)	12068	3373 (27.9%)	21652	6683 (30.9%)	5226	1659 (31.7%)	p <.0001
Tranexamic acid given		25698 (61.9%)	668	381 (57.0%)	12831	9135 (71.2%)	22620	12678 (56.0%)	5418	3504 (64.7%)	p <.0001
Intermittent pneumatic calf compression		36113 (86.9%)	668	607 (90.9%)	12831	11755 (91.6%)	22620	19670 (87.0%)	5418	4081 (75.3%)	p <.0001
Intermittent pneumatic foot pump		5789 (13.9%)	668	93 (13.9%)	12831	1195 (9.31%)	22620	3577 (15.8%)	5418	924 (17.1%)	p <.0001
Comorbidity											
Compression stockings		21116 (50.8%)	668	345 (51.6%)	12831	6595 (51.4%)	22620	10468 (46.3%)	5418	3708 (68.4%)	p <.0001
Congestive heart failure		907 (2.25%)	604	21 (3.48%)	12117	240 (1.98%)	22405	460 (2.05%)	5142	186 (3.62%)	p <.0001
Valvular disease		1256 (3.12%)	604	26 (4.30%)	12117	369 (3.05%)	22405	655 (2.92%)	5142	206 (4.01%)	p <.0001
Pulmonary circulation		310 (.770%)	604	14 (2.32%)	12117	68 (.561%)	22405	175 (.781%)	5142	53 (1.03%)	p <.0001
Peripheral vascular disease		877 (2.18%)	604	15 (2.48%)	12117	228 (1.88%)	22405	485 (2.16%)	5142	149 (2.90%)	p <.0001
Paralysis		82 (.204%)	604	< 10	12117	18 (.149%)	22405	46 (.205%)	5142	15 (.292%)	p <.0001
Other neurologic disorder		1824 (4.53%)	604	33 (5.46%)	12117	529 (4.37%)	22405	1034 (4.62%)	5142	228 (4.43%)	p <.0001
Chronic lung disease		6695 (16.6%)	604	108 (17.9%)	12117	1887 (15.6%)	22405	3861 (17.2%)	5142	839 (16.3%)	p <.0001
Diabetes without chronic complications		7678 (19.1%)	604	121 (20.0%)	12117	2009 (16.6%)	22405	4340 (19.4%)	5142	1208 (23.5%)	p <.0001
Diabetes with chronic complications		711 (1.77%)	604	14 (2.32%)	12117	206 (1.70%)	22405	385 (1.72%)	5142	106 (2.06%)	p <.0001
Hypothyroidism		7606 (18.9%)	604	118 (19.5%)	12117	2169 (17.9%)	22405	4415 (19.7%)	5142	904 (17.6%)	p <.0001
Renal failure		2086 (5.18%)	604	47 (7.78%)	12117	561 (4.63%)	22405	1142 (5.10%)	5142	336 (6.53%)	p <.0001
Liver disease		402 (.998%)	604	16 (2.65%)	12117	125 (1.03%)	22405	223 (.995%)	5142	38 (.739%)	p <.0001
Peptic ulcer disease		11	604	< 10	12117	< 10	22405	< 10	5142	< 10	N/A

		(.027%)									
Acquired immune deficiency syndrome		< 10	N/A	N/A	N/A	N/A	22405	< 10	5142	< 10	N/A
Lymphoma		112 (.278%)	604	< 10	12117	30 (.248%)	22405	65 (.290%)	5142	16 (.311%)	p <.0001
Metastatic cancer		19 (.047%)	604	< 10	12117	< 10	22405	10 (.045%)	5142	< 10	N/A
Solid tumor with or without metastasis		140 (.348%)	604	< 10	12117	45 (.371%)	22405	72 (.321%)	5142	20 (.389%)	p <.0001
Arthritis		1741 (4.32%)	604	32 (5.30%)	12117	526 (4.34%)	22405	946 (4.22%)	5142	237 (4.61%)	p <.0001
Coagulopathy		778 (1.93%)	604	40 (6.62%)	12117	177 (1.46%)	22405	466 (2.08%)	5142	95 (1.85%)	p <.0001
Obesity		11207 (27.8%)	604	178 (29.5%)	12117	3179 (26.2%)	22405	6349 (28.3%)	5142	1501 (29.2%)	p <.0001
Weight loss		81 (.201%)	604	< 10	12117	34 (.281%)	22405	34 (.152%)	5142	11 (.214%)	p <.0001
Electrolyte imbalance		2596 (6.45%)	604	56 (9.27%)	12117	639 (5.27%)	22405	1584 (7.07%)	5142	317 (6.16%)	p <.0001
Blood loss		514 (1.28%)	604	11 (1.82%)	12117	115 (.949%)	22405	348 (1.55%)	5142	40 (.778%)	p <.0001
Deficiency anemia		4412 (11.0%)	604	85 (14.1%)	12117	1049 (8.66%)	22405	2798 (12.5%)	5142	480 (9.33%)	p <.0001
Alcohol abuse		405 (1.01%)	604	< 10	12117	134 (1.11%)	22405	221 (.986%)	5142	42 (.817%)	p <.0001
Drug abuse		319 (.792%)	604	< 10	12117	74 (.611%)	22405	218 (.973%)	5142	20 (.389%)	p <.0001
Psychiatric disorder		805 (2.00%)	604	18 (2.98%)	12117	212 (1.75%)	22405	496 (2.21%)	5142	79 (1.54%)	p <.0001
Depression		6385 (15.9%)	604	119 (19.7%)	12117	1890 (15.6%)	22405	3629 (16.2%)	5142	747 (14.5%)	p <.0001
Hypertension (complicated or uncomplicated)		27134 (67.4%)	604	409 (67.7%)	12117	7813 (64.5%)	22405	15151 (67.6%)	5142	3761 (73.1%)	p <.0001

*SD: standard deviation

[+]Kruskal-Wallis Test: non-parametric testing of continuous variables for comparing independent groups

[++] Pearson Chi-square tests: testing of association between two variables;

†Den: Denominator

‡Num: Numerator

Actual numbers for cell size <10 are not shown

eTable 2. Adjusted Odds Ratio for the Primary Outcome VTE/Death and Secondary Outcome Bleeding Event: Excluding patients with VTE history

Confounders considered in propensity score model include: age, age^2, BMI, BMI^2, preoperative hemoglobin, platelets and creatinine, sex, ASA, race, smoking status, insurance, marital status, preoperative narcotic, steroid, or antiplatelet use, bleeding disorder, use of assistive devices, Elixhauser variables, surgical approach, operative duration, pneumatic compression devices, foot pumps, tranexamic acid, anesthesia type.

	VTE/Death*					Bleeding Event*				
Comparisons	OR (95% CI)	*P* value for OR	Absolute change in OR†: $\Delta_{OR} = \lvert OR_2 - OR_1 \rvert$	Relative change in OR‡: 100% X Δ_{OR} / min(OR_1, OR_2)	*p for inferiority*	OR (95% CI)	*P* value for OR	Absolute change in OR†: $\Delta_{OR} = \lvert OR_2 - OR_1 \rvert$	Relative change in OR‡: 100% X Δ_{OR} / min(OR_1, OR_2)	*p for inferiority*
None vs. anticoagulant only	6.23 (4.46, 8.72)	<.0001	1.1	21.44%		1.21 (0.70, 2.07)	0.50	0.01	0.83%	
Aspirin only vs. anticoagulant only	1.02 (0.80, 1.30)	0.89	0.17	20.00%	0.0177	0.81 (0.64, 1.02)	0.08	0.01	1.25%	0.0085
Both vs. anticoagulant only	1.11 (0.84,1.47)	0.45	0.1	9.90%		0.94 (0.71,1.25)	0.68	0.04	4.26%	
Sensitivity of excluding VTE history	***Significance conclusion unchanged***			***Greatest possible relative change< 21.5%***	***Significance conclusion unchanged***	***Significance conclusion unchanged***			***Greatest possible relative change < 5%***	***Significance conclusion unchanged***

Note

* Historical VTE cases excluded (n = 2320 which is 5.6% of the total)

† Absolute change in OR point estimates is calculated by the absolute changes in odds ratio (OR), i.e., $\Delta_{OR} = \lvert OR_2 - OR_1 \rvert$, where OR_1 is the OR obtained using the complete dataset including VTE history cases, while OR_2 is the OR excluding VTE history cases.

‡ Relative changes in OR point estimates is the relative difference in OR including VTE history vs excluding VTE history, calculated by Δ_{OR} /min(OR_1, OR_2) X 100%, where OR_1 is the OR obtained using the complete dataset including VTE history cases, while OR_2 is the OR excluding VTE history cases. The minimum value of min(OR_1, OR_2) allows to capture the biggest relative differences.