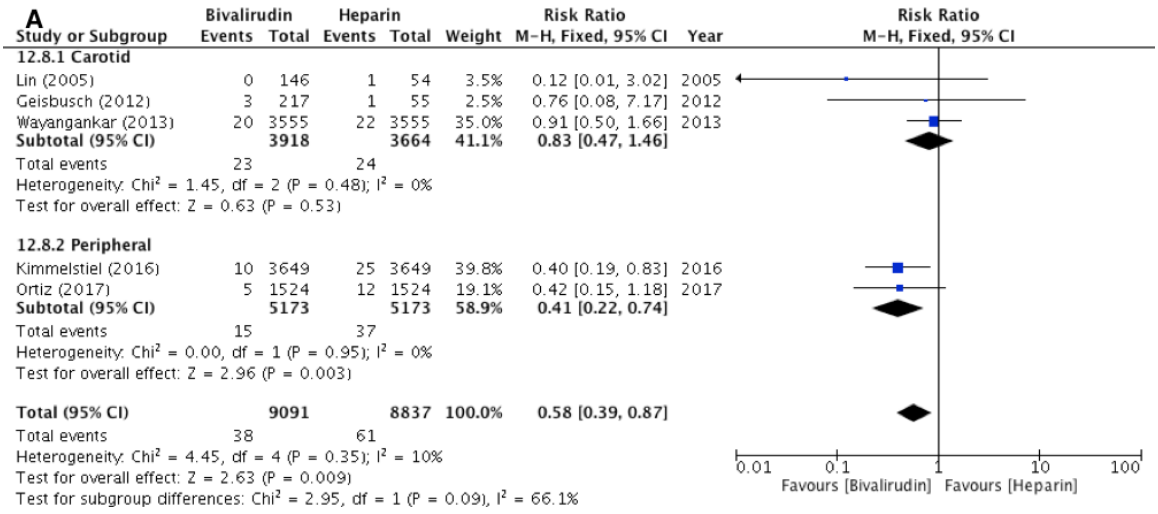
Supplemental table 1. Bleeding definitions

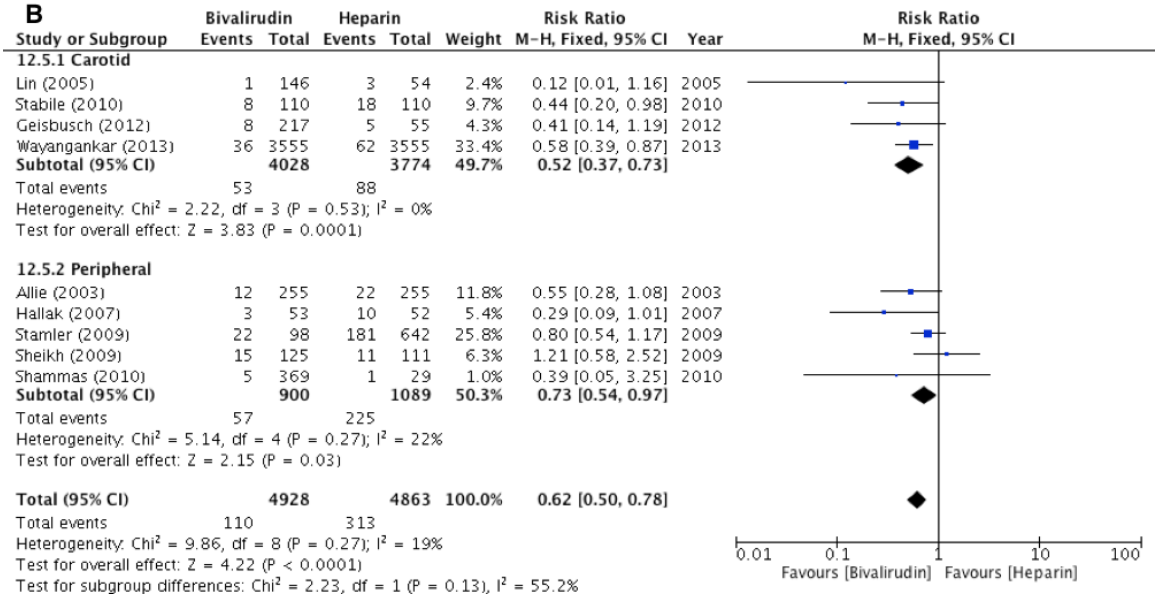
Study	Major Bleeding	Minor Bleeding	All bleeding
Allie et al	Drop in hemoglobin of ≥ 3 g/dl, cerebrovascular accident, any complications requiring surgery, intracranial bleeding, retroperitoneal hematoma, > 5 cm groin hematoma, or > 2 units packed cell transfusion.	Non-intracranial or retroperitoneal bleeding, small (< 5 cm) groin hematomas and transfusion of ≤ 2 units packed cells.	Combination of major and minor bleeding was used
Lin et al	Major groin or retroperitoneal bleeding requiring operative evacuation or blood transfusion		Major bleeding was used
Hallak et al	Hemorrhagic event leading to surgery or death, extended or unexpected hospitalization, intracranial hemorrhage, transfusion of >2 units of whole blood or packed red blood cells, a fall in hemoglobin (Hgb) >5 g/dl (or >15% of hematocrit) with no bleeding site identified	Drop in hemoglobin of >3 g/dl but <5 g/dl, with bleeding from a known site; a spontaneous gross hematuria, hemoptysis, or hematemesis; as well as any bleeding event that did not meet the criteria for a major hemorrhage	Combination of major and minor bleeding was used
Sheikh et al	Intracranial or retroperitoneal hemorrhage, a fall in hemoglobin of 5 g/dl, and/or transfusion of 2 U of packed red blood cells (PRBCs) for any reason	Bleeding that did not meet the major bleeding criteria	Combination of major and minor bleeding was used
Stamler et al	Overt blood loss resulting in a decrease of hemoglobin level of more than 3 g/dL, any decrease in hemoglobin of more than 4 g/dL, transfusion of at least 2 U of whole blood or packed red blood cells, or intracranial or retroperitoneal hemorrhage	All hematomas that did not meet the criteria for major bleeding, transfusion of less than 2 U of packed red blood cells, or other non-intracranial or retroperitoneal bleeding	Combination of major and minor bleeding was used
Shammas et al	Drop in hemoglobin .3 g/dL with a source of bleed-ing, any .4-g/dL decrease in hemoglobin, and/or intracranial or retroperitoneal bleeding	Bleeding that did not meet the major bleeding criteria	Combination of major and minor bleeding was used
Stabile et al	Hemorrhagic stroke or if hematocrit decreased by 15 points or by 10 to 15 points with clinical bleeding	Hematocrit decreased by 10 points with clinical bleeding or by 10 to 15 points without clinical bleeding	Combination of major and minor bleeding was used
Geisbuch et al	Bleeding requiring any surgical or interventional repair, bleeding requiring any transfusion of whole blood or packed red blood cells, intracerebral hemorrhage and clinical bleeding with a hematocrit decrease of >10 points	onset of hematoma clinical bleedings with a hematocrit decrease of <10 points	Combination of major and minor bleeding was used
Wayangankar et al			Procedure-related bleeding or hematoma requiring red blood cell transfusion, and intracerebral hemorrhage

Supplemental table 1. Quality assessment

Author	Year	Selection				Comparability		Outcome			Total
		1	2	3	4	1	2	1	2	3	
Allie et al	2003	*	*	*	*	*	*	*	*	*	9
Lin et al	2005	*	-	*	*	-	*	*	*	*	7
Hallak et al	2007	*	-	*	-	*	-	*	*	*	6
Sheikh et al	2009	*	*	*	-	*	*	*	*	*	7
Stamler et al	2009	*	*	*	-	-	*	*	*	*	7
Shammas et al	2010	*	-	*	*	-	*	*	*	*	7
Stabile et al	2010	*	*	-	*	*	*	*	*	*	8
Geisbuch et al	2012	-	*	*	*	-	-	*	*	*	6
Wayangankar et al	2013	*	*	*	*	*	*	*	*	*	9
Kimmelstiel et al	2016	*	*	*	*	*	*	*	*	*	9
Ortiz et al	2017	*	*	*	*	*	*	*	*	*	9

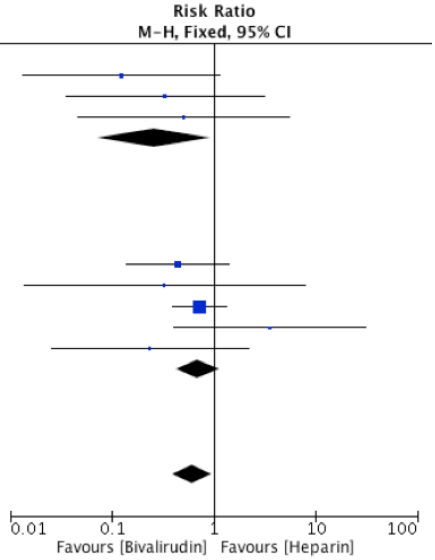
Supplemental figure 1. **Forest plot**. Comparison of subgroups according to anatomic location of intervention (Carotid versus other peripheral interventions) in patients undergoing peripheral interventions for all-cause mortality (A), all-bleeding (B), major bleeding (C), and access site complications (D) between bivalirudin versus heparin.





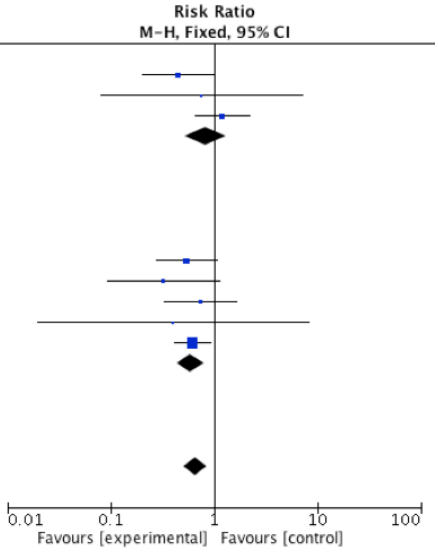
C

Study or Subgroup	Bivalirudin Events	Bivalirudin Total	Heparin Events	Heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
12.6.1 Carotid							
Lin (2005)	1	146	3	54	9.4%	0.12 [0.01, 1.16]	2005
Stabile (2010)	1	110	3	110	6.5%	0.33 [0.04, 3.16]	2010
Geisbusch (2012)	2	217	1	55	3.4%	0.51 [0.05, 5.49]	2012
Subtotal (95% CI)		**473**		**219**	**19.3%**	**0.26 [0.07, 0.94]**	
Total events	4		7				
Heterogeneity: Chi^2 = 0.77, df = 2 (P = 0.68); I^2 = 0%							
Test for overall effect: Z = 2.06 (P = 0.04)							
12.6.2 Peripheral							
Allie (2003)	4	255	9	255	19.4%	0.44 [0.14, 1.42]	2003
Hallak (2007)	0	53	1	52	3.3%	0.33 [0.01, 7.85]	2007
Stamler (2009)	10	98	91	642	51.8%	0.72 [0.39, 1.33]	2009
Sheikh (2009)	4	125	1	111	2.3%	3.55 [0.40, 31.31]	2009
Shammas (2010)	3	369	1	29	4.0%	0.24 [0.03, 2.20]	2010
Subtotal (95% CI)		**900**		**1089**	**80.7%**	**0.69 [0.42, 1.14]**	
Total events	21		103				
Heterogeneity: Chi^2 = 3.85, df = 4 (P = 0.43); I^2 = 0%							
Test for overall effect: Z = 1.45 (P = 0.15)							
Total (95% CI)		**1373**		**1308**	**100.0%**	**0.61 [0.39, 0.96]**	
Total events	25		110				
Heterogeneity: Chi^2 = 6.18, df = 7 (P = 0.52); I^2 = 0%							
Test for overall effect: Z = 2.13 (P = 0.03)							
Test for subgroup differences: Chi^2 = 1.95, df = 1 (P = 0.16), I^2 = 48.7%							

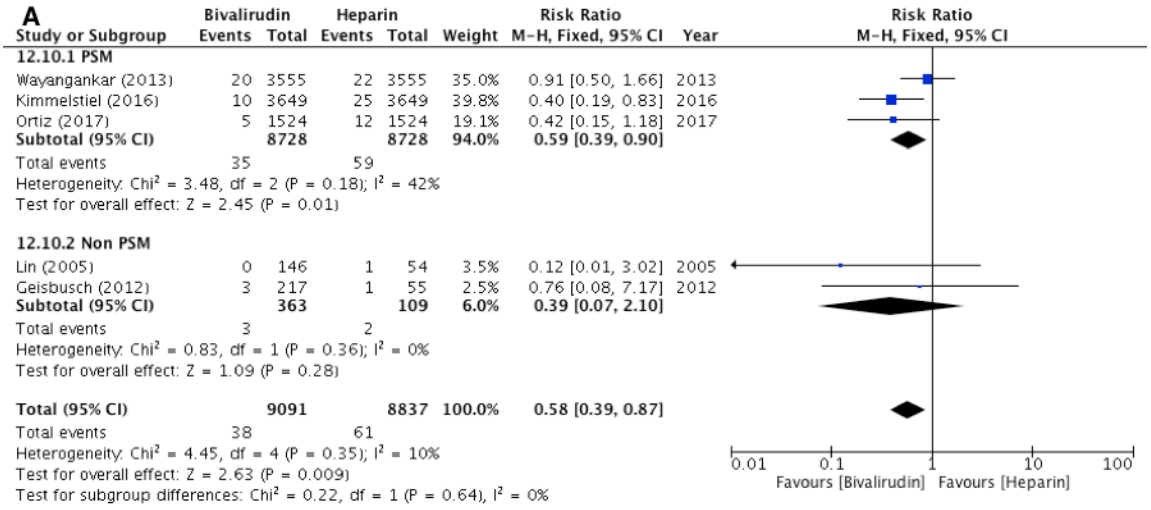


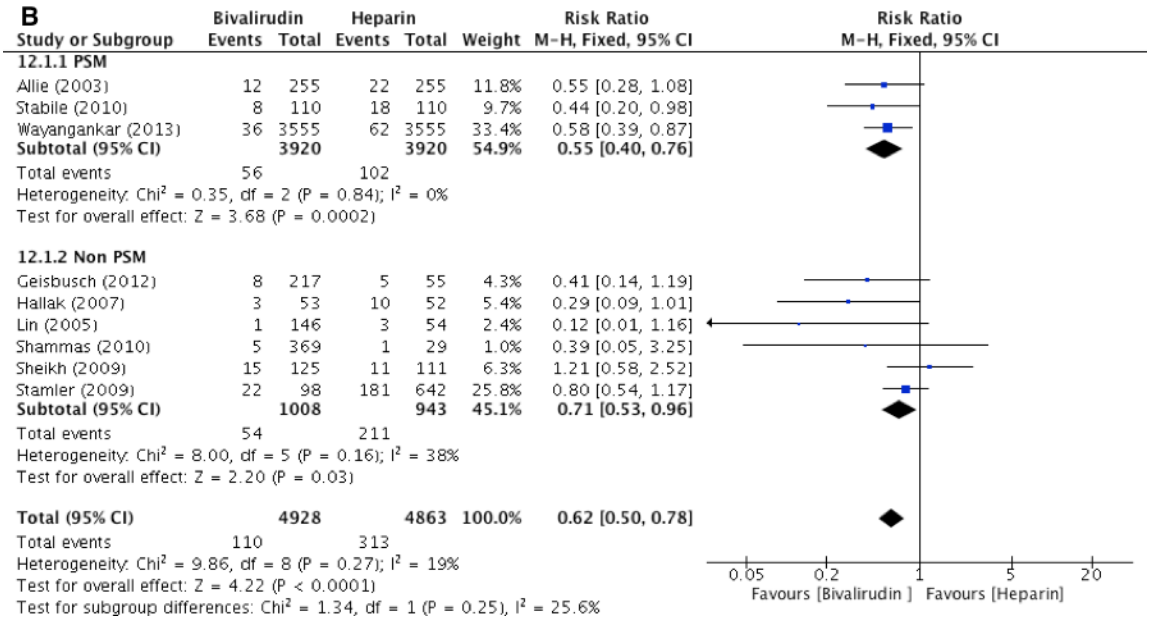
D

Study or Subgroup	Bivalirudin Events	Bivalirudin Total	Heparin Events	Heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
12.9.1 Carotid							
Stabile (2010)	8	110	18	110	12.6%	0.44 [0.20, 0.98]	2010
Geisbusch (2012)	3	217	1	55	1.1%	0.76 [0.08, 7.17]	2012
Wayangankar (2013)	23	3555	19	3555	13.3%	1.21 [0.66, 2.22]	2013
Subtotal (95% CI)		**3882**		**3720**	**26.9%**	**0.83 [0.53, 1.32]**	
Total events	34		38				
Heterogeneity: Chi^2 = 3.90, df = 2 (P = 0.14); I^2 = 49%							
Test for overall effect: Z = 0.77 (P = 0.44)							
12.9.2 Peripheral							
Allie (2003)	12	255	22	255	15.4%	0.55 [0.28, 1.08]	2003
Hallak (2007)	3	53	9	52	6.3%	0.33 [0.09, 1.14]	2007
Sheikh (2009)	10	125	12	111	8.9%	0.74 [0.33, 1.65]	2009
Shammas (2010)	2	369	0	29	0.6%	0.41 [0.02, 8.25]	2010
Ortiz (2017)	37	1524	60	1524	41.9%	0.62 [0.41, 0.92]	2017
Subtotal (95% CI)		**2326**		**1971**	**73.1%**	**0.59 [0.43, 0.80]**	
Total events	64		103				
Heterogeneity: Chi^2 = 1.32, df = 4 (P = 0.86); I^2 = 0%							
Test for overall effect: Z = 3.38 (P = 0.0007)							
Total (95% CI)		**6208**		**5691**	**100.0%**	**0.66 [0.51, 0.84]**	
Total events	98		141				
Heterogeneity: Chi^2 = 6.63, df = 7 (P = 0.47); I^2 = 0%							
Test for overall effect: Z = 3.26 (P = 0.001)							
Test for subgroup differences: Chi^2 = 1.53, df = 1 (P = 0.22), I^2 = 34.7%							

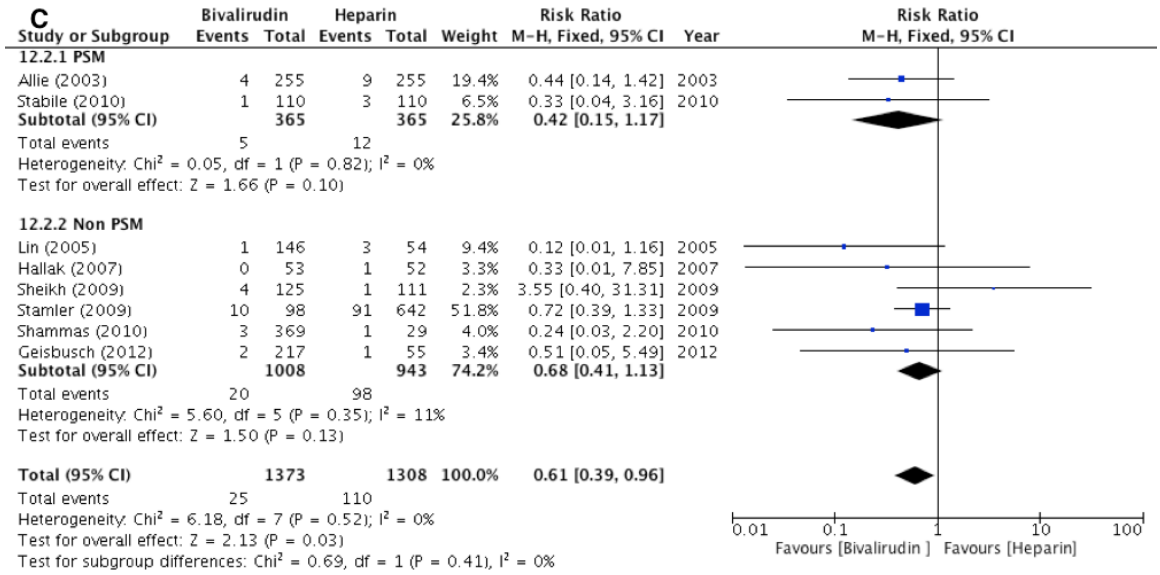


Supplemental figure 2. Comparison of subgroups according to study design (PSM versus non-PSM) in patients undergoing peripheral interventions for all-cause mortatlity (A), all-bleeding (B), major bleeding (C), and access site complications (D) between bivalirudin versus heparin.

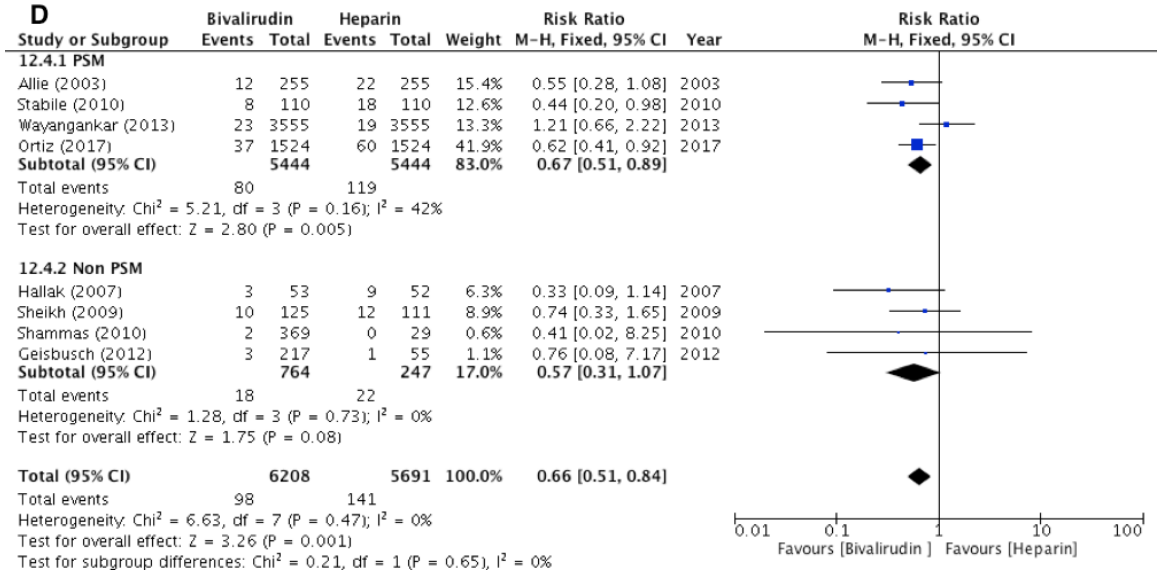




C


Bivalirudin
Heparin
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
12.2.1 PSM
Allie (2003) 4 255 9 255 19.4% 0.44 [0.14, 1.42] 2003
Stabile (2010) 1 110 3 110 6.5% 0.33 [0.04, 3.16] 2010
Subtotal (95% CI) 365 365 25.8% 0.42 [0.15, 1.17]
Total events 5 12
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)
12.2.2 Non PSM
Lin (2005) 1 146 3 54 9.4% 0.12 [0.01, 1.16] 2005
Hallak (2007) 0 53 1 52 3.3% 0.33 [0.01, 7.85] 2007
Sheikh (2009) 4 125 1 111 2.3% 3.55 [0.40, 31.31] 2009
Stamler (2009) 10 98 91 642 51.8% 0.72 [0.39, 1.33] 2009
Shammas (2010) 3 369 1 29 4.0% 0.24 [0.03, 2.20] 2010
Geisbusch (2012) 2 217 1 55 3.4% 0.51 [0.05, 5.49] 2012
Subtotal (95% CI) 1008 943 74.2% 0.68 [0.41, 1.13]
Total events 20 98
Heterogeneity: Chi² = 5.60, df = 5 (P = 0.35); I² = 11%
Test for overall effect: Z = 1.50 (P = 0.13)
Total (95% CI) 1373 1308 100.0% 0.61 [0.39, 0.96]
Total events 25 110
Heterogeneity: Chi² = 6.18, df = 7 (P = 0.52); I² = 0%
Test for overall effect: Z = 2.13 (P = 0.03)
Test for subgroup differences: Chi² = 0.69, df = 1 (P = 0.41), I² = 0%
0.01 0.1 1 10 100
Favours [Bivalirudin] Favours [Heparin]

D


Bivalirudin
Heparin
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
12.4.1 PSM
Allie (2003) 12 255 22 255 15.4% 0.55 [0.28, 1.08] 2003
Stabile (2010) 8 110 18 110 12.6% 0.44 [0.20, 0.98] 2010
Wayangankar (2013) 23 3555 19 3555 13.3% 1.21 [0.66, 2.22] 2013
Ortiz (2017) 37 1524 60 1524 41.9% 0.62 [0.41, 0.92] 2017
Subtotal (95% CI) 5444 5444 83.0% 0.67 [0.51, 0.89]
Total events 80 119
Heterogeneity: Chi² = 5.21, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 2.80 (P = 0.005)
12.4.2 Non PSM
Hallak (2007) 3 53 9 52 6.3% 0.33 [0.09, 1.14] 2007
Sheikh (2009) 10 125 12 111 8.9% 0.74 [0.33, 1.65] 2009
Shammas (2010) 2 369 0 29 0.6% 0.41 [0.02, 8.25] 2010
Geisbusch (2012) 3 217 1 55 1.1% 0.76 [0.08, 7.17] 2012
Subtotal (95% CI) 764 247 17.0% 0.57 [0.31, 1.07]
Total events 18 22
Heterogeneity: Chi² = 1.28, df = 3 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.75 (P = 0.08)
Total (95% CI) 6208 5691 100.0% 0.66 [0.51, 0.84]
Total events 98 141
Heterogeneity: Chi² = 6.63, df = 7 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.26 (P = 0.001)
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%
0.01 0.1 1 10 100
Favours [Bivalirudin] Favours [Heparin]

Supplemental figure 3. **Funnel plot.** Statistically significant outcomes. (A) All-cause mortality, (B) All-bleeding, (C) Major bleeding, (D) Minor bleeding, (E)Access site complications.