DVT PROPHYLAXIS IN HOSPITALIZED MEDICAL PATIENTS

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Introduction

- VTE (DVT/PE) is an important complication in hospitalized patients
- Hospitalization for acute medical illness is associated with an eightfold increased risk of VTE
- VTE in hospitalized patients accounts for about one-fourth of all VTE events in the community

J Crit Care 2002;17:95-104
Chest. 2012;141(2_suppl):e195S-e226S

VTE risk in hospitalized medical patient

- VTE risk in medical-surgical critically ill patients:
  - 13-31% (from observational studies, regardless of thromboprophylaxis)
- VTE risk in hospitalized medical patients :
  - DVT 0.8%, PE 0.4% (Pooled average from control arm of RCTs, not receiving thromboprophylaxis)

- Data from RCTs may be misleading as RCTs are done in highly selective populations
- Incidence estimates from observational studies could also be erroneous because of heterogeneous population and inclusion of non-selective population (Both with and without thromboprophylaxis)

J Crit Care 2002;17:95-104
Chest. 2012;141(2_suppl):e195S-e226S

Risk factors in critically ill patient

- Underlying severe illness
- Sedative and neuromuscular blocker drugs
- Invasive vascular lines
- Prolonged immobilization

- Signs and symptoms are challenging to recognize as there is impaired consciousness and frequently there is bilateral pedal edema due to illness

Modified Padua risk prediction score

Risk Factor	Points
Active cancer	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility	3
Already known thrombophilic condition	3
Recent (≤ 1 mo) trauma and/or surgery	2
Elderly age (≥ 70 y)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥ 30)	1
Ongoing hormonal treatment	1

Reduced mobility: Anticipated bed rest with bathroom privileges for at least 3 d.

N Engl J Med. 2005 Mar 10;352(10):969-77

Modified Padua risk prediction score

- High risk for VTE: ≥ 4 points
- Low risk for VTE: < 4 points
- VTE incidence among patients who did not receive prophylaxis:
  - 11% in high-risk vs 0.3% in low-risk
  - HR, 32.0; 95% CI, 4.1-251.0

N Engl J Med. 2005 Mar 10;352(10):969-77

Bleeding risk in hospitalized patients

- Bleeding risk while on pharmacological thromboprophylaxis: 0.4% (Pooled average from control arm of RCTs)
- Bleeding risk in patients on LMWH: 7-23% (Data from observational studies)

Chest. 2012;141(2_suppl):e195S-e226S
J Crit Care 2009;24:197-205

Risk factors for bleeding in hospitalized medical patients

Risk Factor	Total Patients, No. (%) (N = 10,866)	OR (95% CI)
Active gastroduodenal ulcer	236 (2.2)	4.15 (2.21-7.77)
Bleeding in 3 mo before admission	231 (2.2)	3.64 (2.21-5.99)
Platelet count < 50 × 10^9/L	179 (1.7)	3.37 (1.84-6.18)
Age ≥ 85 y (vs < 40 y)	1,178 (10.8)	2.96 (1.43-6.15)
Hepatic failure (INR > 1.5)	219 (2.0)	2.18 (1.10-4.33)
Severe renal failure (GFR < 30 mL/min/m^2)	1,084 (11.0)	2.14 (1.44-3.20)
ICU or CCU admission	923 (8.5)	2.10 (1.42-3.10)
Central venous catheter	820 (7.5)	1.85 (1.18-2.90)
Rheumatic disease	740 (6.8)	1.78 (1.09-2.89)
Current cancer	1,166 (10.7)	1.78 (1.20-2.63)
Male sex	5,367 (49.4)	1.48 (1.10-1.99)

IMPROVE multinational study (N = 10,866)
25% were on aspirin
48% were on pharmacological thromboprophylaxis

Chest. 2011;139(1):69-79

Available anticoagulant for DVT prophylaxis

Type of agent	Dosage-DVT prophylaxis	DVT treatment	Special circumstance
Unfractionated heparin	5000 U s.c. BD/TDS	80 U/kg bolus followed by 18 U/kg/h	Renal failure: Dose modification Increased incidence of HIT
LMWH Enoxaparin Dalteparin	40 mg s.c. OD 5000 U s.c. OD	1 mg/kg s.c. BD 5000 U s.c. BD	Renal failure: Enoxaparin-0.5 mg/kg s.c. BD Dalteparin: No dosage modification
Fondaparinux	2.5 mg s.c. OD	Weight based normogram	C/I in patients with CrCl<30 ml/min
Rivaroxaban	20 mg PO OD	15 mg PO BD	To be avoided in patients with renal failure

Is thromboprophylaxis necessary?

Any anticoagulation (UFH, LMWH, Fondaparinux) vs none

Outcome	RCTs	N	RR
Symptomatic DVT	4	5206	**0.42 (0.22-1)**
Non-fatal PE	6	5206	0.61 (0.23-1.67)
Major bleeding	8	8605	1.32 (0.73-2.37)
Overall mortality	5	7355	0.97 (0.79-1.19)

Ann Intern Med. 2007 Feb 20;146(4):278-88
J Thromb Haemost. 2008 Mar;6(3):405-14

Patient populations

- Acutely ill medical patients
- Critically ill medical patients
- Newer agents for thromboprophylaxis

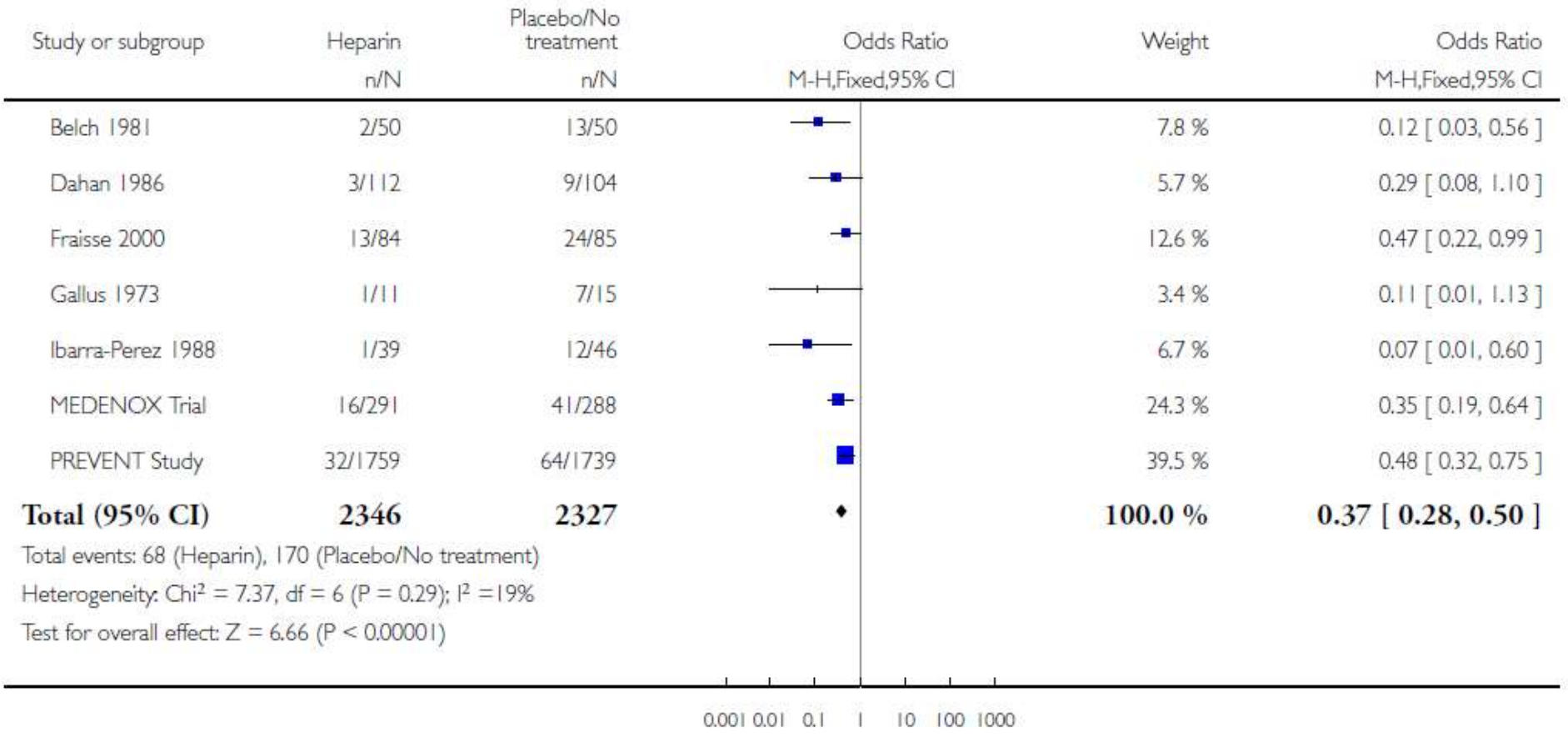
HOSPITALIZED ACUTE ILL MEDICAL PATIENTS

Hospitalized medically ill

HEPARIN (ANY FORM) VS PLACEBO

Heparin (any form) vs placebo: DVT

Outcome: 1 Deep vein thrombosis



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Heparin (any form) vs placebo: PE

Comparison: 1 Heparin versus Placebo / No treatment

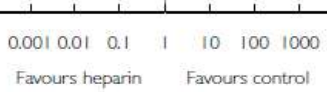
Outcome: 2 Pulmonary embolism

Study or subgroup	Heparin n/N	Placebo/No treatment n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Belch 1981	0/50	2/50		2.3 %	0.19 [0.01, 4.10]
Bergman 1996	10/1230	17/1244		15.9 %	0.59 [0.27, 1.30]
Dahan 1986	1/135	3/135		2.8 %	0.33 [0.03, 3.20]
Fraisse 2000	0/108	0/113			Not estimable
Gallus 1973	0/11	0/15			Not estimable
Gardlund 1996	44/5776	74/5917		68.8 %	0.61 [0.42, 0.88]
Ibarra-Perez 1988	0/39	3/46		3.0 %	0.16 [0.01, 3.14]
MEDENOX Trial	0/291	3/288		3.3 %	0.14 [0.01, 2.72]
PREVENT Study	5/1759	4/1740		3.8 %	1.24 [0.33, 4.61]
Total (95% CI)	**9399**	**9548**		**100.0 %**	**0.58 [0.42, 0.80]**

Total events: 60 (Heparin), 106 (Placebo/No treatment)

Heterogeneity: $Chi^2 = 3.68$, $df = 6$ ($P = 0.72$); $I^2 = 0.0\%$

Test for overall effect: $Z = 3.38$ ($P = 0.00073$)



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Heparin (any form) vs placebo: Mortality

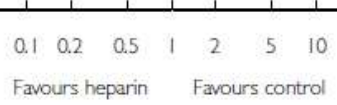
Outcome: 3 Death

Study or subgroup	Heparin n/N	Placebo/No treatment n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bergman 1996	124/1230	128/1244		23.1 %	0.98 [0.75, 1.27]
Dahan 1986	6/135	6/135		1.2 %	1.00 [0.31, 3.18]
Fraisse 2000	8/108	8/113		1.5 %	1.05 [0.38, 2.90]
Gardlund 1996	304/5776	333/5917		62.9 %	0.93 [0.79, 1.09]
MEDENOX Trial	12/360	16/362		3.1 %	0.75 [0.35, 1.60]
PREVENT Study	43/1848	42/1833		8.3 %	1.02 [0.66, 1.56]
Total (95% CI)	**9457**	**9604**		**100.0 %**	**0.95 [0.83, 1.07]**

Total events: 497 (Heparin), 533 (Placebo/No treatment)

Heterogeneity: $Chi^2 = 0.62$, $df = 5$ ($P = 0.99$); $I^2 = 0.0\%$

Test for overall effect: $Z = 0.86$ ($P = 0.39$)



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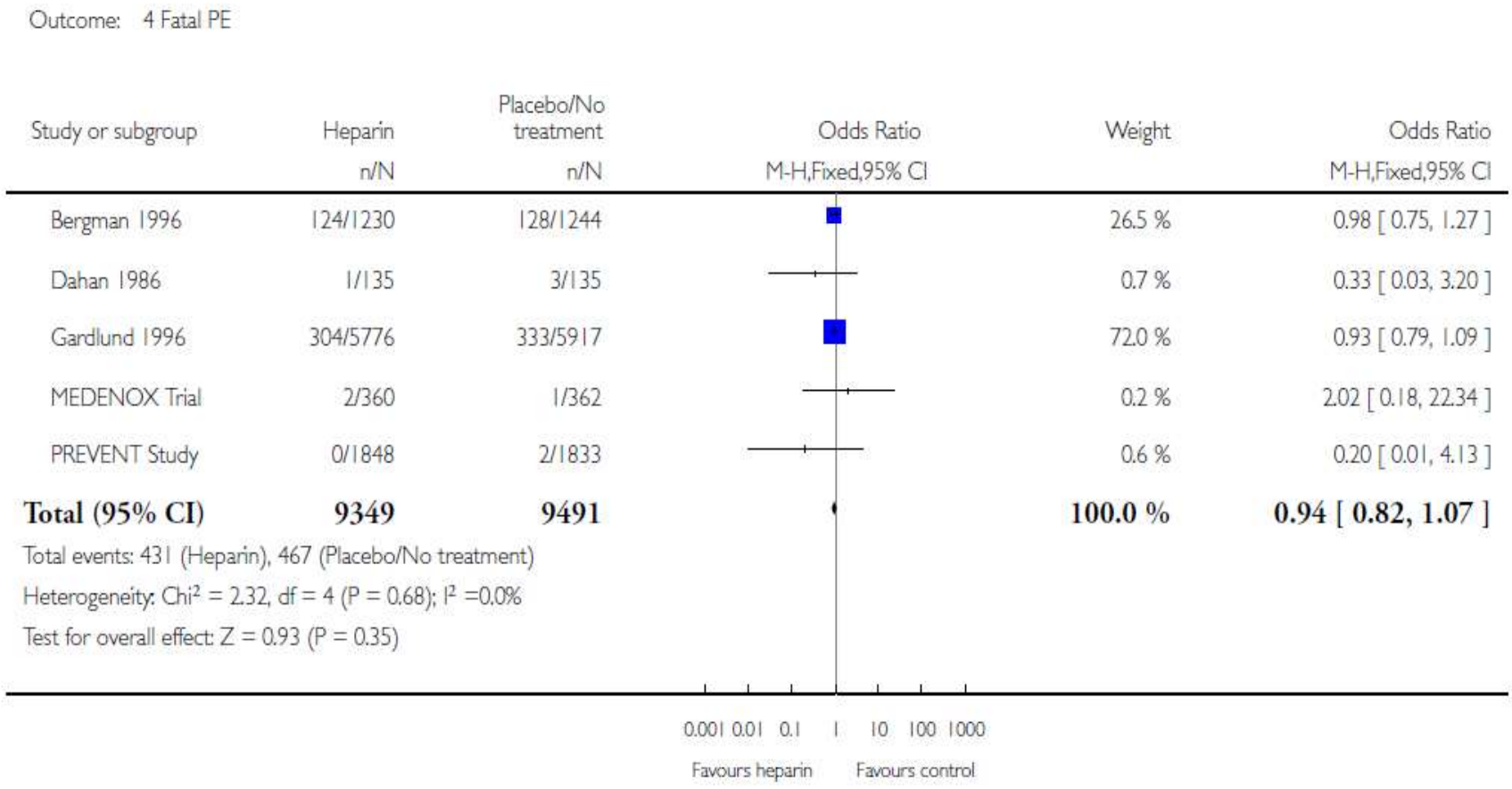
Heparin (any form) vs placebo: Fatal PE



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Heparin (any form) vs placebo: Major bleed

Outcome: 5 Major bleeding

Study or subgroup	Heparin n/N	Placebo/No treatment n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Belch 1981	0/50	0/50			Not estimable
Dahan 1986	1/135	3/135		15.7 %	0.33 [0.03, 3.20]
Fraisse 2000	6/108	3/113		14.6 %	2.16 [0.53, 8.85]
Gardlund 1996	14/5776	6/5917		31.2 %	2.39 [0.92, 6.23]
Ibarra-Perez 1988	4/39	0/46		2.2 %	11.79 [0.61, 226.19]
MEDENOX Trial	7/360	4/362		20.6 %	1.77 [0.52, 6.12]
PREVENT Study	9/1848	3/1833		15.8 %	2.99 [0.81, 11.04]
Total (95% CI)	**8316**	**8456**		**100.0 %**	**2.20 [1.28, 3.78]**

Total events: 41 (Heparin), 19 (Placebo/No treatment)

Heterogeneity: $Chi^2 = 4.28$, $df = 5$ ($P = 0.51$); $I^2 = 0.0\%$

Test for overall effect: $Z = 2.87$ ($P = 0.0042$)

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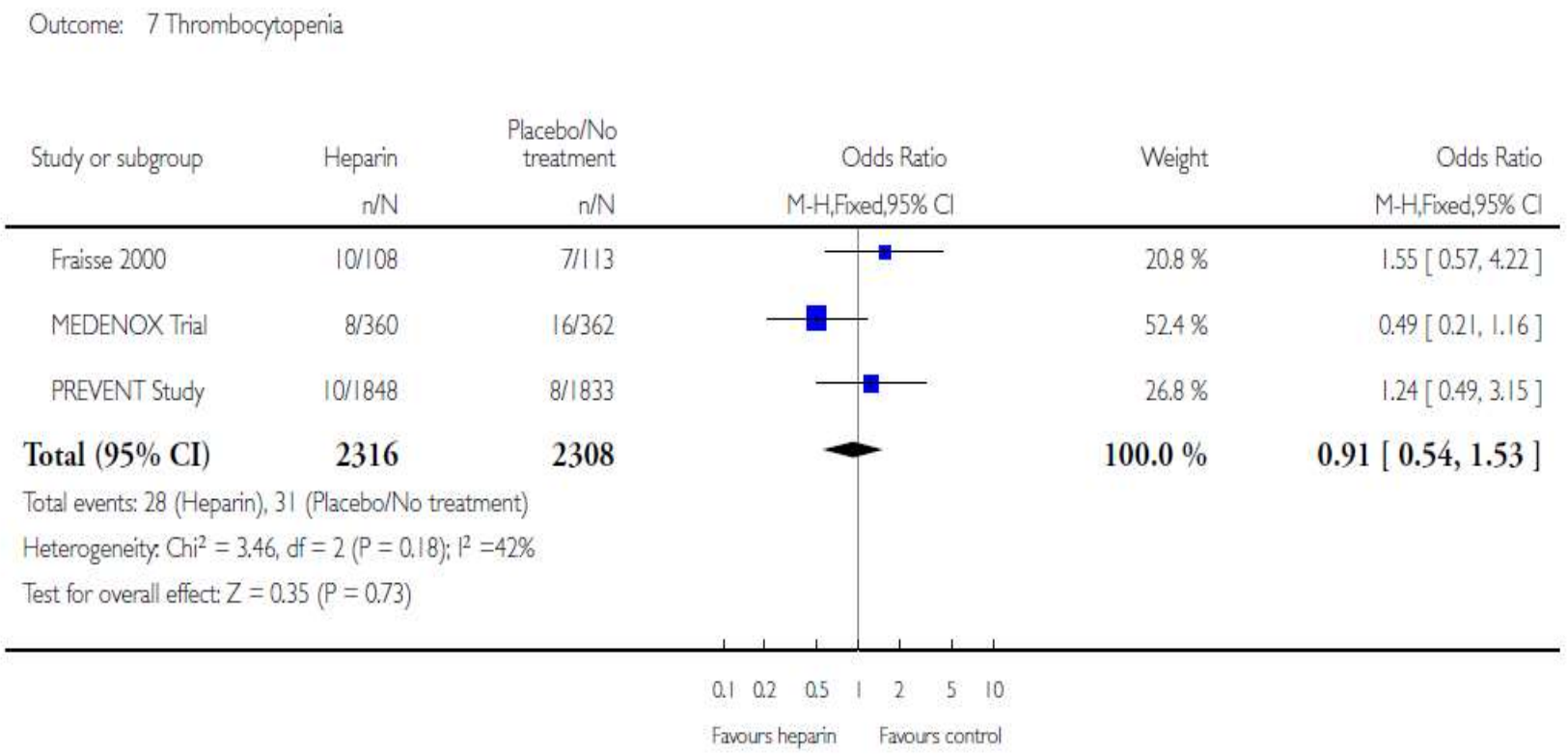
Heparin (any form) vs placebo: Thrombocytopaenia



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UFH vs placebo: Gardlund, 1996

- n= 19,751 consecutive patients, aged 55 years or older
- 5776 were assigned subcutaneous UFH (5000 IU every 12 h) until hospital discharge or for a maximum of 3 weeks
- 5917 were assigned no prophylactic treatment (control group)
- Follow-up was for 3 weeks after discharge from hospital or for a maximum of 60 days from randomisation.

Lancet. 1996 May 18;347(9012):1357-61

UFH vs placebo: Gardlund, 1996

- Non-fatal VTE occurred in more of the control than of the heparin group (116 vs 70, p = 0.0012)
- Significant difference between heparin and control groups in time to fatal PE (28 vs 12.5 days, p = 0.007)
- Mortality similar in the heparin and control groups (5.3 vs 5.6%, p = 0.39)

Lancet. 1996 May 18;347(9012):1357-61

LMWH vs placebo: PREVENT study

- 3706 Medically ill patients
- Age >40 years
- Received subcutaneous Dalteperin 5000 iu od or placebo
- Duration 14 days
- At 14d, VTE was reduced from 4.96% in the placebo group to 2.77% in the dalteparin group, an ARR of 2.19% or a RRR of 45% (RR, 0.55; 95% CI, 0.38 to 0.80; P=0.0015)
- At 90d, the incidence of symptomatic VTE was 0.93% in the dalteparin group and 1.33% in the placebo group, a RRR of 30% (RR, 0.70; 95% CI, 0.36 to 1.35)
- No significant difference in mortality at 14, 21, or 90 days

Blood 2003;102(11):Abstract 1153

UFH vs Placebo: MEDENOX Trial

- N 1,102
- Randomly assigned to receive 40 mg of enoxaparin, 20 mg of enoxaparin, or placebo, given SC OD for 6–14 days
- VTE at 14d was 5.5% in enoxaparin 40mg group as compared with 14.9% in the placebo group ($p < 0.001$)
- 1.9% major bleeding occurred in heparin group as compared to 1.10% in case of placebo
- Thrombocytopenia was also not significantly different between two groups

American Journal of Cardiology 2000;86(12B):48M–52M.

Summary: Heparin (Any form) vs Placebo

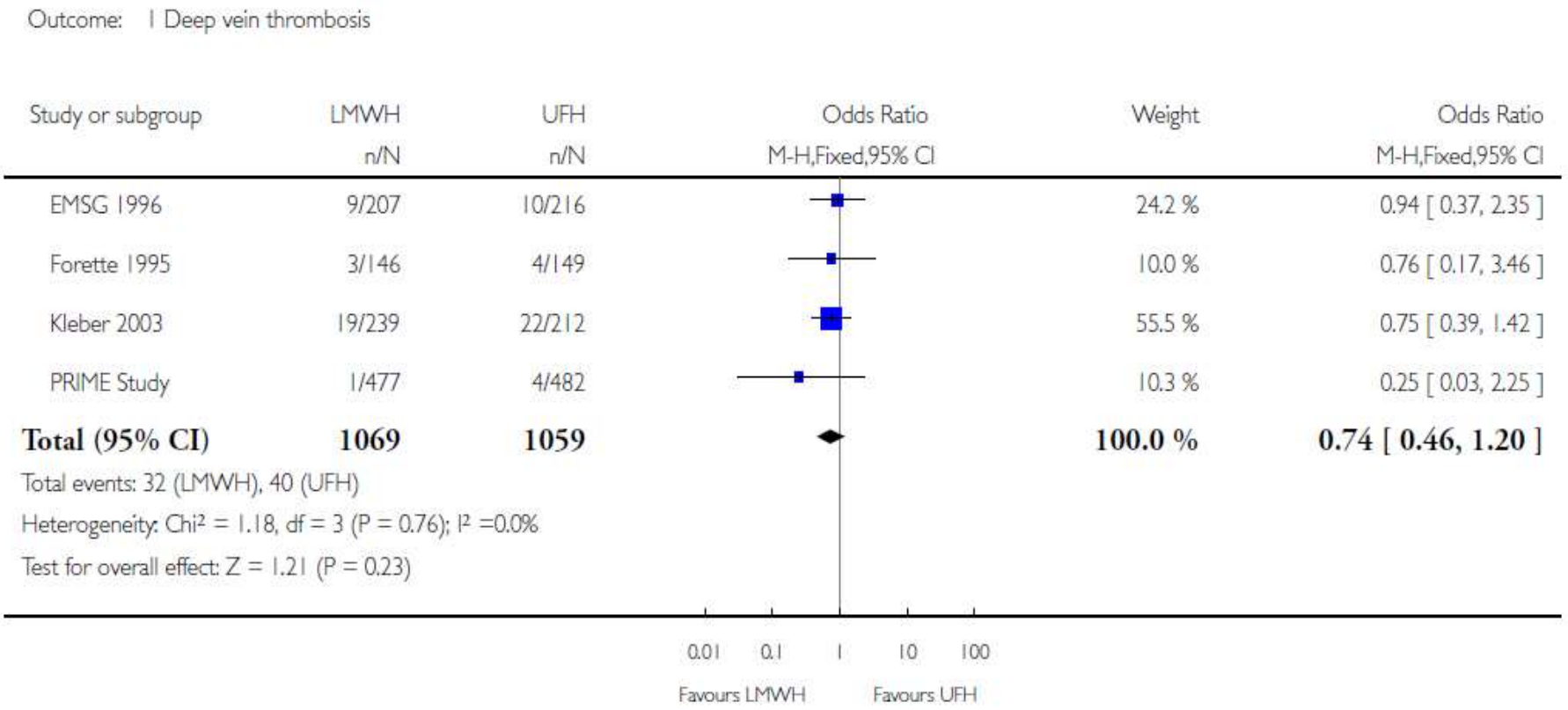
Use of heparin thromboprophylaxis in hospitalized acutely ill patient

- Decreases the incidence of DVT & PE
- But there is no mortality benefit
- There is no significant risk of major bleeding or thrombocytopenia

Hospitalized medically ill

UFH VS LMWH

UFH vs LMWH: DVT



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UFH VS LMWH: PE

Outcome: 2 Pulmonary embolism

Study or subgroup	LMWH n/N	UFH n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
EMSG 1996	1/216	0/226		6.5 %	3.15 [0.13, 77.82]
Forette 1995	0/146	1/149		19.8 %	0.34 [0.01, 8.36]
Kleber 2003	1/239	1/212		14.1 %	0.89 [0.06, 14.26]
PRIME Study	0/477	4/482		59.7 %	0.11 [0.01, 2.07]
Total (95% CI)	**1078**	**1069**		**100.0 %**	**0.46 [0.13, 1.65]**

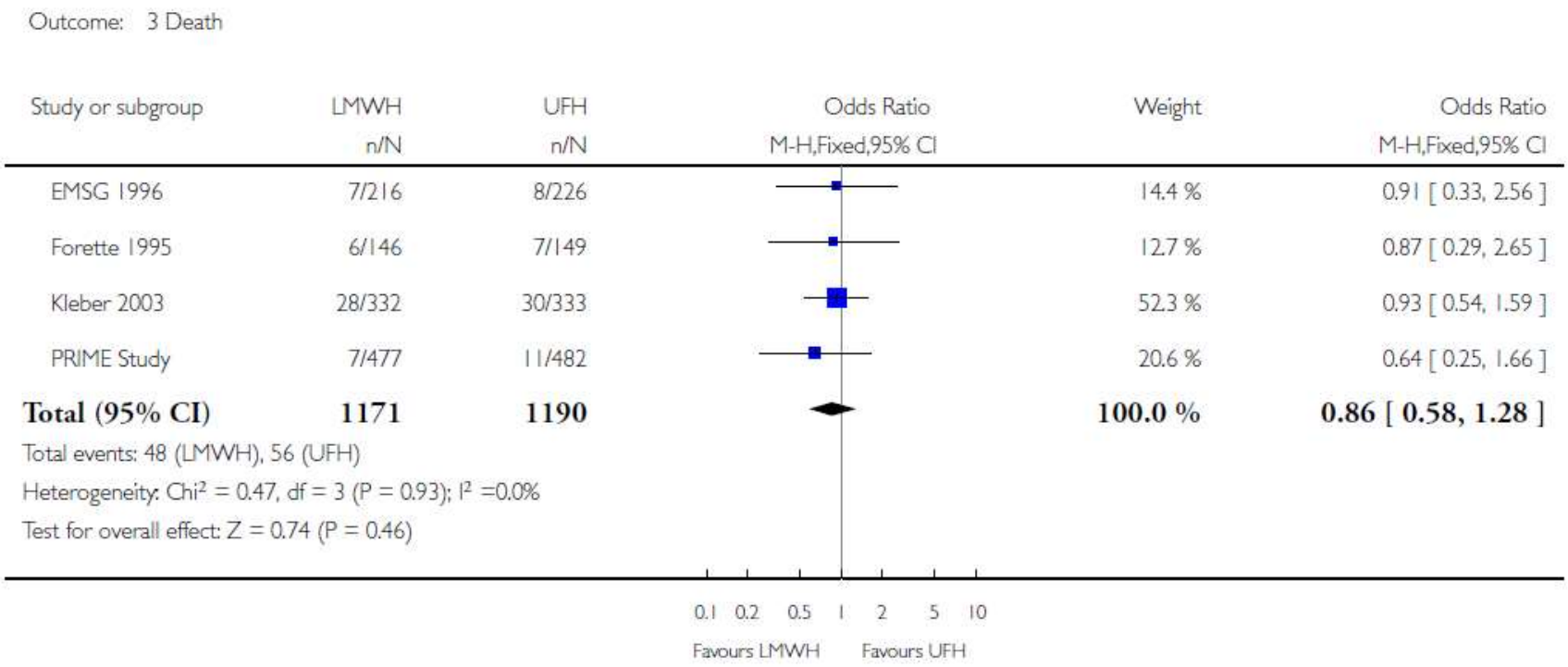
Total events: 2 (LMWH), 6 (UFH)

Heterogeneity: $Chi^2 = 2.54$, $df = 3$ ($P = 0.47$); $I^2 = 0.0\%$

Test for overall effect: $Z = 1.19$ ($P = 0.23$)

Cochrane Database of Systematic Reviews
2014, Issue 5. Art. No.: CD003747

UFH VS LMWH: Death



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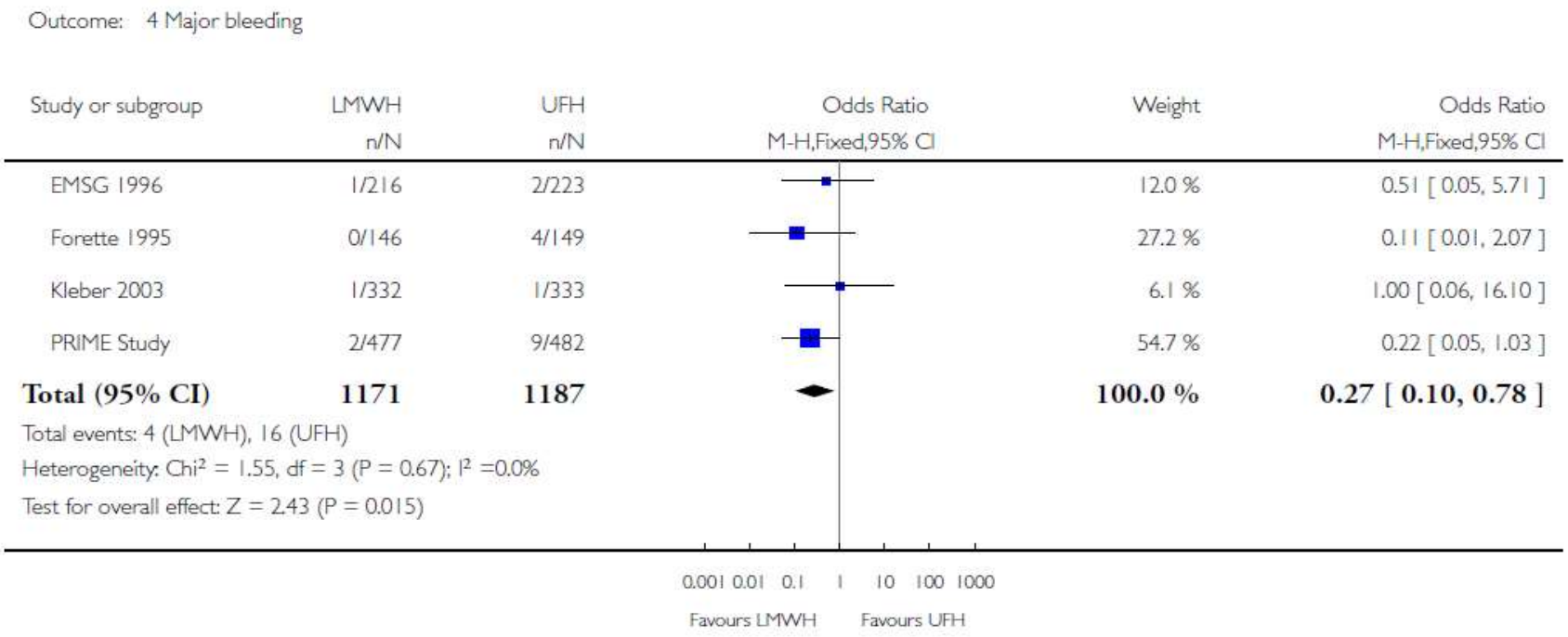
UFH VS LMWH: Major bleed



Cochrane Database of Systematic Reviews
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UFH vs LMWH: KLEBER STUDY

- n-665
- Enoxaparin (40 mg once daily) or UFH (5000 IU 3 times daily)
- Duration- 10 +/- 2 days
- The primary efficacy parameter was a thromboembolic event up to 1 day after the treatment period
- VTE 8.4% with enoxaparin and 10.4% with UFH
- The incidence of PE events was same in two group

American Heart Journal 2003;145:614–21

UFH vs LMWH: Forrette study

- N 295 patients
- 146 patients (mean age 82.8 +/- 0.5 years) received calcium nadroparin and 149 patients (mean age 83.8 +/- 0.6 years) received UFH
- Duration of therapy 28 days
- Death rate was similar in both the arm
- Bleeding rate was 2.6% in heparin arm as compared to none in nadroparin arm (p=0.01%)

Presse Med. 1995 Mar 25;24(12):567-71

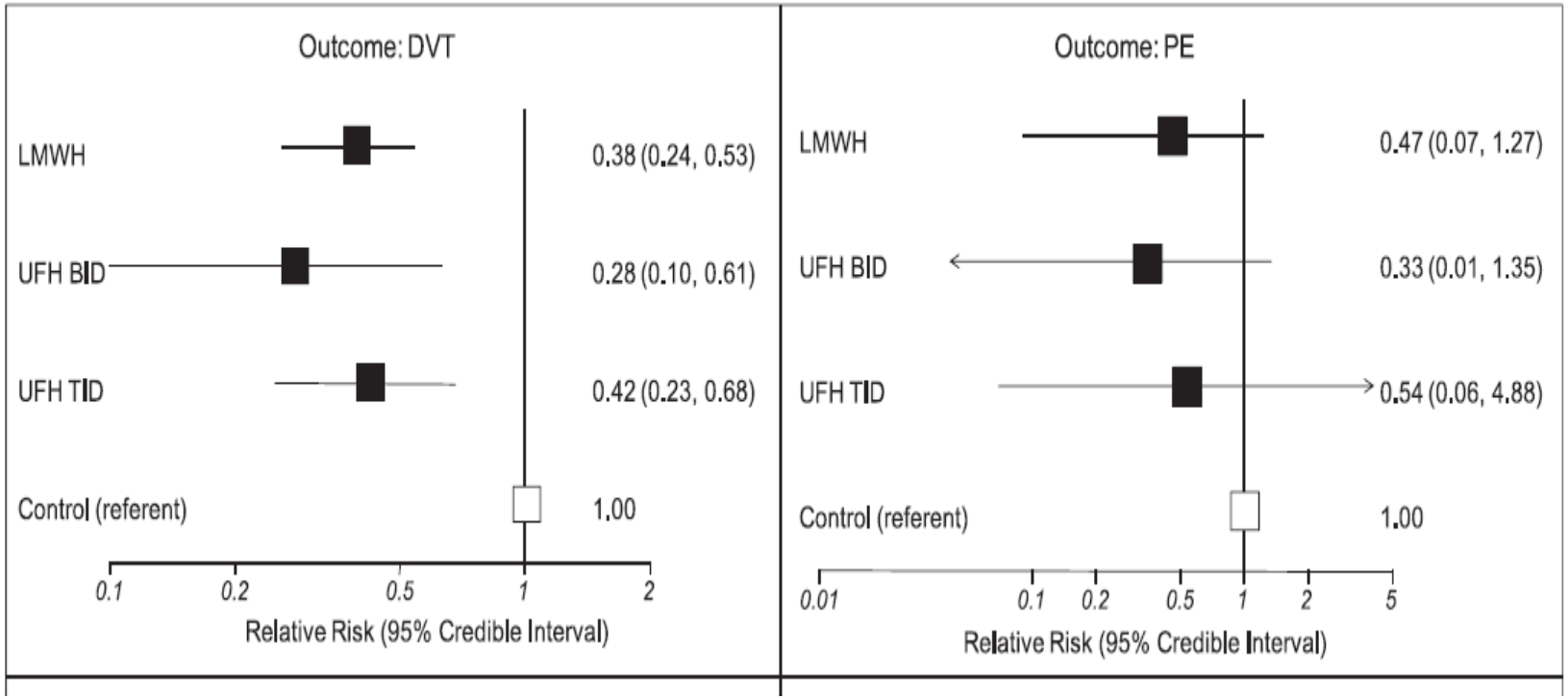
Summary: LMWH vs UFH

- There is no significant difference in incidence of DVT/PE or mortality
- LMWH group has significantly less risk of major bleeding compared to UFH

Hospitalized medically ill

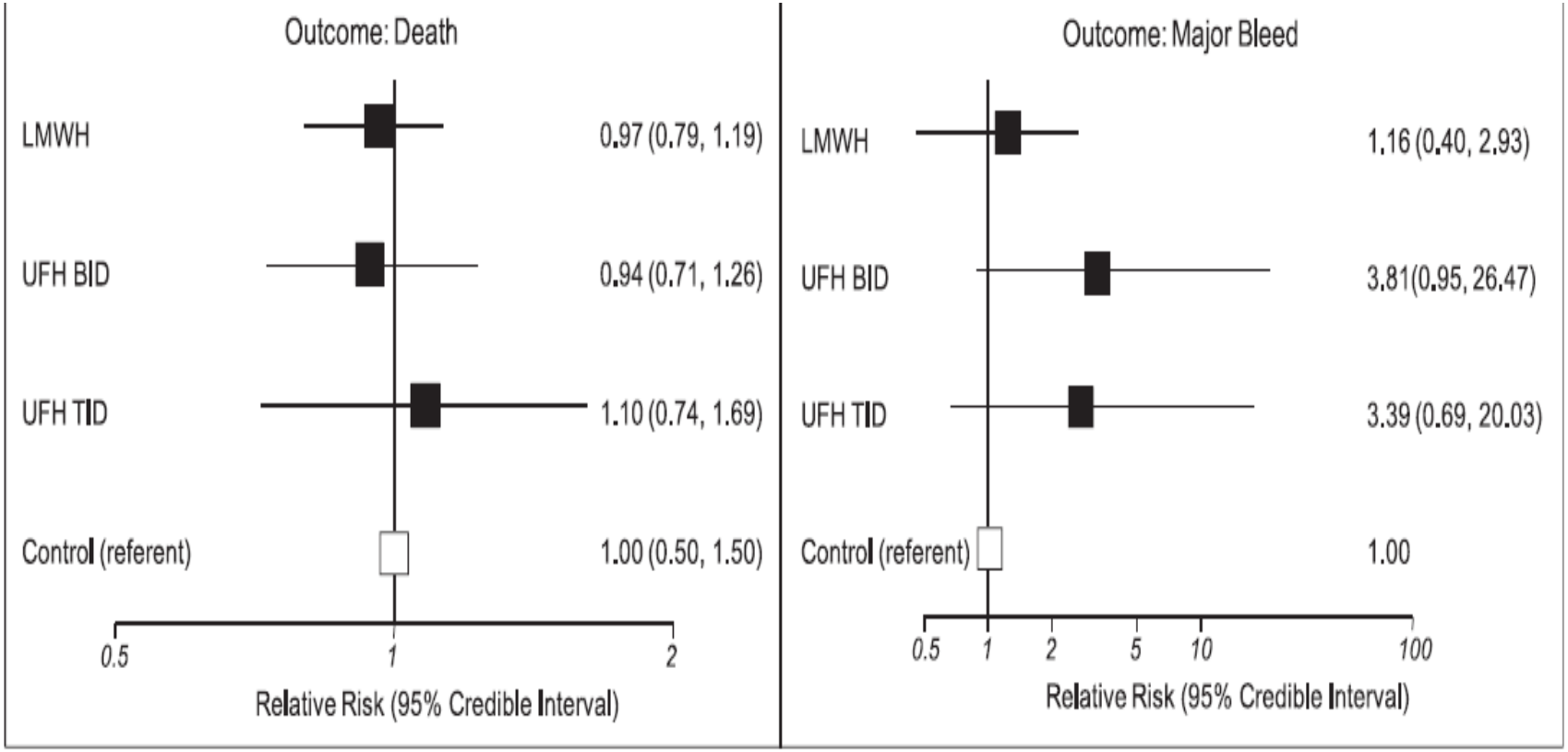
LMWH VS UFH BID VS UFH TID

UFH BID VS UFH TID



CHEST 2011; 140(2):374–381

UFH BID VS UFH TID



CHEST 2011; 140(2):374–381

CRITICALLY ILL PATIENTS

Critically ill patients

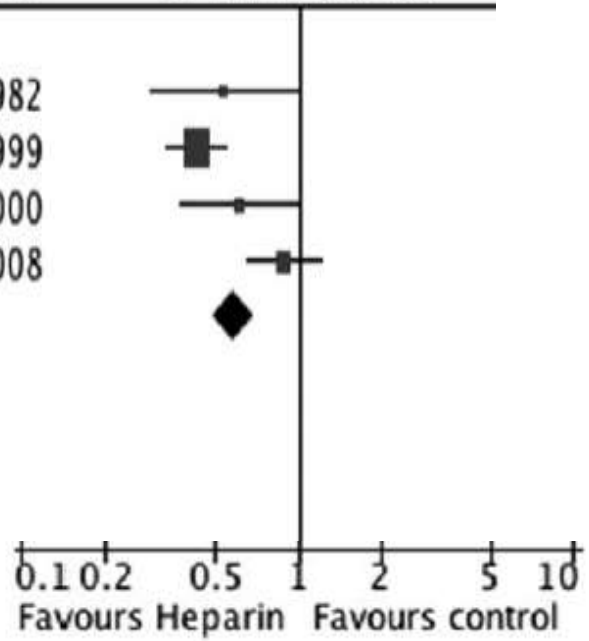
HEPARIN (ANY FORM) VS PLACEBO

Heparin vs placebo: DVT

Study or Subgroup	Heparin Events	Heparin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.1.1 All DVT							
Cade 1982	8	60	17	59	7.8%	0.46 [0.22, 0.99]	1982
Kapoor 1999	44	401	122	390	55.9%	0.35 [0.26, 0.48]	1999
Fraisse 2000	13	84	24	85	10.8%	0.55 [0.30, 1.00]	2000
Shorr 2008	49	976	56	959	25.5%	0.86 [0.59, 1.25]	2008
Subtotal (95% CI)		**1521**		**1493**	**100.0%**	**0.51 [0.41, 0.63]**	
Total events	114		219				

Heterogeneity: $Chi^2 = 13.07$, $df = 3$ ($P = 0.004$); $I^2 = 77\%$

Test for overall effect: $Z = 6.26$ ($P < 0.00001$)

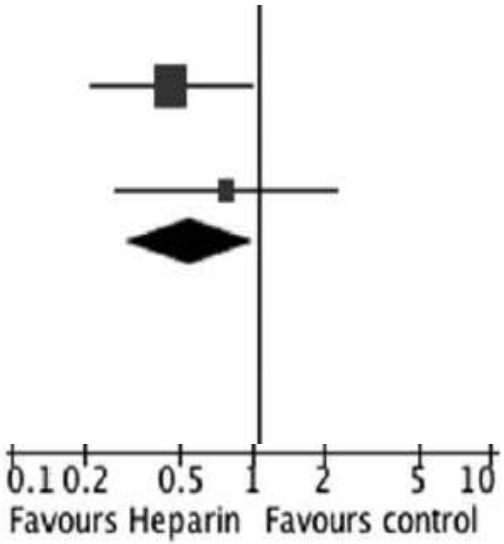


Heparin vs placebo: PE

Study or Subgroup	Heparin Events	Heparin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.1.3 Pulmonary Embolism							
Kapoor 1999	9	401	20	390	71.5%	0.44 [0.20, 0.95]	1999
Fraisse 2000	0	84	0	85		Not estimable	2000
Shorr 2008	6	976	8	959	28.5%	0.74 [0.26, 2.12]	2008
Subtotal (95% CI)		**1461**		**1434**	**100.0%**	**0.52 [0.28, 0.97]**	
Total events	15		28				

Heterogeneity: $Chi^2 = 0.61$, $df = 1$ ($P = 0.43$); $I^2 = 0\%$

Test for overall effect: $Z = 2.05$ ($P = 0.04$)

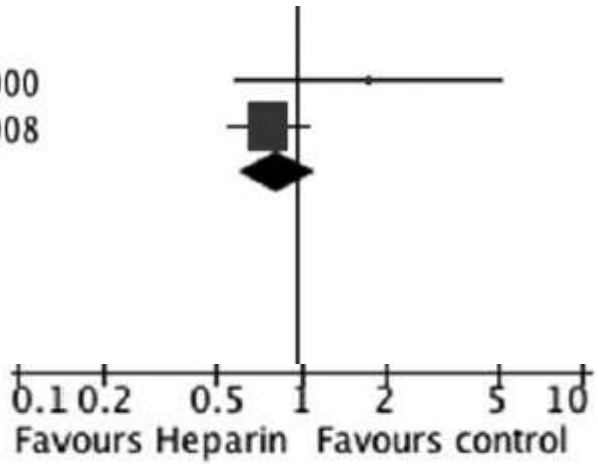


Heparin vs placebo: Bleeding

Study or Subgroup	Heparin Events	Heparin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.1.4 Major Bleeding							
Fraisse 2000	6	108	3	113	5.5%	2.09 [0.54, 8.16]	2000
Shorr 2008	38	976	50	959	94.5%	0.75 [0.49, 1.13]	2008
Subtotal (95% CI)		**1084**		**1072**	**100.0%**	**0.82 [0.56, 1.21]**	
Total events	44		53				

Heterogeneity: $Chi^2 = 2.02$, df = 1 (P = 0.16); $I^2 = 50\%$

Test for overall effect: Z = 0.99 (P = 0.32)

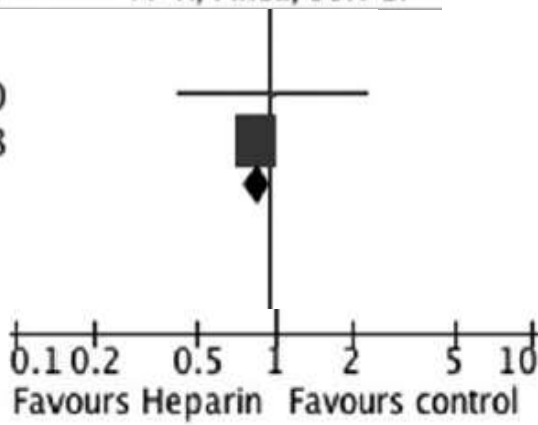


Heparin vs placebo: Mortality

Study or Subgroup	Heparin Events	Heparin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.1.5 ICU Mortality							
Fraisse 2000	8	108	8	113	2.5%	1.05 [0.41, 2.69]	2000
Shorr 2008	275	972	305	955	97.5%	0.89 [0.77, 1.02]	2008
Subtotal (95% CI)		**1080**		**1068**	**100.0%**	**0.89 [0.78, 1.02]**	
Total events	283		313				

Heterogeneity: $Chi^2 = 0.12$, $df = 1$ ($P = 0.73$); $I^2 = 0\%$

Test for overall effect: $Z = 1.69$ ($P = 0.09$)



LMWH vs placebo: Fraisse 2000

- n-223 patients mechanically ventilated for acute, decompensated chronic obstructive pulmonary disease
- Randomized subcutaneous Nadroparin adjusted for body weight 0.4 ml, or 0.6 ml, or placebo
- The average duration of treatment was 11 days
- The incidence of DVT in patients receiving nadroparin was significantly lower than that in patients receiving placebo (15.5 versus 28.2%; p = 0.045)

Am J Respir Crit Care Med 2000; 161(4 Part 1):1109–1114

UFH vs LMWH vs Placebo

- n-1935
- Subjects were randomized to unfractionated heparin, low-molecular-weight heparin, or placebo
- By day 28,2(0.4%) in unfractionated group,4(0.4%) of enoxaparin group and 8(0.8%) subjects developed a developed PE which is not statistically significant
- By day 28,3.8% in heparin group and 5% of placebo group had major bleeding
- There was no mortality benefit between two group

Thromb Haemost. 2009 Jan;101(1):139-44

Critically ill patients

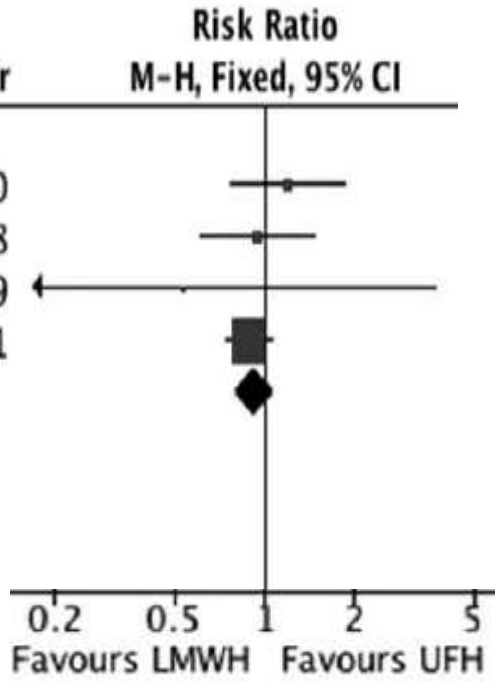
LMWH VS UFH

LMWH vs UFH: DVT

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
2.8.1 All DVT							
Goldhaber 2000	25	156	20	154	9.6%	1.23 [0.72, 2.13]	2000
Shorr 2008	23	478	26	498	12.2%	0.92 [0.53, 1.59]	2008
De 2009	1	81	2	75	1.0%	0.46 [0.04, 5.00]	2009
PROTECT 2011	138	1873	161	1873	77.2%	0.86 [0.69, 1.07]	2011
Subtotal (95% CI)		**2588**		**2600**	**100.0%**	**0.90 [0.74, 1.08]**	
Total events	187		209				

Heterogeneity: $Chi^2 = 1.79$, $df = 3$ ($P = 0.62$); $I^2 = 0\%$

Test for overall effect: $Z = 1.12$ ($P = 0.26$)

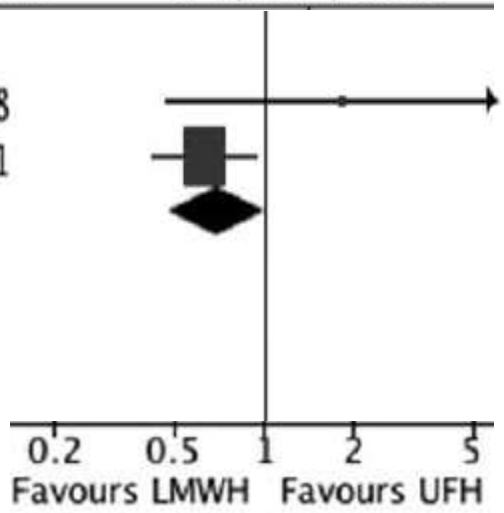


LMWH vs UFH: PE

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
2.8.3 Pulmonary Embolism							
Shorr 2008	4	478	2	498	4.4%	2.08 [0.38, 11.32]	2008
PROTECT 2011	24	1873	43	1873	95.6%	0.56 [0.34, 0.92]	2011
Subtotal (95% CI)		**2351**		**2371**	**100.0%**	**0.62 [0.39, 1.00]**	
Total events	28		45				

Heterogeneity: $Chi^2 = 2.14$, $df = 1$ ($P = 0.14$); $I^2 = 53\%$

Test for overall effect: $Z = 1.97$ ($P = 0.05$)

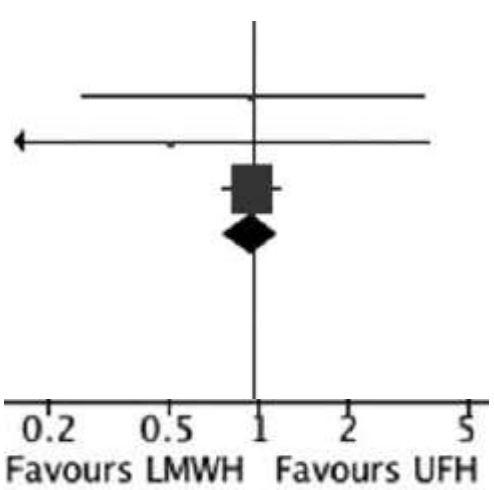


LMWH vs UFH: Bleeding

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
2.8.5 Major Bleeding							
Goldhaber 2000	3	156	3	154	2.7%	0.99 [0.20, 4.82]	2000
De 2009	1	81	2	75	1.9%	0.46 [0.04, 5.00]	2009
PROTECT 2011	103	1873	105	1873	95.4%	0.98 [0.75, 1.28]	2011
Subtotal (95% CI)		**2110**		**2102**	**100.0%**	**0.97 [0.75, 1.26]**	
Total events	107		110				

Heterogeneity: $Chi^2 = 0.38$, $df = 2$ ($P = 0.83$); $I^2 = 0\%$

Test for overall effect: $Z = 0.22$ ($P = 0.83$)

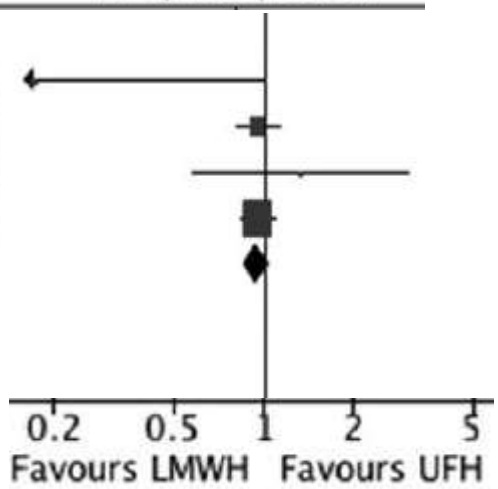


LMWH vs UFH: Mortality

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
2.8.6 ICU Mortality							
Goldhaber 2000	1	156	8	154	1.7%	0.12 [0.02, 0.97]	2000
Shorr 2008	130	477	145	495	30.9%	0.93 [0.76, 1.14]	2008
De 2009	9	81	6	75	1.4%	1.39 [0.52, 3.72]	2009
PROTECT 2011	284	1873	304	1873	66.0%	0.93 [0.81, 1.08]	2011
Subtotal (95% CI)		**2587**		**2597**	**100.0%**	**0.93 [0.82, 1.04]**	
Total events	424		463				

Heterogeneity: $Chi^2 = 4.32$, $df = 3$ ($P = 0.23$); $I^2 = 31\%$

Test for overall effect: $Z = 1.29$ ($P = 0.20$)



LMWH vs UFH

- N- 3764
- subcutaneous dalteparin 5000 IU once daily or unfractionated heparin at a dose of 5000 IU twice daily while they were in the intensive care unit
- The primary outcome proximal leg deep-vein thrombosis, within 2 days after admission, twice weekly, and as clinically indicated
- Additional testing for PTE was performed as clinically indicated
- Deep vein thrombosis occurred 96 of 1873 patients (5.1%) receiving dalteparin versus 109 of 1873 patients (5.8%) receiving unfractionated heparin (hazard ratio in the dalteparin group, 0.92; 95% confidence interval [CI], 0.68 to 1.23; P=0.57

N Engl J Med. 2011 Apr 7;364(14):1305-14. doi: 10.1056/NEJMoa1014475. Epub 2011 Mar 2

LMWH vs UFH

- Pulmonary emboli was significantly lower with dalteparin (24 patients, 1.3%) than with unfractionated heparin (43 patients, 2.3%) (hazard ratio, 0.51; 95% CI, 0.30 to 0.88; P=0.01)
- No significant between-group difference in the rates of major bleeding (hazard ratio, 1.00; 95% CI, 0.75 to 1.34; P=0.98) or death in the hospital (hazard ratio, 0.92; 95% CI, 0.80 to 1.05; P=0.21)

RIVAROXABAN

- Rivaroxaban is an orally active direct factor X a inhibitor
- First oral anticoagulant molecule approved to treat and reduce the recurrence of DVT after warferin
- Approved for prevention of DVT and PE after knee or hip replacement surgery

Magellan trial

- N-8101 (age>40 yrs)
- Enoxaparin, 40 mg once daily, for 10±4 days and oral placebo for 35±4 days or to receive subcutaneous placebo for 10±4 days and oral rivaroxaban, 10 mg once daily, for 35±4 days
- The primary efficacy outcomes were the composite of asymptomatic proximal or symptomatic venous thromboembolism up to day 10 and up to day 35
- safety outcome of major or relevant nonmajor bleeding.

- DVT occurred in 78 of 2938 patients (2.7%) receiving rivaroxaban and 82 of 2993 patients (2.7%) receiving enoxaparin at day 10 (relative risk with rivaroxaban, 0.97; 95% confidence interval [CI], 0.71 to 1.31; P=0.003

- DVT occurred 131 of 2967 patients (4.4%) who received rivaroxaban and 175 of 3057 patients (5.7%) who received enoxaparin followed by placebo at day 35 (relative risk, 0.77; 95% CI, 0.62 to 0.96; P=0.02)

- Safety outcome event occurred in 111 of 3997 patients (2.8%) in the rivaroxaban group and 49 of 4001 patients (1.2%) in the enoxaparin group at day 10 ($P<0.001$) and in 164 patients (4.1%) and 67 patients (1.7%) in the respective groups at day 35 ($P<0.001$).

N Engl J Med. 2013 Feb 7;368(6):513-23. doi: 10.1056/NEJMoa1111096

Summary: Critically ill population

- Heparin thromboprophylaxis decreases DVT and PE in medical-surgical critically ill patients
- LMWH compared with UFH decreases PE and symptomatic PE
- Major bleeding and mortality rates do not appear to be significantly influenced by heparin thromboprophylaxis in the ICU setting
- No one form of heparin is superior to other