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### Mechanical methods for thromboprophylaxis May 2018

Prof Beverley Hunt, Guy's & St Thomas' NHS Foundation Trust Kings College, London Medical Director of Thrombosis UK Twitter @bhwords





King's College Hospital NHS NHS Foundation Trust









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#### Mechanical methods for thromboprophylaxis

Conflicts of interest: I take no monies from pharma But I was a member of the NICE guideline committee

> Prof Beverley Hunt, Guy's & St Thomas' NHS Foundation Trust Kings College, London Medical Director of Thrombosis UK Twitter @bhwords



King's College Hospital NHS Foundation Trust



# Clear Benefits of thromboprophylaxis over placebo in medical patients

	RRR					
MEDENOX <sup>1</sup> <i>P</i> <0.001	<b>63%</b>	Placebo Enoxaparin 40 mg		5.5		14.9*
<b>PREVENT</b> <sup>2</sup> <i>P</i> =0.0015	<b>45%</b>	Placebo Dalteparin	2.8	5.0*		
ARTEMIS <sup>3</sup> <i>p</i> =0.029	<b>47%</b>	Placebo Fondaparinux		5.6	10.5 <sup>+</sup>	

<sup>1</sup>Samama MM *et al. N Engl J Med* 1999;341:793–800 <sup>2</sup>Leizorovicz A *et al. J Circulation* 2004;110:874–9 <sup>3</sup>Cohen AT *et al. J Thromb Haemost* 2003;1 (Suppl 1):P2046

RRR = relative risk reduction



## Mechanical Compression Graduated compression stockings

National Institute for Clinical Excellence

Never shown to reduce the risk of death due to PE

Do not offer stockings to patients who have:

Suspected peripheral arterial disease

Peripheral arterial bypass grafting

Peripheral neuropathy or other causes of sensory impairment

Any local condition in which stockings may cause damage

Known allergy to material of manufacture

Cardiac failure/severe leg oedema

Unusual leg size or shape

If arterial disease suspected seek expert opinion Encourage them to wear them day and night until they no longer have reduced mobility

Remove daily for hygiene purposes and to inspect skin 2-3 times a day for integrity or sensory impairment and discontinue if problems develop. <u>The CLOT Study</u> Dennis M et al, Lancet 2009; 373: 1958

Graduated Stocking Level

2,500 stroke patients Thigh length anti-embolic stockings vs no stockings

Result 10% vs 9.5% VTE rate BUT 5% with stockings had skin problems



## Mechanical Compression Graduated compression stockings

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Cost of purchasing and applying GCS to surgical inpatients in England estimated at £63.1 million per annum

9; 373: 1958

Graduated Stocking Level

Any local condition in which stockings may cause damage

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Cardiac failure/severe leg oedema

Unusual leg size or shape

If arterial disease suspected seek expert opinion Encourage them to wear them day and night until they no longer have reduced mobility Remove daily for hygiene purposes and to inspect

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2,500 stroke patients Thigh length anti-embolic stockings vs no stockings

Result

10% vs 9.5% VTE rate

BUT

5% with stockings had skin problems







Centre for London

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# GAPS: Graduated compression as an Adjunct to Pharmacoprophylaxis in Surgery

3,250 moderate risk surgical patients receive LMWH +/stockings Primary outcome: symptomatic & asymptomatic vTE

Imperial College London



NHS National Institute for Health Research

## **Intermittent Pneumatic Compression (IPC)**

<u>CLOTS 3</u> (Clots in legs after **stroke**) Dennis M et al, Lancet. 2013 Aug 10;382:516-24

2,800+ randomised to IPC post-stroke. Follow up for 6 months

	IPC	No IPC
<b>DVT rate</b>	8.5%	12.1%
Death rate	11%	13% (p=0.057
Skin breaks	3%	1% (p=0.002



### Forest plot showing the effect of intermittent pneumatic compression (IPC) on the risk of pulmonary embolism compared with placebo.

Study or sub-category	IPC n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% CI
Bachmann 1976	1/28	5/26		3.10	0.19 [0.02, 1.49]
Coe 1978	1/29	1/24		1.81	0.83 [0.05, 12.54]
Skillman 1978	0/47	2/48		1.48	0.20 [0.01, 4.14]
Hull 1979	0/32	0/29			Not estimable
McKenna 1980	1/10	4/12		3.27	0.30 [0.04, 2.27]
Borow 1981	2/79	1/89		- 2.36	2.25 [0.21, 24.38]
Butson 1981	0/62	1/57		1.33	0.31 [0.01, 7.38]
Hartman 1982	0/52	1/52		1.33	0.33 [0.01, 8.00]
Clarke-Pearson 1984	2/55	1/52		2.39	1.89 [0.18, 20.23]
Turpie 1989	0/78	1/161		1.32	0.68 [0.03, 16.59]
Hull 1990	1/152	1/158		1.76	1.04 [0.07, 16.47]
Stranks 1992	0/41	1/39		1.33	0.32 [0.01, 7.57]
Wilson 1992	0/28	0/32			Not estimable
Knudson 1994	1/58	1/130		- 1.77	2.24 [0.14, 35.22]
Lieberman 1994	1/113	1/118		1.76	1.04 [0.07, 16.50]
Fisher 1995	6/145	9/159		13.19	0.73 [0.27, 2.00]
Goldhaber 1995	1/172	1/172	+	1.76	1.00 [0.06, 15.86]
Ramos 1996	21/1355	48/1196	-=-	52.19	0.39 [0.23, 0.64]
Rokito 1996	0/1	0/1			Not estimable
Wautrecht 1996	0/25	0/10			Not estimable
Ivanic 2006	0/20	1/21		1.36	0.35 [0.02, 8.10]
Edwards 2008	1/141	1/136		1.76	0.96 [0.06, 15.27]
Chin 2009	0/110	1/110		1.32	0.33 [0.01, 8.09]
Windisch 2011	0/40	0/40			Not estimable
Zhang 2011	0/79	8/83	<b>←</b> • – – – – – – – – – – – – – – – – – –	1.67	0.06 [0.00, 1.05]
Sobieraj-Teague 2012	0/75	0/75			Not estimable
Vignon 2013	1/205	1/202		1.75	0.99 [0.06, 15.65]
Total (95% CI) Total events: 40 (IPC), 91 (Contr Test for heterogeneity: $Chi^2 = 10$ Test for overall effect: Z = 3.92 (	3232 rol) 0.78, df = 20 (P = 0.95), l (P < 0.0001)	3232 ² = 0%	•	100.00	0.48 [0.33, 0.69]
	• everyoddioddiada	(	0.01 0.1 1 10 Eavors IPC Eavors cont	100	

Kwok M. Ho, and Jen Aik Tan Circulation. 2013;128:1003-1020 American Heart

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Association
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#### Forest plot showing the effect of intermittent pneumatic compression (IPC) on the risk of deep vein thrombosis compared with thromboembolic deterrent stockings (TEDS).



Kwok M. Ho, and Jen Aik Tan Circulation. 2013;128:1003-1020 American

Heart Association.

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### Forest plot showing the effect of intermittent pneumatic compression (IPC) on risk of deep vein thrombosis compared with pharmacological thromboprophylaxis.

Study or sub-category	IPC n/N	Drugs n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl
Coe 1978	1/29	6/28		1.72	0.16 [0.02, 1.25]
McKenna 1980	1/10	8/21		1.89	0.26 [0.04, 1.82]
Borow - aspirin 1981	9/79	14/78		5.66	0.63 [0.29, 1.38]
Borow 1981	9/79	23/86		6.06	0.43 [0.21, 0.86]
Salzman 1982	0/20	1/29		0.82	0.48 [0.02, 11.13]
Nicolaides 1983	3/50	7/50		3.37	0.43 [0.12, 1.56]
Mellbring 1986	10/54	2/54		2.85	5.00 [1.15, 21.76]
Hansberry 1991	3/24	2/25		2.31	1.56 [0.29, 8.55]
Kaempffe 1991	12/48	13/52	-+	6.22	1.00 [0.51, 1.97]
Chandhoke 1992	2/47	0/53		0.89	5.63 [0.28, 114.27]
Knudson 1992	5/76	3/37		3.11	0.81 [0.20, 3.21]
Clarke-Pearson 1993	4/101	7/107		3.71	0.61 [0.18, 2.01]
Knudson 1994	4/58	2/63		2.40	2.17 [0.41, 11.42]
Santori 1994	9/67	23/65		6.15	0.38 [0.19, 0.76]
Pambianco 1995	8/117	5/120	_ <b>-</b>	4.14	1.64 [0.55, 4.87]
Knudson 1996	2/82	1/120		1.34	2.93 [0.27, 31.75]
Kosir 1996	0/25	0/38			Not estimable
Rokito 1996	0/33	0/35			Not estimable
Stannard 1996	0/25	5/25	←	0.99	0.09 [0.01, 1.56]
Stone 1996	1/25	1/25		1.07	1.00 [0.07, 15.12]
Warwick 1998	24/136	18/138		6.92	1.35 [0.77, 2.38]
Blanchard 1999	34/63	16/67		7.39	2.26 [1.39, 3.67]
Maxwell 2001	1/106	2/105		1.34	0.50 [0.05, 5.38]
Warwick 2002	57/99	48/89	+	8.59	1.07 [0.83, 1.38]
Ginzburg 2003	6/224	1/218		1.65	5.84 [0.71, 48.10]
Kurtoglu 2004	4/60	3/60		2.89	1.33 [0.31, 5.70]
Pitto 2004	3/100	6/100		3.17	0.50 [0.13, 1.94]
Silbersack 2004	0/68	19/63	←	1.02	0.02 [0.00, 0.39]
Chin 2009	9/110	6/110		4.53	1.50 [0.55, 4.07]
Yang 2009	4/47	1/48		- 1.59	4.09 [0.47, 35.21]
Serin 2010	1/94	3/152		1.48	0.54 [0.06, 5.11]
Hardwick 2011	8/196	8/190	<del></del>	4.71	0.97 [0.37, 2.53]
Total (95% CI)	2352	2451	•	100.00	0.93 [0.69, 1.26]
Total events: 234 (IPC), 254 (I Test for heterogeneity: $Chi^2 = 0$ Test for overall effect: $Z = 0.44$	Drugs) 60.69, df = 29 (P = 0.0005), 4 (P = 0.66)	l² = 52.2%			
			0.01 0.1 1 10	100	
			Favors IPC Favors drugs		

Kwok M. Ho, and Jen Aik Tan Circulation. 2013;128:1003-1020 American Heart

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# Forest plot showing the effect of intermittent pneumatic compression (IPC) on risk of systemic bleeding or bleeding complications from the wound compared with a pharmacological thromboprophylaxis.

Study	IPC n/N	Drugs n/N	RR (random) 95% CI	Weight %	RR (random) 95% Cl
Coe 1978	1/29	2/28		4.01	0.48 [0.05, 5.03]
McKenna 1980	0/10	1/21		2.26	0.67 [0.03, 15.06]
Hansberry 1991	1/24	0/25		2.21	3.12 [0.13, 73.04]
Chandhoke 1992	0/47	1/53		2.18	0.38 [0.02, 8.99]
Knudson 1992	0/76	0/37			Not estimable
Clarke-Pearson 1993	0/101	3/107	←	2.53	0.15 [0.01, 2.89]
Santori 1994	0/67	9/65	<b>←</b>	2.76	0.05 [0.00, 0.86]
Knudson 1996	0/82	2/120		2.41	0.29 [0.01, 6.00]
Rokito 1996	0/33	2/35		2.45	0.21 [0.01, 4.25]
Stannard 1996	0/25	0/25			Not estimable
Stone 1996	3/25	7/25		14.46	0.43 [0.12, 1.47]
Blanchard 1999	0/63	1/67		2.17	0.35 [0.01, 8.54]
Maxwell 2001	0/105	3/106	←	2.53	0.14 [0.01, 2.76]
Warwick 2002	0/111	4/108	<b>←</b>	2.60	0.11 [0.01, 1.98]
Ginzburg 2003	4/224	4/218		11.67	0.97 [0.25, 3.84]
Kurtoglu 2004	1/60	2/60		3.91	0.50 [0.05, 5.37]
Pitto 2004	0/100	3/100	←	2.53	0.14 [0.01, 2.73]
Chin 2009	4/110	9/110		16.71	0.44 [0.14, 1.40]
Yang 2009	0/94	1/96		2.17	0.34 [0.01, 8.25]
Serin 2010	4/94	11/152		17.70	0.59 [0.19, 1.79]
Hardwick 2011	0/198	11/194	←	2.76	0.04 [0.00, 0.72]
Total (95% CI)	1678	1752	•	100.00	0.41 [0.25, 0.65]
Total events: 18 (IPC), 76 (Drug Test for heterogeneity: $Chi^2 = 1$ Test for overall effect: Z = 3.77	gs) 1.55, df = 18 (P = 0.87), l (P = 0.0002)	<sup>2</sup> = 0%			
			0.01 0.1 1 10 Eavors IPC Eavors drug	100	

Kwok M. Ho, and Jen Aik Tan Circulation. 2013;128:1003-1020 American Heart Association.

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#### Cochrane Review IPC vs IPC + pharm in the prevention of DVT & PE *Kakkos et al, 2016*

	IPC	IPC + pharm
Symptomatic PE	2.9%	1.2% OR 0.39 (95% CI 0.2364
All DVT	6.2%	2.9% OR 0.42 (95% CI 0.18-1.03
Bleeding	0.7%	4.1%

Problems

Although trials included >9,000 patients,

Trials overall of moderate quality

IPC used widely intraoperatively & immediately post op pre Pharmacological thromboprophylaxis – no data on benefit

### **Pregnancy is a special case**

VTE in 1/1000 pregnancies

>70% of DVT in left side

>70% ileofemoral

>70% post-phlebitic syndrome

#### Virchow's triad

Increased venous stasis

**Endothelial changes** 

Hypercoagulable changes

↑ fibrinogen, Factor Vc, Factor VIIIc and vWF\*
↓ total and free Protein S
Activated Protein C sensitivity ratio ↓
↑PAI-1 and PAI-2 from placenta
Gradual ↑ Prothrombin Factor 1 +2, TAT<sup>‡</sup> & D-dimers
Persist for up to 6 weeks post-partum

\*vWF = von Willebrand Factor; \*PAI = plasminogen activator inhibitor; \*TAT = thrombin antithrombin

# Causes of maternal death 2012-14



MBRRACE-UK

#### **Distribution of VTE in pregnancy & puerperium**



Jacobsen et al. Am J Obstet Gynecol 2008;198(2):233.e1-7

ORIGINAL ARTICLE

#### Risk of a Thrombotic Event after the 6-Week Postpartum Period

Hooman Kamel, M.D., Babak B. Navi, M.D., Nandita Sriram, B.S., Dominic A. Hovsepian, B.S., Richard B. Devereux, M.D., and Mitchell S.V. Elkind, M.D.

Weeks Post partum	VTE OR	95% CI
0-6	12.1	7.9 to 18.6
7-12	2.2	1.4 to 3.3
13-18	1.6	1.0 to 2.5
18-24	0.9	0.5 to 1.4

Kamel et al New Engl I Med Feb 2011



#### Figure 1. Risk of a Thrombotic Event, According to the Interval after Delivery.

Shown are the results of a post hoc exploratory analysis of the risk of a composite primary outcome of ischemic stroke, acute myocardial infarction, or venous thromboembolism across sequential 3-week periods after labor and delivery, as compared with each patient's risk during the same period 1 year later. The thrombotic risk was still increased during the period of 13 to 15 weeks after delivery (odds ratio, 2.0; 95% CI, 1.1 to 3.6) but was no longer elevated in the period of 16 to 18 weeks after delivery (odds ratio, 1.0; 95% CI, 0.6 to 1.8). The vertical lines indicate 95% confidence intervals.

#### The RCOG guidelines



Royal College of Obstetricians & Gynaecologists

#### Treatment

**Prevention** 

Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Green-top Guideline No. 37a

Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management

Green-top Guideline No. 37b April 2015

# Major gaps in evidence base for obstetric thromboprophylaxis

Inadequate/no evidence in obstetrics for

- mechanical methods
- pharmacological thromboprophylaxis vs placebo
- Emperical dose vs weight adjusted doses
- Length of thromboprophylaxis? especially
   post partum

# What is the new NICE NG89 guideline addressing in obstetrics??

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← → C Secure   https://www.nice.org.uk/guidance/ng89						☆ :
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Home > NICE Guidance > Conditions and diseases > Cardiovascular conditions > Embolism and thrombosis

NICE guideline [NG89] Published date: March 2018

# Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism

Guidance	Tools and resources	Information for the public	Evidence	History		
Overview	ndations	Guidance			<u>Share</u>	<u>Download</u>
Putting thi	s guideline into	A NICE interactive flowchart	- Venous thrombo	pembolism		

# What is the new NICE NG89 guideline addressing in obstetrics??

(!) Beverley N Venous thromboembolism in or X How to take a screenshot on yex Downloads × Secure https://www.nice.org.uk/guidance/ng89 ☆ : **NICE** National Institute for Health and Care Excellence NICE NICE Standards Evidence Sign in Guidance and indicators Pathwavs services **ONLY HOSPITAL ADMISSION IN OBSTETRICS!** 

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NICE guideline [NG89] Published date: March 2018

#### Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism

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Overview Recommer	ndations	Guidance			Share Download
Putting thi	s guideline into	NICF interactive flowchart	- Venous thrombo	pembolism	

#### HOSPITAL ACQUIRED VTE & PREGNANCY

Rate of venous thromboembolism per 100 000 person years by weeks after discharge during antepartum period: 12 events in weeks 1-2 after discharge, 7 events in weeks 3-4 after discharge, and 12 events in weeks 5-10 after discharge.





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#### Evidence for thromboprophylaxis in obstetrics is derived from non-pregnant studies



#### Evidence of pregnancy on the effect of graduated compression stockings: on blood velocity in the deep venous system of the lower limb in the postnatal period.

Jamieson R1, Calderwood CJ, Greer IA. BJOG. 2007 Oct;114(10):1292-4.

This study of 17 women examined the effects of GCS on the deep venous system in the immediate postpartum period and found a statistically significant reduction in the diameter of the common femoral vein (CFV) (pre- versus post stocking diameter: mean 10.39 mm [SD 2.09] versus mean 9.69 mm [SD 1.99]) and an increase in the rate of blood velocity in the CFV (pre- versus post stocking velocity: mean 10.0 cm/s [SD 2.7] versus 13.9 cm/s [SD 4.2]) 30 minutes after application of thigh length GCS in women 1 or 2 days following a singleton vaginal delivery at term.

This confirms reduction in venous stasis in the deep venous system in the immediate postpartum woman by the use of GCS, supporting their use in improving venous function in this context.

#### **RCOG PREVENTION OF VTE 37b 2015**

#### Anti-embolism stockings

- The use of properly applied anti-embolism stockings (AES) of appropriate size and providing graduated compression with a calf pressure of 14–15 mmHg is recommended in pregnancy and the puerperium for women who are hospitalised and have a contraindication to LMWH. These include women who are hospitalised post-caesarean section (combined with LMWH) and considered to be at particularly high risk of VTE (e.g. previous VTE, more than four risk factors antenatally or more than two risk factors postnatally) and women travelling long distance for more than 4 hours. [*New 2015*]
- There are few data regarding the most efficacious length of AES to use in pregnancy and advice in the non pregnant population is contradictory. More DVTs in pregnant women are iliofemoral compared to the non pregnant population where calf vein DVTs are more common. Studies of AES in pregnancy have only concerned full-length stockings.162 However, in the obstetric population, there is the added problem of full-length stockings becoming bloodstained. Therefore, on balance, properly applied full-length AES are advocated for pregnant women but knee-length AES should be considered if (as is often the case) full-length AES are ill-fitting or compliance is poor.

Venous thromboembolism in over 16s: reducing the risk of hospitalacquired deep vein thrombosis or pulmonary embolism Page 26 NICE guideline [NG89] Published date: March 2018

- 1.16 Interventions for pregnant women and women who gave birth or had a miscarriage or termination of pregnancy in the past 6 weeks
- 1.16.1 Consider LMWH for all women who are admitted to hospital or a midwife-led unit if they are pregnant or gave birth, had a miscarriage or had a termination of pregnancy in the past 6 weeks, and whose risk of VTE outweighs their risk of bleeding. [2018]
- 1.16.2 Do not offer VTE prophylaxis to women admitted to hospital or a midwife-led unit who are in active labour. **[2018]**
- 1.16.3 Stop pharmacological VTE prophylaxis when women are in labour. [2018]
- 1.16.4 If using LMWH<sup>[</sup> in pregnant women, start it as soon as possible and within 14 hours of the risk assessment being completed and continue until the woman is no longer at increased risk of VTE or until <u>discharge</u> from hospital or the midwife-led unit. [2018]

Venous thromboembolism in over 16s: reducing the risk of hospitalacquired deep vein thrombosis or pulmonary embolism NICE guideline [NG89] Published date: March 2018

- 1.16.5 If using LMWH in women who gave birth or had a miscarriage or termination of pregnancy, start 4–8 hours after the event unless contraindicated and continue for a minimum of 7 days. **[2018]**
- 1.16.6 Consider combined prophylaxis with LMWH<sup>I</sup> plus mechanical prophylaxis for pregnant women or women who gave birth or had a miscarriage or termination of pregnancy in the past 6 weeks and who are likely to be immobilised, or have <u>significantly reduced mobility</u> relative to their normal or anticipated mobility for 3 or more days after surgery, including caesarean section:

Use intermittent pneumatic compression as first-line treatment.

If intermittent pneumatic compression is contraindicated, use anti-embolism stockings.

Continue until the woman no longer has significantly reduced mobility relative to her normal or anticipated mobility or until discharge from hospital. **[2018]** 



## **VTE in pregnancy**

Still a major modern problem in pregnancy, many had to predict

Can we do trials of LMWH in pregnancy?

To late to do placebo vs LMWH BUT

? length of use?

? empirical dose vs wt. adjusted dose but would need to be v large due to low event rate

Can we trial IPC in pregnancy?







### **Mechanical methods summary**

Poor evidence base for using stockings

Much better evidence base for intermittent pneumatic compression but

- -how useful is it perioperatively
- -for short periods?

#### MORE RESEARCH REQUIRED!



