

# Combined modalities in the prevention of venous thromboembolism: a review of the literature

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## Abstract

**Objective:** Despite recent advances in the field of venous thromboembolism (VTE) prophylaxis and adherence to guideline recommendations, VTE remains a serious problem, especially in high-risk groups. The aim of the present review was to summarize the evidence supporting the use of combined modalities, both physical and pharmacological, in VTE prevention.

**Methods:** Using Medline, original studies on the value of combined modalities in VTE prevention were identified. Keywords used for physical methods included elastic stockings and intermittent pneumatic compression, and for pharmacological methods included unfractionated and low molecular weight heparin. Relevant articles from their bibliography were also retrieved.

**Results:** Combined pharmacological and physical modalities were more effective than each modality alone in a variety of specialties, including orthopaedic, general and cardiac surgery, as shown by 14 of the 18 randomized or case-control studies retrieved. Mean reduction in VTE incidence was 69% (range 16–100%).

**Conclusion:** Combined modalities are more effective than single modalities in VTE prophylaxis. These results endorse their use, especially in high-risk patients, and support this otherwise typical recommendation of the consensus documents on VTE prophylaxis.

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## Introduction

Despite modern advances in pharmacology,<sup>1</sup> and biomedical engineering,<sup>2,3</sup> venous thromboembolism (VTE, defined as deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) remains a serious and not infrequent complication of trauma and surgery.<sup>4,5</sup> VTE is sometimes fatal and its victims face long-term risk of post-thrombotic leg swelling and ulceration. Current guidelines recommend risk stratification to tailor the implementation of prophylactic methods,<sup>6,7</sup> which can be either

physical (graduated elastic compression stockings [GECS] and intermittent pneumatic compression [IPC]),<sup>8,9</sup> or pharmacological (low-molecular weight [LMWH], unfractionated heparins [UFH] and fondaparinux).<sup>1,10,11</sup> While use of combined modalities is recommended in high-risk patients, cost implications and potential adverse events limit their use in low-risk groups. The rationale for using combined modalities is based on the fact that VTE is a multifactorial disease, with Rudolph Virchow getting credit for realizing this during the 19th century.<sup>12</sup> Physical methods improve venous stasis, while pharmacological methods affect hypercoagulopathy; the hypothesis that combined modalities are more effective than single modalities was proven in 1983 by Borow.<sup>13</sup> Since this first report several studies have been published supporting

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this concept. The aim of the present review is to summarize the evidence of the effects of using combined modalities in VTE prevention.

## Methods

A Medline search (US National Library of Medicine, PubMed service, [www.ncbi.nlm.nih.gov/entrez](http://www.ncbi.nlm.nih.gov/entrez)) for articles on the use of combined modalities in VTE prophylaxis was performed using keywords for physical (GECS, IPC) and pharmacological (LMWH and UFH, fondaparinux) methods, as well as VTE, DVT and PE. The retrieved articles and the two consensus documents were searched manually for any additional references on this topic. Since the baseline risk is different in various patient groups, data were grouped and presented for each specialty separately. Only controlled and randomized controlled trials were included. Non-English language articles or studies comparing different modalities from the same group, i.e. GECS versus GECS + IPC, were excluded. GraphPad QuickCalcs ([www.graphpad.com](http://www.graphpad.com), GraphPad Software, Inc, San Diego, CA, USA) was used to calculate *P* values for those articles not providing statistical analysis.

## Results

A total of 18 studies performed in a variety of specialties were found in the literature (Table 1). The latter included cardiothoracic surgery (*n* = 2), general surgery (*n* = 5), gynaecologic oncology (*n* = 1), neurosurgery (*n* = 3), orthopaedic surgery (*n* = 2), trauma/spinal cord injury (*n* = 1), stroke (*n* = 1) and urology (*n* = 3). One study was excluded because of bias since high-risk patients were treated with combined modalities.<sup>14</sup> Combined modalities were more effective than single modalities in 14 of the 18 randomized or case-control studies retrieved. Mean reduction in VTE incidence was 69% (range 16–100%).

### Cardiothoracic surgery

Ramos randomized 2551 patients undergoing cardiac surgery to two groups, UFH or UFH + sequential compression device (SCD).<sup>15</sup> Combined modalities decreased the incidence of PE by 62%, from 4% to 1.5%. Similar results were published by Tsutsumi who published a case-control study comparing UFH with UFH + IPC in patients undergoing oesophagectomy.<sup>16</sup> Combined modalities reduced the incidence of PE from 3.2%

to 0.7%. Incidence of DVT was not reported in these two studies.

### General surgery

Torngren performed the first ever study that showed a 75% decrease in the incidence of DVT when GECS were combined with UFH, compared with UFH alone.<sup>17</sup> In this study the same patient's contralateral leg was used as a control; however, these results were confirmed by subsequent larger randomized studies.<sup>18,19</sup> Two studies have so far investigated the role of combining pharmacological prophylaxis with IPC. Borow in 1983 reported a 1.5% incidence of DVT with combined modalities compared with controls that received no prophylaxis where DVT occurred in 26.8%.<sup>13</sup> This was a case-control study; using the data from the article that he published the combination of pharmacological treatment (UFH, warfarin, aspirin or dextran) and SCD reduced the incidence of DVT from 1.9% when a combination of pharmacological treatment and GECS was used to 0.8% (*P* = 0.63). More recently, the APOLLO trial randomized a total of 1309 patients into two groups, fondaparinux + IPC (*n* = 650) or placebo + IPC (*n* = 659).<sup>5</sup> Fondaparinux + IPC produced a highly significant reduction in the incidence of all VTE from 5.3% (placebo + IPC) to 1.7% (odds ratio reduction – 70%, *P* = 0.004). A significant reduction in proximal DVT in the fondaparinux + IPC group (0.2%) versus the placebo + IPC group (1.7%; *P* = 0.037) was also observed. The incidence of any major bleeding was 1.6% in the fondaparinux + IPC group versus 0.2% in the placebo + IPC group (*P* = 0.006), but none of these were fatal bleeds or bleeds into critical organs.

### Gynaecologic surgery

A single study failed to show any benefit of adding UFH to SCD in patients undergoing surgery for suspected gynaecological malignancies.<sup>20</sup>

### Neurosurgery

There were three studies performed in the 1990s,<sup>21–23</sup> two of them were randomized;<sup>22,23</sup> these showed that by adding UFH or a LMWH to a physical modality (IPC or GECS) the incidence of DVT was reduced. In two of the studies background modality was GECS and in one it was IPC. IPC was more effective than GECS alone and when combined with UFH, no patient developed VTE.

Table 1

Author	Year	Patient group	Control group		Treatment group		P
			VTE prophylaxis	VTE incidence	VTE prophylaxis	VTE incidence	
Ramos <sup>*,15</sup>	1996	Cardiothoracic surgery	UFH	4% (48/1196) <sup>†</sup>	UFH+IPC	1.5% (21/1355) <sup>†</sup>	<0.001
Tsutsumi <sup>16</sup>	2000	Cardiothoracic surgery	UFH	3.2% (24/745) <sup>†</sup>	UFH+IPC	0.7% (2/278) <sup>†</sup>	0.024
Torngren <sup>17</sup>	1980	General surgery	UFH	12% (12/98)	UFH+GECS	4% (4/98)	<0.004 <sup>‡</sup>
Borow <sup>13</sup>	1983	General surgery	Pharm+GECS	1.9% (3/158)	Pharm+IPC	0.8% (1/130)	0.63
Wille-Jorgensen <sup>18</sup>	1985	General surgery	UFH	12% (11/90)	UFH+GECS	2% (2/86)	0.07
Wille-Jorgensen <sup>*,19</sup>	1991	General surgery	UFH	15% (12/81)	UFH+GECS	2.5% (2/79)	0.001
Turpie <sup>*,5</sup>	2005	General surgery	IPC	5.3%	IPC+fondaparinux	1.7%	0.004
Ailawadi <sup>20</sup>	2001	Gynecology	IPC	6.4% (6/94)	IPC+UFH	5.4% (4/74)	0.79
Frim <sup>21</sup>	1992	Neurosurgery	IPC	3.2% (15/473)	IPC+UFH	0% (0/138)	0.02
Nurmohamed <sup>*,22</sup>	1996	Neurosurgery	GECS	26.3% (47/179)	GECS+LMWH	18.7% (31/166)	0.047
Agnelli <sup>*,23</sup>	1998	Neurosurgery	GECS	33% (43/130)	GECS+LMWH	17% (22/130)	0.004
Kalodiki <sup>*,24</sup>	1996	Orthopedic surgery	LMWH	38% (12/32)	LMWH+GECS	25% (8/32)	0.42
				28% (9/32) <sup>§</sup>		13% (4/32) <sup>§</sup>	0.21 <sup>§</sup>
Silbersack <sup>*,25</sup>	2004	Orthopedic surgery	LMWH+GECS	28.6% (18/63)	LMWH+IPC	0% (0/68)	<0.0001
Winemiller <sup>26</sup>	1999	Spinal cord injury	Pharmacological or Physical	21% (84/344)	UFH+IPC	0% (0/36)	0.0006
Kamran <sup>27</sup>	1998	Stroke	LMWH or GECS	12% (29/249)	LMWH or GECS+IPC	0.02% (1/432)	<0.0001
Bigg <sup>*,28</sup>	1992	Urology	IPC or GECS	11% (4/36) <sup>†</sup>	IPC or GECS+UFH <sup>†</sup>	0% (0/32)	0.05
Sieber <sup>29</sup>	1997	Urology	IPC	4% (4/101)	IPC+UFH	2.2% (11/478)	0.31

UFH, unfractionated heparin; IPC, intermittent pneumatic compression; GECS, graduated elastic compression stockings; LMWH, low molecular weight heparin. Pharmacological: UFH, warfarin, aspirin or dextran. Physical: IPC, GECS

\*Randomized controlled trial

<sup>†</sup>Pulmonary embolism

<sup>‡</sup>Contralateral leg served as control

<sup>§</sup>Proximal deep vein thrombosis

Incidence of bleeding was not significantly increased.

### Orthopaedic surgery

Kalodiki published the first randomized study which showed that GECS reduce the incidence of DVT when added to LMWH in patients undergoing total hip replacement, however this was not statistically significant.<sup>24</sup> More recently, Silbersack showed in a randomized study that the combination of LMWH + IPC was better than GECS + IPC, with no patient getting any VTE in the former group.<sup>25</sup>

### Spinal cord injury

Winemiller studied the role of various prophylactic modalities in patient with acute spinal cord injury.<sup>26</sup> He showed that IPC + UFH were associated with reduced incidence of DVT on multivariate analysis. The incidence of DVT in the UFH + IPC group was 0% (0/36) compared with 21% (84/344) in the rest of the patients that used one pharmacological or physical modality.

### Stroke

Kamran has published the single case-control study, which shows that the addition of IPC to LMWH + GECS reduces the incidence of DVT from 12% (29/249) (when only LMWH + GECS are used) to 0.02% (1/432) ( $P < 0.0001$ ).<sup>27</sup>

### Urology

Bigg showed in a randomized trial that the combination of UFH with IPC or GECS reduces the incidence of DVT from 11% (4/36) when IPC or GECS are used to 0% (0/32).<sup>28</sup> However, this trial was discontinued because of bleeding complications of UFH. A more recent study did not show any statistical benefit of adding UFH to IPC.<sup>29</sup>

### Discussion

Our review showed that combined modalities are more effective in reducing the incidence of VTE than single modalities. This improved outcome was present in a variety of patient groups; DVT and also PE being reduced by an average of 69% as shown by several randomized controlled and case-controlled studies.

The mechanism responsible for the improved effectiveness of combined modalities is probably due to the fact that VTE is a multifactorial process. Virchow in 1856 suggested that venous stasis, coagulopathy and endothelial injury are all the causes of VTE.<sup>12</sup> By treating different causes of VTE it is only expected to improve efficacy in DVT prevention. Rosendaal more recently extended Virchow's theory by proposing a model of risk factors, which considered the importance of the additive role and interaction of multiple risk factors.<sup>30</sup> Based on the additive role of mechanical and pharmacological modalities, the results of this review suggest that venous stasis and hypercoagulopathy are truly independent risk factors.

GECS by reducing the cross-sectional area of veins and probably by diverting blood from the superficial towards the deep system, increase venous flow,<sup>31</sup> and therefore reduce venous stasis; they have also been shown to reduce venous wall distension,<sup>32</sup> while high grade compression used in treating patients with chronic venous insufficiency improves valvular function.<sup>33</sup> IPC produces active flow enhancement,<sup>3</sup> and increases the plasma levels of tissue factor pathway inhibitor.<sup>34</sup> Heparins and fondaparinux inhibit factor X; these totally different mechanisms of action are responsible for the synergy between the two modality types.

Both mechanical modalities, GECS and IPC improve the results of pharmacological prophylaxis. However, IPC was more effective than GECS (83% versus 67% mean reduction) and this should be taken into consideration when prescribing a mechanical modality. IPC produces active flow enhancement,<sup>3</sup> which could explain its improved efficacy.

Combined modalities have been shown to be effective in VTE prevention in a wide range of patient groups undergoing cardiothoracic, orthopaedic, urological, general surgery and neurosurgical procedures. Patients with leg paralysis due to stroke or spinal cord injury have also show reduction in VTE rate.

The results of our review endorse the recommendations of the consensus documents that high-risk patients should get multimodal prophylaxis.<sup>6,7</sup> Most patients that used combined modalities in the studies reviewed were at high risk of developing VTE. Although the magnitude of VTE reduction was large in this patient group, the same cannot be extrapolated for patients at moderate risk. Future studies should address this question and also take into account cost-effectiveness issues. Since half of the studies reviewed were case-controlled studies,

future research by randomized trials in patient groups these are lacking is warranted.

In conclusion, this review showed that combined modalities were more effective than single modalities in VTE prophylaxis. The results support the recommendations of the consensus documents on VTE prophylaxis and accordingly multimodality prophylaxis should be used routinely in high-risk patients.

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