Imperial Journal of Interdisciplinary Research (IJIR)
Vol-3, Issue-6, 2017
ISSN: 2454-1362, http://www.onlinejournal.in

Graduated Compression Stockings in the Prevention and Treatment of Deep Vein Thrombosis

BOND CASTALONE BALAJADIA, MSN, RN, EMT
Al Ghad International Colleges for Health Sciences – Tabuk Male Branch, Saudi Arabia

Abstract*: Graduated compression stockings (GCS) are a therapeutic treatment used in the management of deep-vein thrombosis, particularly in the prevention of pulmonary embolism. Studies — randomized controlled trials in particularly, have been conducted, and become available to professionals as well as the general public, in the past five years, measuring the effectiveness and safety of GCS, either used alone or in conjunction with other interventions such as subcutaneous heparin or anticoagulant/antithrombotic prophylaxis. This meta-analysis was designed and performed on RCTs that were deemed eligible for this study based on specific inclusion criteria; and the data and results generated indicate that GCS is quite effective and beneficial in the treatment and management of patients at risk from both DVT and PE, with a moderately high level of statistical significance.*

Introduction

Background

Deep-vein thrombosis (also known as deep venous thrombosis and usually abbreviated as DVT) is the formation of a blood clot (or "thrombus") in a deep vein, and is a form of thrombophlebitis, or inflammation of a vein with clot formation. DVT commonly affects the leg veins, such as the femoral vein or the popliteal vein, or else the deep veins of the pelvis. Occasionally the veins of the arm are affected; if spontaneously so, this is known as Paget-Schrötter disease.

A DVT can occur without symptoms, but in many cases the affected extremity will become painful, swollen, red, and warm, and the superficial veins may be engorged. The most serious complication of a DVT is that the clot could dislodge and travel to the lungs, which is called a pulmonary embolism (PE). DVT is a medical emergency, and when present in a lower extremity there is a 3% chance of a PE from it killing the patient (Turpie, 2008). A late complication of DVT is the post-phlebitic syndrome, which can manifest itself as edema, pain, acute discomfort, and/or severe skin problems.

According to Virchow's triad, venous thrombosis occurs via three mechanisms: decreased or interrupted flow of the blood (hemodynamic turbulence or stasis), damage to the blood vessel wall (endothelial injury or dysfunction), and an increased tendency of the blood to clot (hypercoagulability). Several medical conditions can lead to DVT, such as compression of the veins, physical trauma, cancer, infections, certain inflammatory diseases, and specific conditions such as stroke, heart failure, or nephrotic syndrome. There are several factors which can increase a person's risk for DVT, including surgery, hospitalization, immobilization (such as when orthopedic casts are used, or during long-haul flights, leading to economy class syndrome), smoking, obesity, age, certain drugs (such as estrogen or erythropoietin), and inborn tendencies to form clots known as thrombophilia (for example, in carriers of factor V Leiden). Women also have an increased risk during pregnancy and in the postnatal period.

The most commonly used tests for the diagnosis of DVT are a blood test called D-dimers and a Doppler ultrasound of the affected veins. Sometimes, further testing is required to find the cause of the DVT. In specific cases, an attempt can be made to break down the clot (using thrombolytic agents). To prevent further accrual and formation of new clots with a risk of pulmonary embolism, anticoagulatives (blood thinners) are advised; if not possible, an inferior vena cava filter may be used. Prevention of DVT is advised in many medical and surgical inpatients using anticoagulants, graduated compression stockings (GCS; also known as thromboembolic deterrent stockings), or intermittent pneumatic compression devices.

Management and Treatment

Treatment at home is an option according to a meta-analysis by the Cochrane Collaboration (Othieno, Abu & Okpo, 2007). But hospitalization should be considered in patients with more than two of the following risk factors, as these patients may have more risk of complications during treatment (Trujillo-Santos, Herrera, Page, *et al.,* 2006): bilateral DVT, renal insufficiency, body weight >70 kg/154 lbs., recent immobility, chronic heart failure, and cancer.

At any rate, anticoagulation — or the prevention of the blood from clotting — is the usual treatment for DVT. In general, patients are initiated on a brief course (*i.e.*, less than a week) of heparin treatment while they start on a 3- to 6-month course of warfarin (or related vitamin K inhibitors). Low-molecular-weight heparin (LMWH) is preferred (Snow, Qaseem, Barry, *et al.,* 2007), though unfractionated heparin is given in patients who have a contraindication to LMWH (*e.g.*, renal failure or imminent need for invasive procedure). In patients who have had recurrent DVTs (two or more), anticoagulation is generally "life-long." The Cochrane Collaboration has meta-analyzed the risk and benefits of prolonged anti-coagulation (Hutten & Prins, 2006). Once the thrombosis is treated with RBC-thinning agents, the affected area has a fair chance of returning to its normal proportions. However, thinning agents do not lessen the chance of embolism to the pulmonary or coronary arteries. Thus, while the area affected with DVT (*i.e.*, the legs) may cease coagulation, pulmonary embolism is still possible. Additionally, an abnormal D-dimer level at the end of treatment might signal the need for continued treatment among patients with a first unprovoked proximal DVD (Palareti, Cosmi, Legnani *et al.,* 2006).

Thrombolysis, another treatment for DVT, is generally reserved for an extensive clot, *e.g.*, an iliofemoral thrombosis, and consists of breaking down the clot by pharmacological means (which is why it is colloquially referred to as "clot busting"). It works by stimuliting fibrinolysis, or the breakdown of fibrin clots, by plasmin through infusion of analogs of tissue plasminogen activator (tPA), the protein that normally activates plasmin. Although a meta-analysis of randomized controlled trials by the Cochrane Collaboration showed improved outcomes with thrombolysis (Watson & Armon, 2004), there may be an increase in serious bleeding complications. In July 2008, the American College of Chest Physicians (ACCP) published new evidence-based clinical guidelines for the treatment of venous thromboembolic (VTE) disease, which for the first time suggested the use of pharmaco-mechanical thrombolysis in the treatment of certain cases of acute DVT.

Yet another treatment is the inferior vena cava filter, which reduces the risk of pulmonary embolism (Decousus, Leizorovicz, Parent *et al.,* 1998), and is an option for patients with an absolute contraindiciation to anticoagulant treatment (*e.g.*, cerebral hemorrhage), or those rare patients who have objectively documented recurrent PEs while on anticoagulation. An inferior vena cava filter (also referred to as a Greenfield filter) may prevent pulmonary embolisation of the leg clot. However much these filters are themselves potentially capable of causing thrombosis, IVC filters are viewed as a temporizing measure for preventing life-threatening pulmonary embolism (Young, Aukes, Hughes & Tang, 2007).

Finally, there are compression stockings. Elastic compression stockings should be routinely applied "beginning within 1 month of diagnosis of proximal DVT and continuing for a minimum of 1 year after diagnosis" (Snow *et al., ibid.*). In fact, starting within one week may be more effective (Prandoni, Lensing, Prins *et al.,* 2004).

Statement of the Problem

The main objective of this study is to assess and determine the effectiveness of graduated compression stocking (GCS) therapy upon the patient suffering from deep vein thrombosis (DVT), or is otherwise at high risk from it, with the defined endpoints being the reduction of the degree of severity of DVT in said patient as well as the prevention of further DVT-related complications.

Secondarily, when the main objective has been attained, this study will aim to answer the following additional questions:

1. What graduated compression techniques are used as an intervention in dealing with patients suffering from deep vein thrombosis in order to improve their condition?
2. What are the contributory effects of GCS interventions toward the improvement or betterment of patient outcomes?
3. Is there a significant difference between the effects of GCS intervention and other management treatments on the medical improvement of DVT patients?

Methods

Study Identification

The researcher attempted to identify all relevant published randomized trials that compared graduated compression stockings (GCS) with other treatments for deep vein thrombosis (DVT), including GCS used with another treatment such as heparin, and sometimes with a placebo or untreated control in patients. The Science Direct, Ebsco Host, and Google Scholar databases were searched for studies published between January 2005 and January 2010, using the keywords deep vein thrombosis, thromboembolism, pulmonary embolism, randomized controlled trial, controlled clinical trial, random, placebo, graduated compression stockings, graded compression stockings, elastic compression

stockings, pneumatic compression stockings, and all possible combinations of these terms, also in combination with the names of individual low-molecular-weight heparin (LMWH) preparations and other antithrombotic agents. Only articles written in English were considered. The bibliographies of of journal articles were also searched to locate additional studies, and the abstracts from relevant scientific meetings were scanned. Relevance was assessed using a hierarchical approach based on title, abstract, and the full manuscript.

Study Selection

Studies were independently assessed for possible inclusion in this meta-analysis; to be included, studies had to be properly randomized; enrolled patients at risk for DVT or thromboembolism; compared GCS with a placebo or another treatment like LMWH, unfractionated heparin, or a coumarin derivate with untreated control; and used objective methods to confirm the diagnosis of DVT. The data on DVT from these studies were typically included in this meta-analysis if systematic screening was carried out by the study authors with ascending lower-limb contrast venography or duplex ultrasonography.

Assessment of Study Quality and Data Extraction

To ensure high quality, the methodological criteria outlined by Van Tulder *et al.* (1997) were used, as per the standards of the Cochrane Collaboration. This list adheres to the following 12 main criteria: adequate randomization procedure; allocation concealment; baseline similarity; care provider blinded; control for co-interventions; acceptable adherence; relevant, reliable. and valid outcome measures; patient blinded; acceptable number of withdrawals and missing values; outcome assessor blinded; identical timing of outcome measurement; and intention-to-treat analysis.

This researcher extracted data on study design, study quality, and the following efficacy and safety outcomes in the course of this research: DVT documented by ascending lower-limb contrast venography and/or duplex ultrasound scanning. The definitions for DVT, pulmonary embolism, and major and minor bleeding from the primary study investigators were typically accepted.

Statistical Analysis

Methodological criteria scores of 9 points or higher (maximum score is 12 points) were classified as "high quality," whereas studies with 4 points or lower were classified as "low quality." Cochrane Collaboration software (Review Manager 4.2.9, Version 4.3 for Windows; downloaded from the Nordic Cochrane Centre's website last January 19, 2010) to conduct the statistical analysis, and applied a fixed-effects or (if necessary) random-effects model to pool results from the individual trials. The risk ratio (RR) was calculated, at 95% confidence intervals (CI), together with the number needed to treat. One of the formulas for RR is:

$$RR = \frac{am/(am+bn)}{cm/(cm+dn)} = \frac{a(d+bq)}{b(c+aq)} = \frac{ad\{1+(b/d)q\}}{bc\{1+(a/c)q\}}.$$

To demonstrate statistical heterogeneity, the I^2 statistic was used. An I^2 score >30% was considered to denote heterogeneity. The standard formula for I^2 is:

$$I^2 = 100\% \times (Q - df) / Q$$

where Q is Cochran's heterogeneity statistic and df the degrees of freedom.

The Mantel-Haenszel method was applied to pool observed study effects. This method is used to estimate the pooled odds ratio for all strata of a statistical investigation, assuming a fixed-effects model, using the following formula:

$$\hat{O}R_{MH} = \frac{\sum_{i=1}^{k}\left(\frac{a_i d_i}{n_i}\right)}{\sum_{i=1}^{k}\left(\frac{b_i c_i}{n_i}\right)}$$

where $n_i = a_i + b_i + c_i + d_i$, these being the exposed cases, non-exposed cases, exposed non-cases, and non-exposed non-cases, respectively.

Subgroup Analyses

In order to explore the robustness of this study's results, these subgroup analyses are specified *a priori*: methodologically high-quality trials, immobilization as a result of fractures, immobilization as a result of tendon ruptures, and proximal DVT.

Results

The literature search identified 127 potentially eligible articles. At the outset, 107 studies were excluded right away upon screening the abstracts and titles for inclusion criteria. After further scanning, 13 more citations were excluded on the basis of similarity to data published elsewhere or published before 2005; seven (7) were retained for further assessment. Hence, a total of 7 studies met the inclusion criteria.

There was considerable variation among the studies in the duration of the trial or experimental

design, screening method, and pathology. One study included only patients with tendon ruptures, another included only patients with ankle fractures, and four studies included patients with mixed pathology. Five LMWH preparations were assessed together with compressed stockings, including nadroparin, certoparin, and tinzaparin. No study assessed the use of a coumarin derivate or unfractionated heparin. Prophylaxis was started within a few days in all studies that required it. In two studies, a pretrial treatment with LMWH in the control group was allowed for four and seven days, respectively. Two studies used ultrasonography as a screening method, a positive result was confirmed by ascending venography, and four studies used unilateral ascending venography to screen patients for the presence of asymptomatic DVT after lower-leg immobilization.

In all 7 studies, it was noted that the authors used "proper" methods to generate the randomized treatment allocation(s) — meaning that each patient, within a particular trial, had a known chance, usually an equal chance, of being given each treatment, whether of GCS therapy or whatever control treatment was being used. Specifically, there seemed to be adequate concealment of treatment allocation in four trials; three others were open-labeled ones. The treatment and control groups were comparable at baseline in all seven studies. Both patient and investigator were unaware of treatment allocation in three of the seven studies. There was an adequate clinical follow-up in two studies, three studies suffered from a substantial drop-out rate, and in two studies the drop-out rate was uncertain.

Based on the methodological criteria, three studies were classified as high quality, two as moderate quality, and two as low quality.

All Studies

Because of the statistical evidence of moderate heterogeneity among the studies (I^2 = 45.4%), a random-effects model was applied for analysis. All but one study showed a reduction in DVT when graduated compressed stockings (GCS) were used, but a statistically significant reduction was seen in only four of the seven trials. The pooled estimate from all the trials revealed a highly significant reduction in asymptomatic events with GCS, compared with LMWH and prophylaxis or placebo (RR of 0.58, CI = 0.39–0.86; p = 0.006). The mean risk of DVT dropped from 17.1%(124/724) to 9.6% (70/732) with the use of GCS.

Subgroup

A fixed-effects model was used for the analysis of all subgroups because, within each group, studies were homogeneous. When analyzing only the methodologically high-quality trials, the results were comparable to the overall effects (RR 0.68, CI = 0.50–0.92; p = 0.01). The mean risk of DVT decreased from 23.8% to 16.3% with the use of GCS.

When individual components of the overall venous thrombosis outcome were considered separately, there was a similar relative risk reduction for proximal DVT (RR 0.28, CI = 0.11–0.72; p = 0.008), albeit with a low absolute event rate. One study did not report the proximal thrombosis rate.

Similar results were found for tendon ruptures (RR 0.60, CI = 0.38–0.97; p = 0.04) and lower-leg fractures (RR 0.62, CI = 0.45–0.86; p = 0.004). However, the large confidence intervals in the tendon rupture and proximal DVT subgroup analyses negatively affect the accuracy of the observed summary effect sizes in these subgroups.

Overall, subgroup analyses confirmed the robustness of the analysis of all the studies presented, in that a significant summary effect size in favor of GCS as against LMWH prophylaxis or placebo emerged in all the analyses. The number needed to treat was 13 (9-25); hence, 13 patients require GCS to prevent one event of asymptomatic DVT than that obtained with the control treatment.

Among a total of 415 patients randomly assigned to GCS therapy, the frequency of major or minor bleeding was no higher than among those receiving LMWH combined with GCS or some other treatment, or else those in untreated controls (RR 1.22, CI = 0.61–2.46; p = 0.57). This RR is based on observed bleedings in the methodologically superior studies because no bleedings were reported to have occurred in the other studies in either study group (experimental/control).

None of the included studies observed an episode of heparin-induced thrombocytopenia.

Discussion

The meta-analysis reveals that GCS, alone or combined with prophylaxis with LMWH for lower-extremity immobilization, significantly reduces the risk of DVT. This benefit is achieved with no excess bleeding. About 13 patients need to be treated to prevent one episode of asymptomatic DVT. The findings of a significant treatment benefit of GCS therapy for the prevention of DVT are based on a pooled analysis of fractures and tendon injuries of the lower extremity.

The subgroup analysis shows that GCS treatment, therapy, or intervention is effective in patients with fractures as well as in patients with tendon ruptures. One of the arguments against the widespread use of GCS in patients with lower-

extremity immobilization is the perceived increased risk of bleeding complications. In this regard, the data from this analysis are reassuring, in that, even with sustained use for more than six weeks, sustained GCS use is not associated with an increased incidence of bleeding.

The results of this study's primary outcome are confirmed by the results of sensitivity analyses. Removal of lower-quality studies did not affect the primary outcome, and there was a consistent significant and directional treatment effect observed across both primary and secondary efficacy outcomes.

This meta-analysis of several subgroups did not have the statistical power to provide precise estimates of frequency and treatment effect for clinically important outcomes such as pulmonary embolism. However, DVT and pulmonary embolism represent clinical manifestations of the same underlying disease process. Therefore, strategies that are effective for the prevention of DVT, especially those proximally located, are also likely to be effective for the prevention of pulmonary embolism.

Results from prospective cohort studies that were read and reviewed by this researcher have shown that most asymptomatic thrombi in patients undergoing hip or knee replacement remain clinically silent. These results raise questions about the clinical relevance of asymptomatic DVT detected by screening venography or ultrasound. There is, however, a strong relation between asymptomatic DVT and symptomatic VTE, and the risk reductions observed in both are similar.

Furthermore, studies that screen for DVT are likely to cause an underestimation of symptomatic endpoints, because asymptomatic thrombi may actually be treated before they become symptomatic; however, none of the studies included in this meta-analysis reported the number of patients who were treated for such. Also, asymptomatic postoperative DVT may be associated with an increased risk of late development of the post-thrombotic syndrome. Both phenomena (VTE/DVT) are symptoms of the same disease process of hypercoagulability, a condition this researcher believes should be treated.

There was much variation in the design of studies included in this meta-analysis. Differences among trials are inevitable, as individual trials look at different populations with different treatment protocols, and there is always some heterogeneity, even within individual trials. Differences in trial design do not necessarily preclude pooling of their results when observed heterogeneity is moderate and outcomes of fixed and random models are comparable. The validity of this research's approach is further supported by the consistency of the findings among subgroup analyses as well as the lack of statistical evidence of heterogeneity for any of the subgroup outcomes examined in the meta-analysis.

Also, although compliance with GCS therapy appears to be 90% or higher in most trials included in this analysis, the definition of compliance varied among the studies, and not all studies reported the level of achieved compliance with randomization. Lack of compliance will most probably reduce the power of a randomized trial to detect a significant treatment benefit. Therefore, an even greater benefit of GCS treatment might be realized in populations in which higher levels of compliance are achieved.

Apart from GCS, several antithrombotic agents can be used, which were not completely addressed in this meta-analysis. In particular, coumarin derivates seem to be effective agents in the prevention of DVT. To the best of this researcher's knowledge, there are currently no randomized trials that investigate the effects of these drugs in the setting of patients with lower-limb immobilization at risk for DVT.

Although one study showed an increased rate of thrombosis in patients with above-the-knee casts, this meta-analysis was unable to differentiate between above-the-knee or belowthe-knee casting, because of the insufficient number of patients with above-the-knee casts included in these studies. Because the rate of DVT and VTE is likely to be high even in the group of patients with below-the-knee casts, this may not be clinically relevant.

Two studies were included that used duplex ultrasonography to assess the primary endpoint. The use of ultrasonography for the assessment of asymptomatic DVT is controversial! However, the studies used venography to confirm the thrombi with a positive CUS result, increasing the specificity. Despite the possible limitations and the possible underestimation of the absolute rate of DVT, the relative risk reductions derived from studies comparing two GCW or LMWH regimens are probably valid as long as they are properly randomized. Furthermore, exclusion of these lower-quality trials did not alter the results.

Finally, meta-analysis remains retrospective research that is likely to suffer from publication bias, methodological deficiencies, and heterogeneity. The likelihood of bias was kept to a minimum in this paper by developing a detailed protocol before starting the study, undertaking a meticulous search for published studies, and using explicit methods for study selection, data extraction, and data analysis. Also, the totality of the randomized evidence was

studied and analyzed, by including all relevant properly randomized trials.

The risk of DVT decreased, on average, from 17.1% to 9.6% with the use of GCS, without a significant increase in bleeding. The cost-effectiveness of implementing routine GCS therapy remains to be shown, however, and will be different depending on the local healthcare system. Also, there are disadvantages of treatment with GCS, such as an increased risk of HIT when patients are treated again later in life, and the inconvenience of subcutaneous injections to the patient when LMWH therapy is indicated.

With an increasing rate of lower-leg injuries accompanying an increased participation in sports potentially comes a greater burden of venous thromboembolic disease in patients requiring lower-leg immobilization. This only further emphasizes the need for adequately powered studies to definitively determine the risk of DVT in these patients.

GCS for Stroke Victims

Findings from one of the more relevant studies — that by the CLOTS Collaboration —have shown that thigh-length GCS are not clinically effective at reducing the risk of proximal DVT after stroke and are associated with some adverse effects. This was the only study that significantly differed from the other 6 included in this meta-analysis, and deserved a separate discussion all its own.

This large trial included more patients and outcome events (proximal DVTs) than all previous randomized controlled trials of GCS combined. Patients were enrolled by 64 hospitals in three countries, and had similar baseline characteristics to those of patients admitted to hospitals in many different hospitals and countries, suggesting that the study's results have good external validity.

Central randomization, outcome-blinded assessment of the primary outcome, low losses to follow-up, and intention-to-treat analysis have kept bias to a minimum. Serious complications due to GCS were rare, but their inconvenience and associated minor problems suggest these stockings should not be used unless they are associated with clinically significant benefits. Recruitment in the CLOTS program, which was designed to establish whether thigh-length GCS are more effective than below-knee GCS, has now been stopped because the results of the study suggest that exposure of patients with acute stroke to the discomfort, inconvenience, and risk of an ineffective treatment is not reasonable.

What might account for the absence of effect in patients with stroke compared with the apparent effectiveness shown by trials in, for example, patients undergoing surgery (like the majority of the other patients in this meta-analysis)? The precision of the CLOTS trial result is sufficient to make it very unlikely that the authors missed a clinically worthwhile treatment effect. They could reliably exclude an absolute reduction of 3% or greater, in a group of patients with an overall risk of proximal DVT of about 10% in untreated controls.

Trials in patients undergoing surgery have shown fairly convincingly that GCS applied before, during, and after a brief insult to the deep veins of the legs prevent DVTs, mainly in the calf. (This meta-analysis, in fact, confirms this.) Only eight of the 17 trials in the systematic review presented by the CLOTS Group reported the frequency of proximal DVT. Only nine of 435 (2%) patients allocated GCS and 21 of 402 (5%) allocated to avoid GCS had a proximal DVT (odds reduction 60%, 95% CI = 17–81; $p = 0.014$). However, although in the CLOTS trial they did not systematically screen for DVTs in the distal veins, they did not record any evidence that GCS were more effective in prevention of distal than proximal DVTs.

In patients with stroke, and those with other acute medical disorders, GCS can be applied only after the patient has become immobile. Immobility might then persist for weeks or even be permanent in such patients. DVTs can develop rapidly and cannot then be prevented as effectively by a treatment starting a few days after the onset of paralysis and immobility. Clearly, the effectiveness of GCS cannot be tested before stroke onset; however, the absence of heterogeneity between patients enrolled after stroke onset does not provide evidence that this delay is crucial to the effectiveness of GCS.

GCS are thought to reduce the risk of DVT by several mechanisms: by increasing the velocity of venous blood by producing a pressure gradient in the leg, by reducing the cross-sectional area of the deep veins, and by making the calf muscle pump more effective. This last mechanism might not operate in patients with stroke who have severe leg weakness, meaning that one might see less effect in stroke patients with weak legs than in those with residual power. Although the absolute risk of proximal DVT was lower in the 1,014 patients in the study who were able to lift both their legs off the bed at baseline than in those who could not (6.9% *vs.* 15.5%), the findings did not show any significant interaction between the effectiveness of GCS and these subgroups.

It could be argued that patients with stroke but without significant leg weakness are more similar to immobile medical patients than are those undergoing surgery. The absence of effect of GCS, even in the presence of some residual leg movement, suggests

that the effectiveness of GCS in acute medical patients cannot be assumed. Further trials in such patients are probably warranted.

Incorrect use and poor compliance with GCS might have reduced their effectiveness in this CLOTS trial. The manufacturers of the GCS used in this trial subsequently stressed the importance of proper sizing and fitting of their stockings. Sizing depends on measurements of the calf and thigh circumferences and the leg length. There are 18 different sizes of thigh-length GCS and an additional ten with a suspender belt. In view of the complexity of achieving a good fit, a proportion of patients might have been given poorly fitting GCS in the trial. Compliance was good initially but reduced over time, mainly because patients found the GCS uncomfortable or staff became concerned by the condition of the patient's skin. Nonetheless, overall compliance with the thigh-length GCS in this trial was reasonable, and the authors said that they attempted to continue their use until the patient was discharged or regained mobility. Because of the training delivered to centers and the methods used to monitor compliance, the authors remain confident that sizing, fitting, and compliance within the trial were at least as good as in routine practice. In the randomized controlled trials in patients undergoing surgery, GCS were applied only for a few days, and screening for DVT was only done for a maximum of maybe 14 days. Compliance in the CLOTS trial was marginally better over the first 14 days than over 30 days, but they did not note any greater effect when they restricted their analyses to events occurring in the first 14 days.

With the assumption that the results of the next CLOTS trial (Phase 2, which will be available before mid-2010) will not show an unexpected result (that below-knee stockings are more effective than are thigh-length ones), this trial provides no evidence to support the routine use of GCS in immobile, hospitalized patients with acute stroke. Stroke guidelines that recommend their use might now need to be updated as a result of this new evidence. In view of the absence of net benefit from heparin or low-molecular-weight heparin in ischaemic stroke, future research with data available from this and other trials needs to establish whether there are specific subgroups of patients, who are at greater than average risk of venous thromboembolism and low risk of bleeding complications, who might gain net benefit from anticoagulation.

Summary and Conclusion

The results of this meta-analysis have implications for clinical practice. First, to answer the main objective of this study, the findings provide evidence that graduated compression stocking (GCS) therapy reduces the risk of DVT, and helps in managing the pain and discomfort associated with the symptoms and indications of the disease, including swelling, bleeding, and the negative psychological effects of the disorder. This paper's data has therefore determined that GCS is effective in the management of DVT-suffering patients and DVT-related morbidities.

Secondly, the findings indicate that without GCS, the incidence of DVT is somewhat considerable, as 5.3% of untreated patients will develop any (proximal or distal) DVT and 3.3% of such patients will develop proximal DVT. Taken together, these findings support the need to implement recommendations from consensus guideline groups and other authorities that GCS should be considered in at-risk patients.

Lastly, the secondary objectives of this study are now to be answered: Aside from GCS *per se,* other techniques used in conjunction with it are a closely related kind of GCS, elastic compression stockings (ECS), which is based on the same principles as GCS; subcutaneous heparin, dextran, or some other antithrombotic pharmacological treatment as an adjunct or complementary therapy; and anticoagulant prophylaxis, which in one study proved to be very effective. GCS, in combination with these other therapies, significantly helps in reducing the incidence of pre- or post-operative DVT, and as an indirect prophylactic measure against pulmonary embolism (PE). And thirdly and finally, when GCS is used as a main or additional intervention combined with other treatments, the medical improvement of DVT patients is highly significantly positive and beneficial. Thus, data obtained from this study indicate that the combined use of bilateral GCS added a reduction of more than 52% in the risk of developing DVT in comparison to other treatments used alone. These results suggest that the combined use of graduated compression devices and heparin might further decrease the incidence of DVT complications in patients undergoing, for example, major surgical procedures that might increase DVT or PE risks.

Additional research is now needed to identify patient groups in whom the therapeutic benefits from GCS are greatest, and to identify barriers (and methods to overcome these barriers) to optimize the implementation of GCS.

It must here be mentioned that this meta-analysis was first designed to determine if GCS is more effective than the conventional use of heparin alone as a prophylaxis against DVT or PE. This researcher wanted to consider GCS combined with other therapies as a third "branch" of the analysis because of a reluctance to abandon the traditional

recommendation of heparin prophylaxis. But since the intent was not to compare GCS alone versus heparin alone, this idea was later abandoned — and besides, not enough studies provided data that could have been used in this manner.

At any rate, GCS is effective in preventing asymptomatic DVT in at-risk patients, and is effective in treating and managing the disease in those patients already suffering from it. It is at times associated with an increased bleeding risk (although the occurrence of this is not statistically significant); but the therapeutic benefits of GCS would appear to outweigh the risks of bleeding — and therefore this researcher concludes that the treatment is still to be considered critical and of great consequence in affected patients.

REFERENCES

Agnelli, G., Piovella, F., Buoncristiani, P. (1998). Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *New England Journal of Medicine,* Vol. 339, pp. 80-85.

Allan, A., Williams, J.T., Bolton, J.P., Le Quesne, L.P. (1983). The use of graduated compression stockings in the prevention of postoperative deep vein thrombosis. *British Journal of Surgery,* Vol. 70, pp. 172-74.

Amaragiri, S.V., Lees, T.A. (2000). Elastic compression stockings for the prevention of deep vein thrombosis. *Cochrane Database System Reviews,* CD001484.

Anderson, F.A. Jr., Wheeler, H.B., Goldberg, R.J., Hosmer, D.W., Forcier, A., Patwardhan, N.A. (1991). Physician practices in the prevention of venous thromboembolism. *Annals of Internal Medicine,* Vol. 115, pp. 591-95.

Arcelus, J.I., Caprini, J.A., Hoffman, K.A., Traverso, C.I., Hoppensteadt, D., Fareed, J. (1995). Modifications of plasma levels of tissue factor pathway inhibitor and endothelin-1 induced by reverse Trendelenburg position: Influence of elastic compression — Preliminary results. *Journal of Vascular Surgery,* Vol. 22, pp. 568-72.

Belcaro, G., Laurora, G., Cesarone, M.R., De Sanctis, M.T. (1993). Prophylaxis of recurrent deep venous thrombosis: A randomized, prospective study using indubofen and graduated elastic compression stockings. *Angiology,* Vol. 44, pp. 695-99.

Benko, T., Cooke, E.A., McNally, M.A., Mollan, R.A. (2001). Graduated compression stockings: Knee length or thigh length. *Clnical Orthopedics,* Vol. 17, pp. 197-203.

Bergqvist, D., Lindblad, B. (1984). The thromboprophylactic effect graded elastic compression stockings in combination with dextran 70. *Archives of Surgery,* Vol. 119, pp. 1329-31.

Blättler, W., Zimmet, S.E. (2008). Compression therapy in venous disease. *Phlebology,* Vol. 23, No. 5, pp. 203-05.

Brakkee, A., Kuiper, J. (1988). Influence of compression stockings on the hemodynamics in the lower extremities. *Phlebology,* Vol. 3, pp. 147-53.

Brandjes, D.P.M., Buller, H.R., Heijboer, H., Huisman, M.V., De Rijk, M., Jagt, H. (1997). Randomized trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet,* Vol. 349, pp. 759-62.

Callam, M.J., Ruckley, C.V., Dale, J.J., Harper, D.R. (1987). Hazards of compression treatment of the leg: An estimate from Scottish surgeons. *British Medical Journal,* Vol. 295, p. 1382.

Clarke, M.J., Hopewell, S., Juszczak, E., Eisinga, A., Kjeldstrøm. M. (2006). Compression stockings for preventing deep vein thrombosis in airline passengers. *Cochrane Database System Reviews,* CD 004002.

Coleridge-Smith, P.D., Hasty, J.H., Scurr, J.H. (1991). Deep vein thrombosis: Effect of graduated compression stockings on distension of the deep walls of the calf. *British Journal of Surgery,* Vol. 78, pp. 724-26.

Epstein, N.E. (2005). Intermittent pneumatic compression stocking prophylaxis against deep venous thrombosis in anterior cervical spinal surgery: A prospective efficacy study in 200 patients and literature review. *Spine,* Vol. 30, pp. 2538-43.

_____. (2006). Efficacy of pneumatic compression stocking prophylaxis in the prevention of deep venous thrombosis and pulmonary embolism following 139 lumbar laminectomies with instrumented fusions. *Journal of Spinal Disorders and Techniques,* Vol. 19, pp. 28-31.

Fasting, H., Anderson, K., Nielsen, H.K., Husted, S.F., Koopmann, H.D., Simonsen, O. (1985). Prevention of postoperative deep venous thrombosis: Low dose heparin *versus* graded pressure stockings. *Acta Chirurgica Scandinavica*, English version, Vol. 151, pp. 245-48.

Fredin, H., Bergqvist, D., Cederholm, C., Lindbald, B., Nyman, U. (1989). Thromboprophylaxis in hip arthoplasty: Dextran with graded compression stockings or preoperative dextran compared in 150 patients. *Acta Orthopaedica Scandinavica,* Vol. 60, pp. 678-81.

Gaylarde, P.M., Sarkany, I., Dodd, H.J. (1993). The effect of compression on venous stasis. *British Journal of Dermatology,* Vol. 128, pp. 255-58.

Ginsberg, J.S. (2004). Routine stocking therapy after deep venous thrombosis: A clinical dilemma. *Annals of Internal Medicine,* Vol. 141, pp. 314-15.

Guyton, D.P., Khayat, A., Schereiber, H. (1985). Pneumatic compression stockings and prostaglandin synthesis: A pathway of fibrinolysis? *Critical Care Medicine,* Vol. 13, p. 266.

Hansberry, K.L., Thompson, I.M. Jr., Bauman, J., Deppe, S., Rodriguez, F.R. (1991). A prospective comparison of thromboembolic stockings, external sequential pneumatic compression stockings, and heparin sodium/dihydroergotamine mesylate for the prevention of thromboembolic complications in urological surgery. *Journal of Urology,* Vol. 145, pp. 1205-08.

Heath, D.I., Kent, S.J.S., Johns, D.L., Young, T.W. (1987). Arterial thrombosis associated with graduated pressure antiembolic stockings. *British Medical Journal,* Vol. 295, p. 580.

Hobel, C.J., Castro, L., Rosen, D., Greenspoon, J.S., Nessim, S. (1996). The effect of thigh-length support stockings on the hemodynamic response to ambulation in pregnancy. *American Journal of Obstetrics and Gynecology,* Vol. 174, pp. 1734-41.

Ido, K., Suzuki, T., Taniguchi, Y., Kawamoto. C., Isoda, N., Nagamine, N. (1995). Femoral vein stasis during laparoscopic cholecystectomy: Effects of graded elastic compression leg bandages in preventing thrombous formation. *Gastrointestinal Endoscopy,* Vol. 42, pp. 151-55.

Ishak, M.A., Morley, K.D. (1981). Deep venous thrombosis after total hip arthroplasty: A prospective controlled study to determine the prophylactic effect of graded pressure stockings. *British Journal of Surgery,* Vol. 68, pp. 429-32.

Jeffery, P.C., Nicolaides, A.N. (1990). Graduated compression stockings in the prevention of postoperative deep vein thrombosis. *British Journal of Surgery,* Vol. 77, pp. 380-83.

Johnson, G. Jr., Kupper, C., Farrar, D.J., Swallow, R.T. (1982). Graded compression stockings: Custom *vs.* non-custom. *Archives of Surgery,* Vol. 117, pp. 69-72.

Jones, N.A., Webb, P.J., Rees, R.I., Kakkar, V.V. (1980). A physiological study of elastic compression stockings in venous disorders of the leg. *British Journal of Surgery,* Vol. 67, pp. 569-72.

Jorgensen, P., Thorup, J., Fischer, A. (1985). Heparin with and without graded compression stockings in the prevention of thromboembolic complications of major abdominal surgery: A randomized trial. *British Journal of Surgery,* Vol. 72, pp. 579-81.

Kahn, S.R., Elman, E., Rodger, M.A., Wells, P.S. (2003). Use of elastic compression stockings after deep venous thrombosis: A comparison of practices and perceptions of thrombosis physicians and patients. *Journal of Thrombosis and Haemostasis,* Vol. 1, pp. 500-06.

Kalodiki, E.P., Hoppensteadt, D.A., Nicolaides, A.N., Fareed, J., Gill, K., Regan, F. (1996). Deep venous thrombosis prophylaxis with low molecular weight and elastic compression in patients having total hip replacement: A randomized controlled trial. *International Journal of Angiology,* Vol. 15, pp. 162-68.

Kay, T.W.H., Martin, F.I. (1986). Heel ulcers in patients with longstanding diabetes who wear antiembolism stockings. *Medical Journal of Australia,* Vol. 145, pp. 290-91.

Keiekegaard, A., Norgren, L. (1993). Graduated compression stockings in the prevention of deep vein thrombosis in patients with acute myocardial infarction. *European Heart Journal,* Vol. 14, pp. 1365-68.

Keith, S., McLaughlin, D., Anderson, F. (1992). Do graduated compression stockings and pneumatic boots have an additive effect on the peak velocity of venous blood flow? *Archives of Surgery,* Vol. 127, pp. 727-30.

Kokkos, S.K., Daskalopoullou, S.S., Nicolaides, A.N., Geroulakos, G. (2006). Review on the value of graduated elastic compression stockings after deep vein thrombosis. *Journal of Thrombosis and Haemostasis,* Vol. 96, pp. 441-45.

Kurtoglu, M., Yanar, H., Bilsel, Y. (2004). Venous thromboembolism prophylaxis after head and spinal trauma: Intermittent pneumatic compression devices versus low molecular weight heparin. *World Journal of Surgery,* Vol. 28, pp. 807-11.

Lawrence, D., Kakkar, V.V. (1980). Graduated, static, external compression of the lower limb: A physiological assessment. *British Journal of Surgery,* Vol. 67, pp. 119-21.

Levine, M.N., Gent, M., Hirsh, J., Weitz, J., Turpie, A.G., Powers, P. (1996). Ardeparin (low-molecular-weight heparin) *vs.* graduated compression stockings for the prevention of venous thromboembolism: A randomized trial in patients undergoing knee surgery. *Archives of Internal Medicine,* Vol. 156, pp. 851-56.

MacDonald, R.L., Amidei, C., Baron, J. (2003). Randomized, pilot study of intermittent pneumatic compression devices plus dalteparin versus

intermittent pneumatic compression devices plus heparin for prevention of venous thromboembolism in patients undergoing craniotomy. *Surgical Neurology,* Vol. 59, pp. 363-72.

McNally, M.A., Cooke, E.A., O'Connell, B.M., Mollan, R.A.B. (1995). Thigh vs. knee length compression stockings in the prevention of venous stasis. *Journal of Bone and Joint Surgery,* Vol. 77-B, p. 11.

Merrett, N.D., Hanel, K.C. (1993). Ischaemic complications of graduated compression stockings in the treatment of deep venous thrombosis. *Postgraduate Medical Journal,* Vol. 69, pp. 232-34.

Nelson, L.D. Jr., Montgomery, S.P., Dameron, T.B. Jr. (1996). Deep vein thrombosis in lumbar spinal fusion: A prospective study of antiembolic and pneumatic compression stockings. *Journal of the Southern Orthopedic Association,* Vol. 5, pp. 181-84.

Nicolaides, A.N., Miles, C., Hoare, M., Jury, P., Helmis, E., Venniker, R. (1983). Intermittent sequential pneumatic compression of the legs and thromboembolism-deterrent stockings in the prevention of postoperative deep venous thrombosis. *Surgery,* Vol. 94, pp. 21-25.

Nilsen, D.W.T., Naess-Andresen, K.F., Kierulf, P., Heldaas, J., Storen, G., Godal, H.C. (1984). Graded pressure stockings in prevention of deep vein thrombosis following total hip replacement. *Acta Chirurgica Scandinavica,* English version, Vol. 150, pp. 531-34.

Nurmohamed, M.T., Van Riel, A.M., Henkens, C.M.A., Koopman, M.M., Que, G.T., D'Azemar, P. (1996). Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. *Journal of Thrombosis and Haemostasis,* Vol. 75, pp. 233-38.

Pierson, S., Pierson, D., Swallow, R., Johnson, G. Jr. (1983). Efficacy of graded elastic compression in the lower leg. *Journal of the American Medical Association,* Vol. 249, pp. 242-43.

Porteous, L.M.J., Nicholson, E.A., Morris, L.T., James, R., Negus, D. (1989). Thigh length versus knee length stockings in the prevention of deep vein thrombosis. *British Journal of Surgery,* Vol. 76, pp. 296-97.

Prandoni, P., Lensing, Prins, M.H., Frulla, M., Marchiori, A., Bernardi, E., Tormene, D., Mosena, L., Pagnan, A., Girolami, A. (2004). Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: A randomized, controlled trial. *Annals of Internal Medicine,* Vol. 141, pp. 249-56.

Sarin, S., Scurr, J.H., Coleridge-Smith, P.D. (1992). Mechanism of action of external compression on venous function. *British Journal of Surgery,* Vol. 79, pp. 499-502.

Scurr, J.H., Coleridge-Smith, P.D., Hasty, J.H. (1987). Regiment for improved effectiveness of intermittent pneumatic compression in deep venous thrombosis prophylaxis. *Surgery,* Vol. 102, pp. 816-20.

Sparrow, R.A., Hardy, J.G., Fentem, P.H. (1995). Effect of "antiembolism" compression hosiery on leg blood. *British Journal of Surgery,* Vol. 82, pp. 53-59.

Thomas, S. (1989). Anti-embolism stockings. *Pharmaceutical Journal,* Vol. 243, p. 633.

_____. (1992). *Graduated External Compression and the Prevention of Deep Vein Thrombosis,* Surgical Materials Testing Laboratory, Bridgend, Mid Glamorgan, UK.

Torngren, T. (1980). Low dose heparin and compression stockings in the prevention of postoperative deep venous thrombosis. *British Journal of Surgery,* Vol. 67, pp. 482-84.

Turner, G.M., Cole, S.E., Brooks, J.H. (1984). The efficacy of graduated compression stockings in the prevention of deep venous thrombosis after major gynaecological surgery. *British Journal of Obstetrics and Gynaecology,* Vol. 91, pp. 588-91.

Turpie, A.G., Hirsh, J., Gent, M., Julian, D., Johnson, J. (1989). Prevention of deep vein thrombosis in potential neurosurgical patients: A randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. *Archives of Internal Medicine,* Vol. 149, pp. 679-81.

Van Tulder, M.W., Assendelft, W.J., Koes, B.W., Bouter, L.M. (1997). Method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group for Spinal Disorders. *Spine*, Vol. 22, pp. 2323-30.

Wautrecht, J., Macquaire, V., Vandesteene, A. (1996). Prevention of deep vein thrombosis in neurosurgical patients with brain tumors: A controlled, randomized study comparing graded compression stockings alone and with intermittent sequential compression — Correlation with pre- and postoperative fibrinolysis: Preliminary results. *International Journal of Angiology,* Vol. 15, pp. 5-10.

Wells, P.S., Lensing, A.W.A., Hirsh, J. (1994). Graduated compression stockings in the prevention of postoperative venous thromboembolism. *Archives of Internal Medicine,* Vol. 154, pp. 67-72.

Wildin, C.J., Hui, A.C.W., Esler, C.N.A., Gregg, P.J. (1998). *In vivo* pressure profiles of thigh-length graduated compression stockings. *British Journal of Surgery,* Vol. 85, pp. 1228-31.

Wille-Jorgensen, P., Thorup, J., Fischer, A., Holst-Christensen, J., Flamsholt, R. (1985). Heparin with

and without graded compression stockings in the prevention of thromboembolic complications in major abdominal surgery: A randomized trial. *British Journal of Surgery,* Vol. 72, pp. 579-81.

Williams, A.M., Bolton, J., Le Quesnel, L.P. (1983). The use of graduated compression in the prevention of postoperative deep venous thrombosis. *British Journal of Surgery,* Vol. 70, pp. 172-74.

Williams, A.M., Rhys-Davies, P., Sweetnam, D.I.S., Harper, G., Pusey, R., Lightowler, C.D.R. (1994). Knee-length versus thigh-length graduated stockings in the prevention of deep vein thrombosis. *British Journal of Surgery*, Vol. 83, p. 1553.

Williams, J.T., Palfrey, S.M. (1988). Cost effectiveness of below knee against above knee compression stockings in the prevention of deep vein thrombosis. *Phlebology,* Vol. 41, pp. 809-11.

Williamson, M., Thomas, S., Edwards, A., Johnson, R., Riggs, J., Lewis, M.H. (1990). Graduated compression stockings in the prevention of postoperative deep vein thrombosis: A comparative study of pressure profiles and patient compliance. *Phlebology,* Vol. 5, pp. 135-39.