Compression stockings and the prevention of symptomatic venous thromboembolism: data from the Tinzaparin in Acute Ischaemic Stroke Trial.

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Running title

Do compression stockings reduce VTE in acute stroke?

Acknowledgements

Laura Gray is supported, in part, by The Stroke Association (UK) and BUPA Foundation (UK). Philip Bath is Stroke Association Professor of Stroke Medicine; the Division of Stroke Medicine receives a core grant from The Stroke Association (UK). We thank the principal investigators, centres, and patients who took part in the TAIST trial, see [4] for a listing of the participating centres.

ABSTRACT

Background

Venous thromboembolism (VTE) is a well recognised and preventable complication of acute stroke. While graduated compression stockings reduce the risk of VTE in surgical patients their benefit in acute stroke remains uncertain.

Methods

The relationship between symptomatic VTE and use of stockings using observational data from the 'Tinzaparin in Acute Ischaemic Stroke Trial', which compared 10 days of treatment with tinzaparin (175 $IU.kg^{-1}$ or 100 $IU.kg^{-1}$) with, aspirin (300 mg od), was assessed using logistic regression adjusted for known VTE risk factors and treatment.

Results

Symptomatic VTE occurred in 28 patients (1.9%, DVT 18, PE 13) within 15 days of enrolment in 1,479 patients. Patients wearing one or two stockings for any period of time during the first 10 days (n=803) had a non-significant increase (odds ratio, OR 2.45, 95% confidence interval, CI 0.95 - 6.32) in the risk of symptomatic VTE. In contrast, those wearing bilateral stockings for 10 days (n=374) had a non-significant reduction in the odds of symptomatic VTE as compared to those who wore no stockings or wore them for less than 10 days (OR 0.65, 95% CI 0.26-1.65). Mild stroke and treatment with tinzaparin were associated with a reduced risk of VTE.

Conclusions

Bilateral graduated compression stockings may reduce the incidence of VTE by one-third in patients with acute ischaemic stroke. However, the uncertainty in this finding, low frequency of symptomatic VTE, potential for stockings to cause harm, and cost of stockings highlight the need for a large randomised-controlled trial to examine the safety and efficacy of stockings in acute stroke.

INTRODUCTION

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and/or pulmonary embolism (PE), were common clinical events in acute stroke 30 years ago.[1, 2] Symptomatic VTE (sVTE) rates have declined in the intervening time to a rate of 3-5%.[3-5] However, a recent study to detect sub-clinical DVT suggested that the rate of sub-clinical DVT remains high.[6] This is important as asymptomatic DVT is the commonest precursor of symptomatic PE,[7] a major cause of mortality in acute stroke,[8] and the usual precursor of fatal PE.[9]

VTE can be prevented using drugs or compression stockings.[10] Unfractionated and low molecular weight heparins (LMWH) protect against DVT in surgical and medical patients [11, 12] and are used to treat diagnosed DVT and PE.[13] Aspirin also reduces the development of VTE [14] although probably less effectively so than anticoagulants. When considering patients with acute stroke, heparin offers effective prophylaxis against symptomatic DVT (sDVT) and symptomatic (sPE) but at the risk of causing intracranial haemorrhage.[3-5] Aspirin also reduces PE in acute stroke but at less risk of bleeding.[3] The individual effects of early mobilisation, rehydration and stockings are not well quantified.

Compression stockings produce a pressure gradient from ankle to thigh, displacing blood from the superficial venous system and compressing the vein reducing its cross sectional area [15] thereby minimising venous stasis. Stockings reduced the risk of DVT by 57-64% in surgical patients,[16] and are also effective in medical patients.[17] There is no evidence as to whether full or

knee length stockings provide more benefit.[18] One randomised controlled trial (RCT) (n=98) was unable to demonstrate any significant benefit in acute stroke patients, although a trend towards DVT reduction was found (odds ratio 0.43, 95% CI 0.14-1.36).[19] Stroke patients differ from post-operative surgical patients in important ways which might mean that stockings are less effective after stroke. In surgical prophylaxis, immobilisation is preceded by application of stockings and lasts only a few days. In contrast, paralysis occurs prior to stocking application in patients with stroke and may last weeks or months. The use of stockings may cause complications in patients with peripheral vascular disease and diabetes.[20, 21]

Despite the theoretical effectiveness and widespread use of stockings, their clinical effectiveness needs further appraisal in stroke patients. We describe here the relationship between the use of stockings and effect on VTE using data from the 'Tinzaparin in Acute Ischaemic Stroke Trial' (TAIST).

METHODS

Design

We performed a nested-observational study assessing the relationship between the use of graduated venous compression stockings and subsequent venous thromboembolic events. Data were obtained from the TAIST randomised controlled trial [4] and adjusted for confounding factors.

TAIST

TAIST was a prospective, randomised, multicentre, double-blind, aspirin-controlled trial assessing the safety and efficacy of tinzaparin, a low molecular weight heparin, in 1,484 patients with acute ischaemic stroke.[4] Patients were enrolled within 48 hours of ictus and randomly assigned to 10 days of treatment with high-dose tinzaparin (175 $IU.kg^{-1}$), medium-dose tinzaparin (100 $IU.kg^{-1}$), or aspirin (300 mg). The stroke centres taking part in TAIST were all expert in stroke care and experienced in trials.

Stockings and venous thromboembolic events

The decision to prescribe stockings and how these would be used was left to the responsible physician and local practice and is likely, therefore, to have been dependent on certain clinical features such as stroke severity, immobility and contraindications to stockings. Similarly, the decision to refer patients for physical therapy and early mobilisation, factors which can also reduce VTE, was left to local practice. The use of stockings and whether these were bilateral or unilateral was prospectively recorded on a daily basis during the 10 days of drug treatment.

During the treatment period patients were examined for signs and symptoms of sVTE on a daily basis with venography or venous duplex scanning being used to confirm the diagnosis of sDVT, and ventilation perfusion scan to confirm the diagnosis of PE. The incidence of sDVT and/or sPE was documented again at 90 and 180 days of follow-up after a review of medical records and patient interview. An independent committee blinded to treatment assignment (and the wearing of stockings) adjudicated the diagnosis of major events, including DVT, PE and death.

Data management

Patients were categorised into those who wore stockings (on either leg at any point during the treatment period or those who wore bilateral stockings for the whole treatment period) and those who did not. The primary analysis focused on VTE events occurring within 15 days of enrollment, equivalent to the ten days of randomised treatment plus 5 days to allow for the antithrombotic effects of the trial interventions to dissipate.[4] Comparisons of VTE were also made at 90 and 180 days.

Statistical analysis

Intention-to-treat analyses were performed using SAS version 8 (SAS Institute, Cary NC). Data are given as frequency (%), median (interquartile range), and odds ratio (OR) with 95% confidence intervals (95% CI). Differences between groups were assessed with either a chi square test or the Wilcoxon test.

Differences in the incidence of VTE were investigated using logistic regression adjusted for the use of stockings, treatment (high dose tinzaparin, medium dose tinzaparin, aspirin) and known VTE risk factors, including age, gender, smoking status (current smoker vs. past or non smoker), weight, stroke severity (assessed using the Scandinavian Stroke Scale, SSS) and time to enrollment. Logistic regression models were created comprising accepted VTE risk factors even if these were not significant univariate factors in this study. Two models were produced: a comparison of patients who wore: (i) one or two stockings at any point during the 10 days versus those who wore none; and (ii) bilateral stockings for the whole ten days versus those who wore no stockings or wore them for less than 10 days.

RESULTS

Subjects

Of the 1,499 patients randomised, 15 were excluded from the trial's primary analysis due to emerging exclusion criteria (such as the discovery of contra-indications to treatment), leaving 1,484 patients (aspirin 491, medium dose tinzaparin 507, high dose tinzaparin 486).[4] A further 5 patients were excluded from the present analyses because no information on stockings was recorded at any time point.

Stockings

The baseline characteristics of the 1,479 (99.7%) included patients are shown in table 1. Just over half (803, 54%) wore stockings at some point during the first 10 days post enrollment. Patients given stockings had more severe stroke, judged by their lower baseline SSS score and the greater proportion of patients with a total anterior circulation syndrome (TACS).[22] The frequency of other characteristics, including demographic and vascular risk factors (including prior stroke, myocardial infarction, smoking, atrial fibrillation, diabetes and intermittent claudication), were similar between stocking and non-stocking users (table 1).

Venous thromboembolism

Patients with a severe stroke (lower SSS score, TACS clinical syndrome), leg weakness, or right-sided weakness were more likely to suffer a VTE (table 2). Other risk factors were similar (data not shown). VTE occurred more frequently

in those wearing stockings or taking aspirin (as compared to those receiving medium or high dose tinzaparin).

The overall incidence of sVTE by 15 days post-enrollment was low at 1.9% (table 3). Patients given stockings had a significantly higher incidence of sVTE at 15 days as compared to non stocking wearers (0.9% versus 2.7%, p=0.01, table 3). Similar increases in the components of sVTE, sDVT and sPE were seen in those with stockings. The difference in sVTE was maintained during the subsequent 180 days (table 3). The median time to sVTE was 10 days (IQR 5.5-13) and did not differ between those with and without stockings.

Case-fatality by 15 days post-enrollment was comparable between stocking and non-stocking wearers (table 3). Of the 216 deaths by day 180, PE was adjudicated to be the cause of death in 11 cases (5.1%) and was clinically evident in 10 of these (3 patients had an autopsy confirming PE as cause of death). The remaining patient had unexplained sudden death with PE diagnosed at autopsy. A total of 22 autopsies were performed out of 216 deaths (10.2%); only 4 patients showed evidence of PE at postmortem.

Stockings and symptomatic venous thromboembolism

Patients wearing one or two stockings for any period of time during the first 10 days (n=803) had a non-significant 2.45 (95% CI, 0.95 - 6.32) fold increase in the risk of sVTE during the first 15 days, with adjustment for age, gender, impairment, weight, smoking, time to enrollment, and treatment (figure 1). Tinzaparin reduced sVTE in a dose-dependent fashion as compared with aspirin.

Symptomatic VTE events were few in number (6, 1.6%) when considering the 374 patients who wore bilateral stockings for the whole of the first ten days after enrollment. Patients wearing bilateral stockings for 10 days had a non-significant 35% reduction in the odds of symptomatic VTE as compared to those who wore no stockings or wore them for less than 10 days, OR 0.65 (95% CI, 0.26 - 1.65, figure 2).

DISCUSSION

This study is the largest in stroke to assess, in a systematic manner, whether graduated compression stockings reduce symptomatic VTE events. The incidence of sVTE was low at 2 weeks and 6 months post stroke (1.9% and 4.9% respectively) confirming recent findings [3, 5] that it is becoming less common, presumably secondary to improved care including early mobilisation, early rehydration and increased use of aspirin.

In univariate analyses, the wearing of stockings was associated with a significant increased risk of sVTE. Since it is likely that this reflected confounding by known risk factors, especially stroke severity, two logistic regression models were used to adjust for potential confounders. The first model compared patients who wore any stockings at any time during the first 10 days with those who wore no stockings whatsoever; the wearing of stockings was still associated with an increase in sVTE, albeit non-significant. In the second model, rigorous wearing of stockings bilaterally for the first 10 days was associated with a reduction in sVTE of about 35% as compared with patients who wore no stockings or who only wore them for part of the 10 days. The lack of statistical significance could simply reflect chance, in which case stockings are apparently ineffective in preventing sVTE in patients with acute stroke. However, a number of other factors are relevant potentially. First, very few sVTE events were recorded thereby limiting the power of these analyses. Second, the point estimate in the second model appears to be less than that seen in surgical prophylaxis where the reduction approximates to 57-64%,[16] perhaps reflecting that prevention should, ideally, commence before the period of risk starts. Third, comparison of

the two models suggests that the use of stockings should be systematic and rigorous, i.e. they should be placed bilaterally and used to cover the whole period of immobility rather than be used *ad hoc*. Forth, other powerful modulators of VTE may have concealed part of the effect of stockings, especially the use of a LMWH. This is very relevant in a non-randomised observational study where the factor being assessed has a moderate treatment effect. Last, the multivariate models may not have included important confounding factors.

A number of caveats need to be made about the findings reported here. First, this was a longitudinal substudy of a randomised-controlled trial. Observational studies are susceptible to bias, as was apparent here with the increased use of stockings in more severe patients. Such bias can mask or inflate findings. The univariate analysis and one of the models suggested that stockings might increase VTE. Full-length stockings can slip or roll down [23] and lead to a tourniquet effect around the knee thereby, potentially, reducing venous return [24] and increasing the risk of DVT. Additionally, patients with sensory loss (e.g. due to diabetes), perceptual changes (e.g. neglect) or dysphasia may not be able to signal distress from inappropriately applied or maintained stockings. Hence, the possible ineffectiveness or even hazard with stockings needs to be refuted in a randomised controlled trial. (Interestingly, the frequency of diabetes mellitus and intermittent claudication, conditions which are relative contraindications for the use of stockings, did not differ between the two groups.) Second, the subjects in TAIST were selected because of inclusion/exclusion criteria relating to a trial of a low molecular weight heparin. Hence, the results here may not be generalisable to all patients with ischaemic stroke, and have questionable relevance to patients with primary intracerebral haemorrhage. Third, the use of

stockings was only recorded for the first 10 days after enrollment thereby potentially reducing the apparent effect of stockings.

Forth, this study recorded only sVTE and it is possible that a substantial number of asymptomatic VTE cases were missed. As mentioned previously this is important as asymptomatic DVT is the usual precursor of fatal PE.[9] Using DVT as a surrogate marker for PE, it is possible to hypothesize that reducing DVT will reduce PE; however these reductions in PE are inferred, rather than based on trial data. To date, the largest thromboprophylactic trial in medical patients showed that there was no beneficial effect of heparin on the incidence of fatal PE and total mortality.[25] Furthermore, the signs and symptoms of VTE may be misinterpreted, e.g. PE may be diagnosed as pneumonia.[26] Fifth, despite the diagnosis of VTE being independently adjudicated, varying diagnostic techniques were used at different centers (e.g. DVT was confirmed using either venography and duplex ultrasound) thereby introducing the potential for variation in the incidence of DVT across centers. Sixth, the information recorded on the use of stockings was limited and did not include data on the type of stocking (full length versus below knee, manufacturer), or adverse events and discontinuations related to the wearing of stockings. Last, DVT might be diagnosed less in patients wearing stockings since these mask signs such as swelling, temperature and colour change (unless they are removed regularly to expose the legs) whilst stroke patients often have communication difficulties, e.g. confusion and dysphasia, thereby limiting their ability to mention the presence of symptoms.

Despite these limitations, the results come from a large study with high fidelity data collection and blinded adjudication of sVTE events. Overall, stockings

might reduce the rate of sVTE by around one-third in patients with acute ischaemic stroke. However, the uncertainty in this finding, low frequency of symptomatic VTE, potential for stockings to cause harm (e.g. gangrene in patients with peripheral artery disease), and cost of stockings (financial, nursing time, patient discomfort) all raise questions as to their place in acute stroke management. These issues highlight the need for one or more large randomised controlled trials to test the safety, efficacy and health economics of stockings in this patient group. The ongoing 'Clots in Legs Or TEDs after Stroke' (CLOTS, www.clotstrial.com) trial is examining whether stockings reduce both symptomatic and asymptomatic DVT, and whether long stockings are more effective than short ones, in over 5,000 patients.[27]

TABLE 1

Baseline characteristics of patients wearing or not wearing stockings. Number (%) or median (interquartile range); comparison by Chi square test or Wilcoxon test.

	Total	No stockings	Stockings †	p value
Subjects	1,479	676 (46)	803 (54)	
Age (years)	74 (66-80)	75 (67-80)	73 (64-79)	**0.004**
Gender, male (%)	804 (55.4)	377 (55.8)	427 (53.2)	0.32
Weight (kg)	72 (63-82)	72 (63-82)	72.7 (63-82)	0.39
Clinical:				
Time to enrollment (hour)	25 (15.3-37.0)	25 (16-38)	25 (14-37)	0.34
Side of lesion, right (%)	769 (53.2)	350 (53.4)	419 (53.1)	0.92
Impairment (SSS), total	34 (24-42)	38 (28-46)	30 (20-39)	**<0.0001**
Impairment (SSS), leg	4 (2-5)	4 (2-5)	4 (0-5)	**<0.0001**
Impairment (SSS), gait	3 (0-6)	3 (0-6)	0 (0-3)	**<0.0001**
Oxford classification:				
TACI (%)	519 (35.1)	193 (28.6)	236 (40.6)	**<0.0001**
PACI (%)	471 (31.9)	216 (32)	255 (31.8)	0.94
LACI (%)	422 (28.5)	243 (36)	179 (22.3)	**<0.0001**
POCI (%)	66 (4.5)	23 (3.4)	43 (5.4)	0.07
Antithrombotic (randomised)				
Tinzaparin, high dose (%)	484 (32.7)	223 (33.0)	261 (32.5)	0.84

Tinzaparin, medium dose (%)	505 (34.1)	229 (33.9)	276 (34.4)	0.84
Aspirin (%)	490 (33.1)	224 (33.1)	226 (33.1)	0.99

† Worn for any number of days within the 10 treatment period on either or both legs

LACI: lacunar infarct; PACI: partial anterior circulation infarct; POCI: posterior circulation syndrome; SSS: Scandinavian Stroke Scale (total, leg and gait scores; low score ~ severe stroke); TACI: total anterior circulation infarct

TABLE 2

Baseline characteristics of patients developing or not developing sVTE. Number (%) or median (interquartile range); comparison by Chi square test or Wilcoxon test.

	No sVTE	sVTE	p value
Subjects	1451 (98.1%)	28 (1.9%)	
Clinical details			
Age (years)	74 (66-80)	71 (69.5-79)	0.99
Gender, male (%)	792 (54.6)	12 (42.9)	0.22
Severity (SSS)	34 (24-43)	22.5 (10-34.5)	**0.0001**
Leg impairment (SSS)	4 (2-5)	2 (0-4)	**0.004**
Gait impairment (SSS)	3 (0-6)	0 (0-3)	**0.05**
Oxford classification, TACI (%)	504 (34.7)	15 (53.6)	**0.04**
Weakness, right (%)	746 (52.7)	23 (82.1)	**0.002**
Management			
Time to enrollment (hours)	25 (15.4-37.0)	25.7 (9.9-42.2)	0.80
Compression stockings, any (%)	781 (53.8)	22 (78.6)	**0.01**
Compression stockings, for 10 days (%)	368 (25.4)	6 (21.4)	0.64
No stockings (%)	670 (46.2)	6 (21.4)	**0.01**
Tinzaparin, high dose (%)	479 (33.0)	5 (17.9)	0.09
Tinzaparin, medium dose (%)	498 (34.3)	7 (25.0)	0.30
Aspirin (%)	474 (32.7)	16 (57.1)	**0.01**

SSS: Scandinavian Neurological Stroke Scale (low score ~ severe stroke); TACI: total anterior circulation infarct

TABLE 3

Venous thromboembolic events and case-fatality by the wearing of stockings. Number (%); comparison by Chi square test.

	No stockings	Stockings	p value
Subjects	676	803	
Day 15:*			
Deep vein thrombosis (%)	5 (0.7)	13 (1.6)	0.12
Pulmonary embolism (%)	2 (0.3)	11 (1.4)	**0.03**
Venous thromboembolic events (%)	6 (0.9)	22 (2.7)	**0.01**
Dead (%)	27 (4.0)	58 (7.2)	**0.01**
Day 90:†			
Deep vein thrombosis (%)	13 (1.9)	39 (4.9)	**0.002**
Pulmonary embolism (%)	2 (0.3)	19 (2.4)	**0.001**
Venous thromboembolic events (%)	14 (2.1)	55 (6.8)	**<0.0001**
Dead (%)	62 (9.2)	116 (14.4)	**0.002**
Day 180:†			
Deep vein thrombosis (%)	13 (1.9)	41 (5.1)	**0.001**
Pulmonary embolism (%)	2 (0.3)	20 (2.5)	**0.001**
Venous thromboembolic events (%)	14 (2.1)	58 (7.2)	**<0.0001**
Dead (%)	76 (11.2)	140 (17.4)	**0.001**

* End of treatment plus 5 days

† Cumulative total

FIGURE LEGENDS

FIGURE 1

Odds ratios and 95% confidence intervals for the occurrence of VTE for all stocking wearers.

FIGURE 2

Odds ratios and 95% confidence intervals for the occurrence of VTE for those wearing stocking bilaterally for 10 days

FIGURE 1

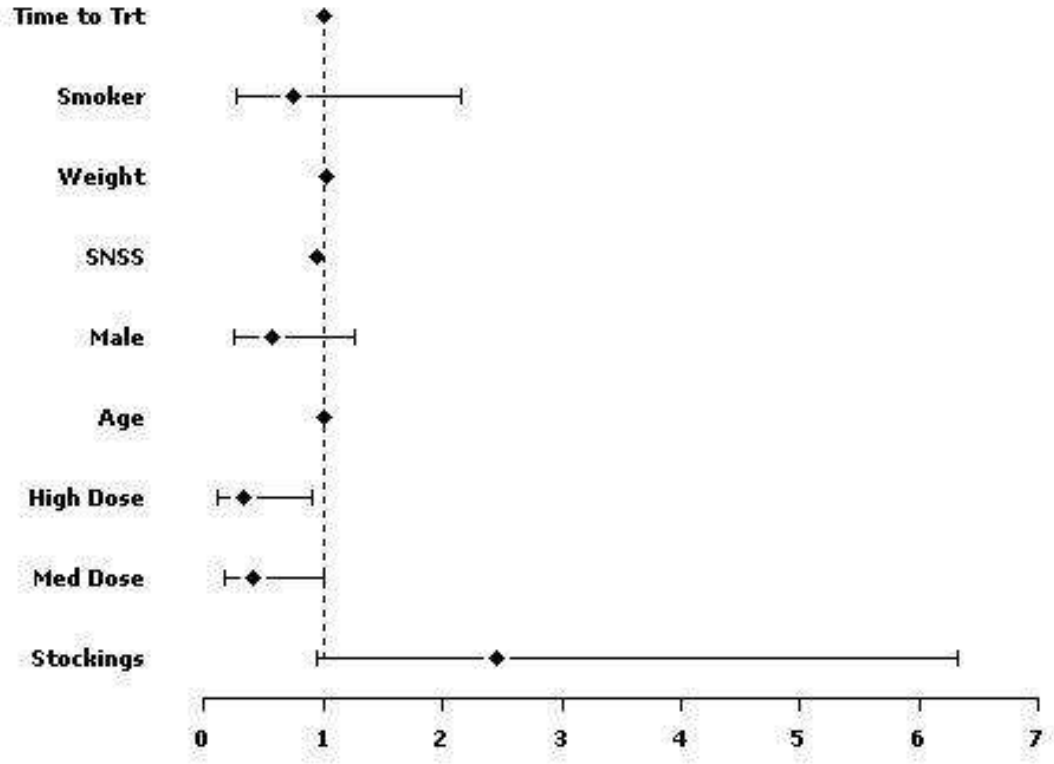
Time to Trt
Smoker
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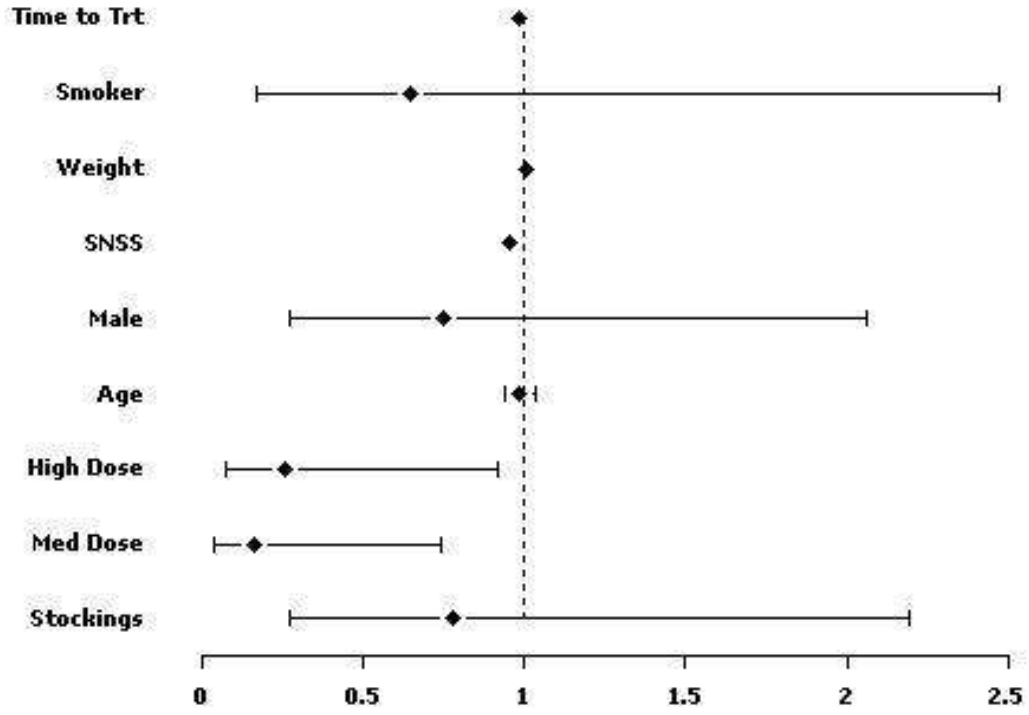
FIGURE 2


Time to Trt
Smoker
Weight
SNSS
Male
Age
High Dose
Med Dose
Stockings
0
0.5
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