Pirogov Russian National Research Medical University

Investigator-initiated research according to the protocol:

Trial to assess the effectiveness of intermittent pneumatic compression in the prevention of postoperative venous thromboembolism in surgical patients at extremely high risk.

Version 1.1 dated on May 15, 2016

Research title: Intermittent Pneumatic Compression in Surgical Patients at Extremely-high Risk of Venous Thromboembolism.

Short title: IPC SUPER

Primary Investigator and author of the Protocol:

Kirill Lobastov, MD, PhD, Associated Professor

Table of contents

IPC SUPER trial, May. 2016, v.1.1

Abbreviations

ABI – ankle-brachial index
ATV – anterior tibial vein
BMI – body mass index
CFV – common femoral vein
CHF – congestive heart failure
CI – confidential interval
CRF – case report form
CRNM – clinically relevant non-major bleeding
CTPA – computed tomography pulmonary angiogram
CVD – chronic venous disease
DIC – disseminated intravascular coagulation syndrome
DUS – duplex ultrasound scan
DVT – deep vein thrombosis
ECS – elastic compression stockings
FV – femoral vein
GSV – great saphenous vein
ICU – intensive care unit
IPC – intermittent pneumatic compression
IQR – interquartile range
IRB – Institutional Reviewal Board
ISTH – International Society of Thrombosis and Hemostasis
ITT – intention-to-treat
IVC – inferior vena cava
LMWH – low-molecular-weight heparin
NNH – number needed to harm
NNT – number needed to treat
PE – pulmonary embolism
PeV – peroneal vein
PTV – posterior tibial vein
PV – popliteal vein
SCD – sequential compression device
SD – standard deviation
SPECT/CT – single-photon emission computed tomography with a conventional computed tomography
SSV – small saphenous vein
SVT – superficial vein thrombosis
UHF – unfractionated heparin
VTE – venous thromboembolism

1. Background

Venous thromboembolism (VTE), including deep vein thrombosis (DVT), superficial vein thrombosis (SVT), and pulmonary embolism (PE), has been considered an important medical-social problem for decades. According to well-known epidemiological data, the VTE incidence in the general population is estimated as 1.0–1.9 cases per 1000 population per year, which can be further classified as 0.5–0.7 cases of pulmonary embolism and 0.5–1.2 cases of deep vein thrombosis [1-9]. The official data of the Statistical Service of the Russian Federation exceed the average world figures and demonstrate the incidence of venous thrombosis at the level of 1.5–1.6 cases per 1000 population per year [10,11]. It is well known that one of the important risk factors for VTE development is the recent inpatient treatment, especially accompanied by major surgery [12-23]. Therefore, stratification of the hospitalized patients according to their individual VTE risk and providing adequate preventive measures are crucial during inpatient treatment [24,25]. Early ambulation, elastic compression stockings, prophylactic anticoagulation, active blood drainage, and a combination of these methods significantly reduce the risk of postoperative VTE, especially fatal pulmonary embolism, in most surgical patients [24,26].

Today, the Caprini score (version 2005) [27] is considered the most validated individual risk assessment model for postoperative VTE. The Caprini score was verified in about 15,000 surgical patients and showed a strong correlation between the total score and the frequency of symptomatic VTE events (personal communication with JA Caprini). In patients with scores of 9 or more, the frequency of VTE was as high as 11%. However, a further increase in Caprini score might be accompanied by an increase in the VTE rate. A prospective analysis taking into account both symptomatic and asymptomatic VTE episodes that occurred at the top of standard prophylaxis (elastic compression and injections of unfractionated heparin [UFH]), demonstrated that in patients with a Caprini score of 11 or more, VTE incidence reached 59%, compared with 3% in those who had Caprini scores of 10 or less [28]. However, there is as yet no consensus on which threshold of Caprini score should be used to choose adequate mechanical and pharmacological prophylaxis. A meta-analysis of 13 studies found that only patients with a Caprini score of 7–8 and >8 had a significant VTE reduction after surgery with chemoprophylaxis (personal communication with JA Caprini). At the same time, in patients with a score of >10, prophylaxis with elastic compression plus standard doses of UFH appears to be

insufficient[28]. So, according to these data, patients with a score of 5–7 might be classified as a high-risk group, a score of 8–10 as the highest-risk group, and a score of 11 and more as an extremely high-risk group. The extremely-high-risk group needs improvement in the VTE preventive protocol.

Intermittent pneumatic compression (IPC) is as effective as pharmacoprophylaxis in reducing VTE risk but does not affect the bleeding rate. The previous meta-analysis of 16,164 hospitalized patients from 70 trials reported a DVT risk reduction (by 57%) and PE risk reduction (by 52%) when IPC was compared with no prophylaxis, and DVT risk reduction (by 39%) when compared with elastic compression alone[29]. In comparison with pharmacoprophylaxys, there was no difference in the risk of DVT (relative risk, 0.93; 95% CI, 0.69–1.26) or PE (relative risk, 1.19; 95% CI, 0.62–2.29), but there was a significant decrease in the risk of bleeding (by 39%) (relative risk, 0.41; 95% CI, 0.25–0.65). These advantages usually suggest IPC as an alternative to anticoagulants in those patients who have an increased risk of hemorrhagic complications, especially after intracranial and spinal surgery[26]. However, the combination of IPC and prophylactic anticoagulation, also known as pharmaco-mechanical modality, is more effective than the mechanical or pharmacological approaches alone. A meta-analysis of 16 clinical trials reported a DVT risk reduction (by 48% accompanied by the 5-fold increase in the bleeding risk) when the pharmaco-mechanical modality was compared with IPC alone; and a PE risk reduction (by 61% without increased bleeding rate) (relative risk, 0.80; 95% CI, 0.30–2.14) when IPC with anticoagulation was compared with prophylactic anticoagulation alone[30].

Thereby, the pharmaco-mechanical modality might be a solution to improve VTE prophylaxis in patients with a Caprini score of 11 or more, who are at extremely high risk for VTE. However, there are some crucial issues with IPC application.

First, there are many types of IPC devices that apply different pressure to the leg surface, provide various insufflation and deflation times (slow or rapid), and employ different sleeves according to the length (foot pump, below knee sleeve, above knee sleeve) and pressure distribution (uniform compression or sequential graduated compression). All these parameters might affect the hemodynamic and clinical response to IPC application[31,32]. Moreover, there is no good clinical evidence that one IPC device is better than another. In one non-randomized open clinical trial that enrolled 1,350 unidentified patients who received IPC during inpatient treatment, was compared five

different IPC manufactures (with various pumps and sleeves) according to the clinical efficacy, compliance, patient's and nurse's satisfaction[33]. The authors found some significant differences in the incidence of DVT, which ranged from 2.0% to 9.8% among the devices (p = 0.003), and the best figures were observed for graduated sequential compression devices (SCD): 2.5% and 2.0% respectively. However, taking into account compliance and patient's and nurse's satisfaction, the best scores were demonstrated for the tight-length intermitted compression, which was associated with a DVT rate of 3.2%.

So, the second critical concern is compliance with IPC. Usually, compliance is far from 100% and typically ranges between 48 and 53%[34-37]. It seems that compliance is higher in the intensive care unit (ICU) than in the profile surgical department[34,37]. The main disadvantages of the IPC devices are related to their cumbersome size and their requirement to be connected to a static power source, both of which tended to confine patients to bed and delayed hospital discharge and rehabilitation[32]. The studies that have aimed to assess compliance with IPC report that there might be a lack of device application as well as device functions. One study found that of all IPC devices that were applied, in 16% the pump did not function during the investigator's control visits[34].

The third point is that the minimal time of IPC application is unclear. Various studies have reported different durations of IPC application per day (14–20 h) depending on the type of device (portable or stationary)[38]. Another trial found that IPC in addition to pharmacoprophylaxis after orthopedic procedures was effective when applied for 6 h or more[39]. However, the usual recommendation is to achieve 18 h of daily compliance[40].

These and other unresolved issues formed the basis of this study. The main hypothesis of the study was that the combination of IPC with standard preventive measures (above knee anti-embolic elastic compression stockings [ECS] and standard doses of low-molecular-weight heparin [LMWH]) would reduce the incidence of postoperative VTE in patients at extremely high risk (Caprini score of 11 or more). Also, to improve the compliance with IPC, we decided to find out if providing a 6-h free-of-compression night interval (from midnight to 6 am) with the preservation of 18 h of target duration for device application will result in better compliance combined with good clinical outcomes.

2. Rationale and objectives

The rationale for the Study. There are no randomized controlled trials examining the effect of the adjunct use of IPC with pharmacologic prophylaxis compared to pharmacologic prophylaxis (LMWH) alone in patients at extremely-high-risk (Caprini score of 11 and more) for VTE prevention.

Use of Trial Results. This trial expects to have significant patient safety implications. If the combined use of IPC with pharmacologic prophylaxis proves to be effective, this would change the standard of practice of thromboprophylaxis and will be a major advancement in patient safety.

Study objectives: To assess the superiority of IPC at the top of standard prophylaxis with LMWH and ECS compared to standard prophylaxis on postoperative asymptomatic venous thrombosis of lower limbs during inpatient treatment.

Secondary objectives:

- To study the effect of IPC on the asymptomatic venous thrombosis occurrence during inpatient treatment in prespecified groups of patients:
    - Surgical profile,
    - Type of surgery,
    - The urgency of surgery,
    - The radicalism of surgery,
    - Type of anesthesia,
    - Malignant or benign disorder;
    - Preoperative, postoperative or delayed start of LMWH injections,
    - Pre-operative or post-operative IPC application,
- To study the effect of IPC on the isolated calf muscle DVT occurrence during inpatient treatment;
- To study the effect of IPC on the proximal DVT occurrence during inpatient treatment;
- To study the effect of IPC on the symptomatic PE occurrence during inpatient treatment;
- To study the effect of IPC on the fatal PE occurrence during inpatient treatment,

- To study the effect of IPC on the total VTE events that occur during inpatient treatment,
- To study the effect of IPC on the leg skin injury occurrence during inpatient treatment;
- To study the effect of IPC on the major and clinically relevant non-major bleeding occurrence during inpatient treatment;
- To study the compliance with IPC applied in the suggested regimen-required night free-of-compression interval;
- To study the effect of IPC on the symptomatic and asymptomatic venous thrombosis of lower limbs, symptomatic pulmonary embolism occurrence, and VTE related and VTE-non-related mortality during outpatient treatment and rehabilitation 30 and 180 days after surgery.

3. Design

A two-center, prospective, randomized (with independent allocation), open-label clinical trial with a blinded assessor for efficacy outcomes, enrolling patients at extremely high risk for postoperative VTE (Caprini score of 11 and more). The patients should be randomly allocated into two groups (experimental [IPC] group and control group) according to the VTE prophylaxis they received. Both groups will receive anti-embolic stockings and injections of LMWH, and patients in the IPC group additionally will receive IPC. The total duration of prophylaxis should amount of 1 month, and patients will be followed-up for 6 months with regular clinical examination and duplex ultrasound scans. Figure 1 represents the global design of the study.
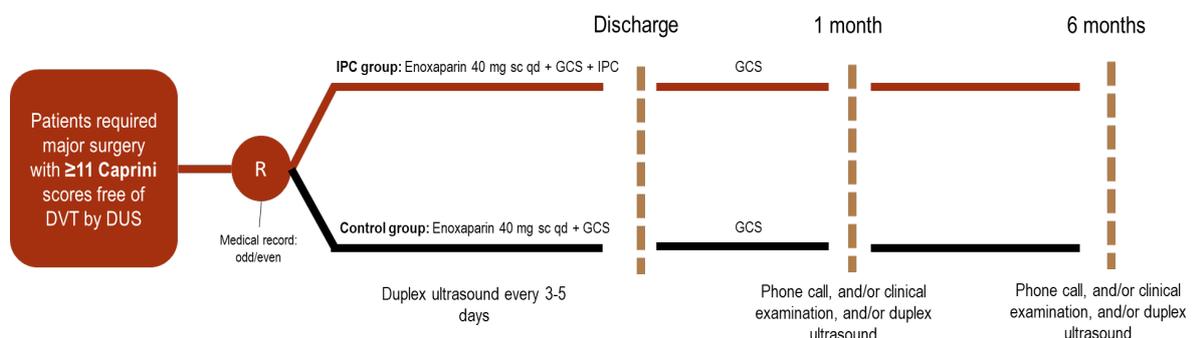

Figure 1. The global design of the study.

3.1. Randomization, Stratification, and Minimizing Bias

The randomization should be performed independently for both clinical centers and should be based on the number of hospital medical records. After screening, only eligible patients will be randomized. If the last digit in the number of the hospital medical record is even, the patient should be allocated to the IPC group, and if odd, to the control group. If the last digit in the number of the hospital medical record is zero, the previous digit should be used. Both clinical centers contain multiple medical departments of different specialties, and the numbering of the medical records is performed sequentially through all departments. It starts at the beginning of the year (for example, the first medical record in 2017 is 1/17) and finishes at the end of the year. Taking into account the large admission rate to all medical departments, there is an extremely low probability that two consistently included patients would have sequential medical records. To reduce the bias of the deliberate non-inclusion of the patients with higher VTE risk in the IPC group all non-eligible subjects should be repeatedly evaluated for exclusion criteria by the Data Monitoring Committee.

After allocation to the group, the patient will be assigned an individual code, containing his index number, initials, and year of birth (for example, 1IV1961). This individual code will be used in all study documentation. The allocation list will be stored by the investigator. The blinded expert who will perform a duplex ultrasound scan (DUS) would not have access to the primary medical record or allocation list; he will use only individual patients code for identification. Also, to achieve blindness, most duplex scans will be performed in a separate room away from the patient's bed. If it will be impossible to transfer a patient to the room, the DUS will be performed at the bed, but the IPC device will be removed before the blinded expert's visit. A schematic diagram of the patient allocations is shown in Figure 2.
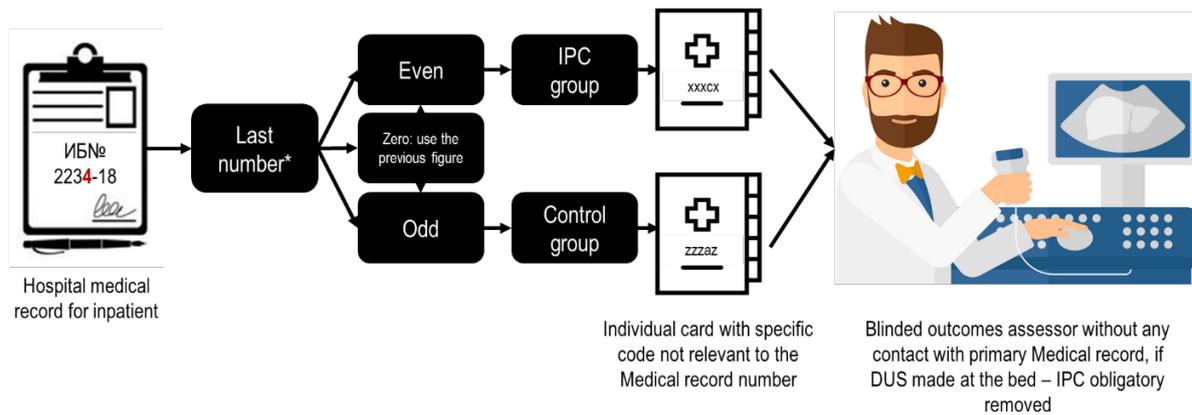
Figure 1. Scheme of the randomization and blindness.

3.2. Study population, inclusion, and exclusion criteria

All patients admitted to the clinical centers for emergent or elective surgery will be screened for eligibility criteria. In the case of elective surgery, patients will be screened 1 day before the intervention, and in case of emergency surgery, just before or within 12 h after the intervention.

Inclusion criteria:
- Age over 40 years;
- Major surgery required;
- High risk of postoperative VTE;
- Caprini score of 11 or more (at extremely high risk of VTE);
- Informed consent is given.

Age over 40 years is suggested as an inclusion criterion by the Russian National Guidelines on VTE prevention[41], which recognize these patients as a standard high-risk group if undergoing major surgery.

Major surgery is recognized as any procedure under general or regional anesthesia with the leg motor block with a duration of 45 min and more that are equal to major surgery (>45 min) or laparoscopic surgery (>45 min) in the Caprini model.

Primary risk assessment for postoperative VTE should be made according to the rules of the Russian National Guidelines[41], and only patients at high-risk (major surgery in patients of 40–60 years old with additional individual risk factors, or major surgery in

patients of 60 and more years old independent of additional risk factors) will be screened for eligibility according to the Caprini score.

The Caprini score should be assessed twice: at the baseline screening before inclusion and before discharge or after death. It will be allowed to include patients with supposed scores of ≥11 (e.g., supposed cancer, supposed long bed rest, supposed CHF, CVD, etc.), but not less than 9. The final assessment of concomitant diseases as risk factors will be performed by an invited specialist. The maximal Caprini score will be taken into account.

Exclusion criteria: acute DVT at baseline; performed IVC plication or implanted IVC filter; regular preoperative anticoagulation; postoperative anticoagulation needed at therapeutic doses; absence of anticoagulation >5 days after surgery; coagulopathy (not related to DIC syndrome); thrombocytopenia; hemorrhagic diathesis; lower limb soft-tissue infection; lower limb skin lesion; ankle-brachial index <0.6.

3.3. Patient's withdrawal from the study

Patient's withdrawal from the study will be possible in case of the patient's refusal from further participation, the occurrence of serious adverse events necessitating early termination of study procedures, as well as meeting the criteria for patient's withdrawal from the study. The criteria for withdrawal are as follows: the occurrence of any VTE event, considered as a primary or secondary endpoint; the occurrence of major or non-major clinically relevant bleeding, considered as secondary endpoints, required the discontinuation of LMWH administration; the occurrence of leg skin injury, considered as a secondary endpoint; required discontinuation of IPC application; the occurrence of any clinical condition required discontinuation of IPC or ECS application (e.g., leg ischemia, compartment syndrome); the occurrence of any clinical condition that required discontinuation of LMWH administration (e.g., thrombocytopenia, allergic reaction); the occurrence of any clinical condition that required changes in the VTE prophylaxis modality (e.g., change in dose and type of anticoagulation); and the occurrence of any exclusion criteria after randomization.

3.4. Protocol deviations

The serious protocol deviations that required patient exclusion from the final analysis are: missed two or more scheduled DUS; missed the final scheduled DUS before discharge; autopsy rejected; inability to assess compliance with IPC (no information in the Compliance sheet); gross inconsistencies between source documentation and an CRF; violations of the procedure for obtaining informed consent; failure to follow the procedures of the trial protocol; the inability to collect all the data used in evaluating the final goals of the study (for example, the lack of records in the source documentation necessary to verify the inclusion/exclusion criteria, safety, and efficiency criteria); any other protocol deviations considered as significant.

3.5. Endpoints and definitions

Primary endpoint: asymptomatic venous thrombosis of the lower limbs detected by DUS during inpatient treatment.

Secondary endpoints:

During inpatient treatment: isolated calf muscle DVT; proximal DVT; symptomatic PE; fatal PE; total VTE events; postoperative mortality; leg skin injury; combination of major and clinically, relevant non-major bleeding; and compliance with IPC.

At 30 days after surgery:
- Combination of symptomatic, asymptomatic venous thrombosis of the lower, limbs and symptomatic PE;
- VTE-related mortality;
- Non-VTE-related mortality.

At 180 days after surgery:
- Combination of symptomatic, asymptomatic venous thrombosis of the lower limbs, and symptomatic PE;
- VTE-related mortality;
- Non-VTE-related mortality.

Following DUS, distal DVT is defined as incompressibility of the affected calf vein, re-occlusion of the previously affected calf vein in case of personal DVT history. Proximal DVT is defined as incompressibility of the affected popliteal and thigh veins, re-occlusion of previously affected popliteal and thigh veins in case of personal DVT history, no blood flow with color flow imaging. Superficial vein thrombosis is defined as incompressibility of the affected superficial vein (GSV and its branches and SSV and its branches). Isolated calf muscle DVT is defined as occlusion of any calf veins except PTV, ATV, and PeV (sural veins, soleal veins). Proximal DVT is defined as occlusion of popliteal and all further cranial venous segments up to the iliac veins (PV, FV, CFV, external iliac vein, common iliac vein). Pulmonary embolism will be suspected according to the classical clinical symptoms and verified with SPECT/CT or CTPA by specific defects of contrast.

Major bleeding is defined by the ISTH criteria[42] as: fatal bleeding; bleeding that is symptomatic and occurs in a critical area or organ; extra-surgical site bleeding causing a fall in hemoglobin level of ≥20 g/L, or leading to transfusion of ≥2 units of whole blood or RDC, with temporal association within 24–48 h to the bleeding; surgical site bleeding that requires a second intervention; or surgical site bleeding that is unexpected and prolonged or sufficiently large to cause hemodynamic instability, as assessed by the surgeon.

Clinically relevant non-major (CRNM) is defined as any other bleeding, that does not match the criteria of major but needs some specific measures for hemostasis and/or interruption or preliminary abortion of anticoagulation.

Leg skin injury is defined as the appearance of skin hyperemia, blisters (and further erosions), and necrosis (and further ulceration) in the zone of contact with GCS, especially at the anterior surface of the ankle joint.

4. Trial interventions

All randomized patients will receive a standard VTE prophylaxis according to the Russian National Guidelines, that are complementary to ACCP 9th Edition[26], contained using of above-knee anti-embolic ECS and LMWH injections. In the experimental group, an IPC device will be applied in adjunction to standard prophylaxis.

4.1. Anti-embolic stockings

Above-knee anti-embolic compression stockings fitted by the leg size should be applied before the surgery. In the case of elective surgery, the size should be fitted before,

and patients should be admitted to the hospital with their own stockings. In the case of emergent surgery, leg sizes should be obtained after admission, and the stockings should be received from the stocking bank. ECS should be applied round-the-clock during the inpatient period of treatment. After discharge, patients will be recommended to use stocking at night and during the long bed rest for 1 month. The manufacturer for the ECSs is not prespecified, so it is possible to use any available product. Stocking application should be controlled within standard medical care.

4.2. Low-molecular-weight heparins

Standard doses of 40 mg Enoxaparin (Clexane, Sanofi-Aventis, France) subcutaneously once daily is prespecified. Following Russian National Guidelines, the first injection should be done 12 h before the surgery (elective surgery without high bleeding risk) or within 12 h after surgery (emergent surgery, procedure with high bleeding risk). In the case of the highest bleeding risk, it is allowed to delay the first LMWH injection for 5 days. The patients who did not receive Enoxaparin after 5 days will be withdrawn from the analysis. The pharmacoprophylaxis should be continued until the patient's discharge from the hospital (not less than 7 days) or death. The prolonged prophylaxis with LMWH is not pre-specified and will depend on the surgeon's preference. The enoxaparin administration and the control for injection should be made within the standard clinical practice.

4.3. Sequential pneumatic compression

Intermitted pneumatic compression should be applied with Cardinal Health™ Kendall SCD™ 700 Series Controller and Kendall SCD™ thigh-length Comfort Sleeves. The pumps will be provided by the Sponsor (10 pumps by Cardinal Health™), and the sleeves will be purchased by the Clinical centers. Sleeves should be fitted according to the manufacturer's instructions and used in a disposable manner. Sleeves should be changed when they become soiled or lost their fixation.

IPC should be started just before the surgery in the operating room during general anesthesia induction or after regional anesthesia application before covering the operating field with the sterile material. Also, it is allowed to apply IPC within 12 h after surgery. The main conditions of IPC application are as follows: no venous thrombosis

confirmed by DUS, no skin lesions on the leg, no signs of skin and soft tissue infections of the legs, ABI >0.6.

IPC should be applied around-the-clock in the ICU, and at the time of bed-rest with a 6 h free-of-compression interval from 0 am to 6 am in the profile surgical department. The IPC required to be used during the whole inpatient treatment period.

5. Follow-up

The follow-up is designed separately for the inpatient and outpatient settings. The total follow-up duration accounts for 6 months.

5.1. Baseline examination

The screening examination is designed to assess patient's eligibility with the inclusion/exclusion criteria. The baseline examination will be performed a day before the surgery in case of elective surgery or just before or within 12 h after the urgent surgery. The basal examination contains the standard diagnostic procedures with special attention to the individual risk factors for postoperative VTE. Patients (or their representatives in case of unconsciousness or deep dementia) should be interviewed for the personal and family VTE history, any obstetrics complications, use of contraceptive pills or other estrogen-containing drugs, and current or previous malignant disorders. Lower limbs should be evaluated for the varicose veins and edema, skin and soft tissue infection, any skin lesions, and pedal pulsation. The relevant co-morbidities, such as congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), serious lung disease or pneumonia, inflammatory bowel disease, sepsis, lower limb paralysis, and stroke should be evaluated and confirmed according to the medical records and involving other specialists. BMI will be calculated with the data from medical records.

5.2. VTE risk assessment

The primary VTE risk assessment should be performed by Russian National Guidelines[41], and if the patient will be classified as having a high risk (major surgery in subjects over 60 years old or major surgery in subjects from 40 to 60 years old having additional individual risk factors for VTE), he should be assessed by Caprini score. A Russian adaptation[43] of the 2005 version of the Caprini score[27] will be used (Fig. 3).

The primary risk assessment will be performed before randomization. Any patients that will receive or will be supposed to receive (e.g., supposed prolonged bed rest in ICU, supposed malignancy, CHF, COPD, bowel inflammatory disease, thrombophilia, etc.) a score of 11 or more, should be invited into the study. The calculation of the final Caprini score should be done before discharge or after patients' death. So, all new condition and complications occurred during the inpatient treatment period will be considered. However, some enrolled patients may decrease their score because of unexpected early ambulation, misdiagnosis of malignant disease or other co-morbidities.

Each Risk Factor Represents 1 Point
- Age 41-60 years
- Swollen legs (current)
- Varicose veins
- Obesity (BMI >25)
- Minor surgery planned
- Sepsis (<1 month)
- Acute myocardial infarction
- Congestive heart failure (<1 month)
- Medical patient currently at bed rest
- History of inflammatory bowel disease
- History of prior major surgery (<1 month)
- Abnormal pulmonary function (COPD)
- Serious Lung disease including pneumonia (<1 month)
- Oral contraceptives or hormone replacement therapy
- Pregnancy or postpartum (<1 month)
- History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant
- Other risk factors_____
Subtotal:

Each Risk Factor Represents 5 Points
- Stroke (<1 month)
- Elective major lower extremity arthroplasty
- Hip, pelvis or leg fracture (<1 month)
- Acute spinal cord injury (paralysis) (<1 month)
- Multiple trauma (<1 month)
Subtotal:

Each Risk Factor Represents 2 Points
- Age 61-74 years
- Arthroscopic surgery
- Malignancy (present or previous)
- Laparoscopic surgery (>45 minutes)
- Patient confined to bed (>72 hours)
- Immobilizing plaster cast (<1 month)
- Central venous access
- Major surgery (>45 minutes)
Subtotal:

Each Risk Factor Represents 3 Points
- Age 75 years or older
- History of DVT/PE
- Positive Factor V Leiden
- Elevated serum homocysteine
- Heparin-induced thrombocytopenia (HIT) (Do not use heparin or any low molecular weight heparin)
- Elevated anticardiolipin antibodies
- Other congenital or acquired thrombophilia
- Family History of thrombosis*
- Positive Prothrombin 20210A
- Positive Lupus anticoagulant
If yes: Type_____
* most frequently missed risk factor
Subtotal:

TOTAL RISK FACTOR SCORE:

Figure 3. The 2005 version of the Caprini score, reproduced from Bahl V et al., Ann Surg. 2010;251(2):344-50.

5.3. Duplex ultrasound scan

Duplex ultrasound scans will be performed by two blinded experts based at different clinical centers. At Center 1, all investigations will be done with MyLab30 (Esaote, Italy) using a linear transducer with a frequency of 5–13 MHz. At Center 2, Voluson I (General Electric, USA) with a linear transducer frequency of 5–13 MHz will be used. All veins of the calf and thigh should be observed during every DUS.

Examinations should be performed in a horizontal position: the common femoral (CFV), the femoral vein (FV), the great saphenous vein (GSV) and its tributaries should be evaluated in the supine position with light bending in the knee joint. The popliteal vein (PV), small saphenous vein (SSV), and its branches should be examined in the prone position. If it is not possible to move the patient or the patient is unconsciousness, the PV

and SSV may be observed during leg supination and bending in the knee joint by ~45 degrees. The posterior tibial veins (PTV) and the medial group of the calf muscle veins should be examined in the supine position with the supinated and slightly bent in the knee joint leg. The peroneal veins (PeV) and lateral calf muscle veins should be examined in the supine position with pronated and knee bent at 45–90 degrees leg. The anterior tibial veins (ATV) should be investigated in the supine position with an unbent knee. In case of any problems with calf vein visualization, the examination should be repeated in the sitting position with the leg bent in the knee joint at 45 degrees.

The main criterion for vein patency is compressibility in the B-mode. If it is necessary, the color flow mode may be used to reveal blood flow in the target vein with the stimulation by manual compression or active movements in the ankle joint. Iliac veins and IVC should be observed in case of clinical suspicion of their thrombosis using convex transducer with the frequency of 2.5–5 MHz.

During the primary DUS, it is obligatory to document all post-thrombotic vein changes, such as residual venous obstruction and valve insufficiency, and their localization in patients with a personal history of DVT. The re-occlusion of the previously affected vein revealed during DUS follow-up must be considered as a new DVT. However, any changes in the degree of residual venous obstruction should not be considered.

Besides venous investigation, the ABI at the posterior tibial artery should be measured using the pulsed wave Doppler method[44] in all screened patients.

5.4. Examination during inpatient treatment

The following data on surgical procedure should be obtained from the medical records after intervention: the surgical profile (e.g., abdominal, thoracic, neck, pelvis, cranial), type of surgery (open, endoscopic, endoscopy assisted), urgency of surgery (emergent = performed in 0–2 h after admission, urgent = performed in 0–6 days after admission, elective = performed independently at the time of admission), radicalism of surgery (radical, palliative), type of anesthesia (general, regional, combined), surgery duration, blood loss, and intraoperative infusion.

The routine clinical examination of the patient will be performed in a daily manner with special attention to the possible complications, such as DVT, SVT, PE, bleeding, and leg skin injury. IPC sleeves should be removed for 15–20 mins every day for skin inspection and investigation of pedal pulsation. Consultation of any relevant specialist

(cardiologist, neurologist, pulmonologist, infections) should be performed if any complication or development of new co-morbidity will be observed during the follow-up.

DUS should be performed every 3–5 days after surgery and in emergency manner if any clinical suspicion for DVT or SVT appeared. In an emergency manner, DUS may be performed by a blinded expert or specialist on duty on weekend and holidays. However, all conclusions of non-investigational medical staff must be verified by a blinded expert.

SPECT/CT or CTPA should be used to verify PE in an emergency manner if clinical suspicion appeared. An autopsy must be performed in all died patients to verify the absence of DVT and PE.

In case of any clinical suspicion for a VTE event, IPC should be interrupted until final verification of the diagnosis. In the case of positive DUS, CTPA, and SPECT/CT, the therapeutic anticoagulation should be prescribed, and IPC should be removed. In the case of clinical suspicion for VTE with negative results of instrumental tests, IPC should not be returned until the proper diagnosis that mimics VTE will be found.

Any revealed leg skin lesion should be judged individually for the possibility to continue ECS and IPC application. If the decision will be made to stop IPC, the patient should be withdrawn from the study according to the protocol.

5.5. Examination during outpatient treatment

After discharge, patients should be evaluated at 30 and 180 days after surgery. The target content of examination should include DUS and clinical examination. However, it is allowed to make a phone call to interview the patient about his status and any new symptomatic VTE events.

During the clinical examination, the investigator should revise the patient's medical records for any symptomatic or asymptomatic VTE episodes, confirmed by appropriate radiological tests.

DUS in the outpatient settings should be performed by a blinded expert using the same methodology. Any new postthrombotic change (residual venous obstruction, valvular insufficiency) revealed on the 30th or 180th day of observation and had not been documented previously should be considered as a new venous thrombosis corresponding with the secondary endpoint.

If the patient would not be available for head-to-head examination, the phone call should be made, and the subject should be interviewed with special attention to possible

clinical signs of symptomatic VTE episode. If the patient will report a VTE episode confirmed by an appropriate test, he should be asked to send the medical records on this issue by e-mail. If the investigator would find that a patient had died, he should to gather appropriate documentation, confirming the cause of the lethal outcome.

5.6. Compliance measure

No specific compliance measures are designed for the use of ECS and LMWH injections. The compliance with the IPC device will be measured as follows. Every day, the investigator (weekdays) or surgeon on duty (weekends and holidays) should visit a patient five times and check that, if the subject is confined to bed, the sleeves are applied to his legs and that the pump is functioning. The results of such visits should be registered in a specifically designed compliance sheet (Fig. 4). The compliance will be calculated as a proportion of all marks testified that IPC was applied to the total number of visits that found patient in the bed.

		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Compliance
Day X	Patient is in bed	√	√	√	√	√	100%
	IPC is turned on	√	√	√	√	√	
Day Y	Patient is in bed	√	-	-	-	√	100%
	IPC is turned on	√	-	-	-	√	
Day Z	Patient is in bed	√	√	√	√	√	40%
	IPC is turned on	√				√	

Figure 4. An example compliance sheet, which assessed compliance with IPC. The right column represents the result of the calculations.

6. Patients safety

Administration of the IPC device is a part of standard clinical practice, so patients will be not exposed to additional risk. The most common complication for ECS and IPC is a skin lesion on the legs. However, patients will be monitored for the possibility of developing any of the following: leg skin injury related to mechanical prophylaxis, ischemic changes in the lower limbs, and patient discomfort. There is no reason to expect the incidence would exceed what is encountered in daily practice.

7. Ethical issues

The study Protocol and all Amendments should be approved by Ethical Committee of the Pirogov Russian National Research Medical University. All subjects must be enrolled in the study after reading the patient's information sheet and providing informed consent. All participants will be able to withdraw their consent and stop participation at any time.

8. Statistical analysis plan and sample size calculation

Statistical analysis plan. The primary statistical analysis is designed as intention-to-treat with the use of two-tailed Fisher's exact test to compare the primary endpoint between two groups. The primary endpoint will be reported as an absolute number, percentage, and relative risk with 95% CI. Secondary statistical analysis of the primary endpoint will be made using an unadjusted Cox proportional-hazards model. The data will be censored on the time of VTE registration, or death, or discharge from the hospital and reported as a hazard ration with 95% CI. Kaplan-Meier curves will be used to compare time-to-event distribution. Cox proportional-hazards models adjusted for the clinical center, surgery profile, type of surgery, emergency of surgery, type of anesthesia, surgical radicalism, malignant disorder, Caprini score, and time to start LMWH injections will be used.

A similar analysis for the per-protocol population, but that excluded patients with gross violations of the protocol and premature discontinuation of at least one component of combined prophylaxis (ECS, IPC or LMWH), will be performed for the primary endpoint.

Secondary endpoints will be analyzed with two-tailed Fisher's exact test and will be represented as an absolute number, percentage, and relative risk with 95% CI.

Cox proportional-hazards models will be used for the prespecified subgroup analysis for the following subgroups: surgical profile; type of surgery; the urgency of surgery; the radicalism of surgery; type of anesthesia; malignant or benign disorder; preoperative, postoperative, or delayed start of LMWH injections; and pre-operative or post-operative IPC application.

Sensitivity analysis will address to the per-protocol analysis, compliance with IPC (restricted for 90% and more), duration of follow-up (restricted to 7 days and more), and the number of postoperative DUS (restricted with two and more).

Missing data on the primary endpoint are not anticipated in the inpatient settings, so no analysis for missing data being planned.

Adjusting for multiple comparisons and imputation for missing values will not be performed. The 95% confidence intervals will be not adjusted for multiplicity, and therefore, inferences drawn from these intervals might be not reproducible. The interim analysis is not planned.

Sample size calculation. The prevalence of asymptomatic postoperative vein thrombosis at the top of standard prophylaxis with ECS and LMWH was assumed as 30% based on our previous observations involving patients at high and extremely high risk[28,45]. Taking into account the fact that pharmaco-mechanical prophylaxis should provide a further 60% VTE risk reduction,[30] the absolute difference of 18% is assumed. Using Fisher's exact test for primary statistic analysis, with a power of 80% and type I error of 0.05, the sample size is estimated as 180 subjects (90+90 in each group). Assuming 10% withdrawal due to the protocol deviations, patient's decision, or incomplete data, the sample size is calculated as 200 subjects. Considering prespecified subgroup analysis for the patients with an early and delayed start of LMWH, we decided to double the sample size to achieve sufficient power for separate analyses of the suggested subgroups. IBM SPSS will be used for data processing.

9. Clinical Centers and collaborators

The author of the study design, study protocol, and principal investigator of the study:

- Kirill Lobastov, MD, Ph.D., Associated professor of the Pirogov Russian National Researching Medical University.

Co-authors of the study design:

- Victor Barinov, MD, Ph.D., Professor of the Central State Medical Academy;
- Leonid Laberko, MD, Ph.D., Professor of the Pirogov Russian National Researching Medical University;
- Valeriy Boyarintsev, MD, Ph.D., Professor of the Central State Medical Academy;
- Grigoriy Rodoman, MD, Ph.D., Professor of the Pirogov Russian National Researching Medical University;

Clinical centers:

- Center 1 - Clinical Hospital no. 1 of the President's Administration of the Russian Federation (10 Starovolynskaya street, Moscow, Russian Federation, 12135)
- Center 2 - Moscow Clinical Hospital no. 24 of the Moscow Health Department (10, Pistsovaya street, Moscow, Russian federation, 127015).

Investigators:

- Center 1: Eleanora Alencheva, MD, Ph.D. student at the Central State Medical Academy;
- Center 2: Ekaterina Sautina, MD, Ph.D. student at the Pirogov Russian National Researching Medical University.

Blinded experts:

- Center 1: Victor Barinov, MD, Ph.D., Professor of the Central State Medical Academy certified for ultrasound diagnostic in 2011;
- Center 2: Astanda Bargandzhiya, MD, Ph.D., Assistant at the Pirogov Russian National Researching Medical University, certified for ultrasound diagnostic in 2012.

Data Monitoring Committee:

- Leonid Laberko, MD, Ph.D., Professor of the Pirogov Russian National Researching Medical University;
- Ilya Schastlivtsev, MD, Ph.D., Associated professor of the Pirogov Russian National Researching Medical University

References

1.   Hippisley-Cox J, Coupland C. Development and validation of risk prediction algorithm (QThrombosis) to estimate future risk of venous thromboembolism: prospective cohort study. Bmj 2011;343:d4656.

2.   Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Journal of Thrombosis and Haemostasis 2000;83:657-60.

3.   Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007;5:692-9.

4.   White RH. The epidemiology of venous thromboembolism. Circulation 2003;107:I4-8.

5.   Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med 2004;117:19-25.

6.   Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. Journal of internal medicine 1992;232:155-60.

7.   Van Beek E, Buller H, Ten Cate J. Epidemiology of venous thromboembolism. A textbook of vascular medicine London: Arnold 1996:471-88.

8.   Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998;158:585-93.

9.   Heit JA. The epidemiology of venous thromboembolism in the community: implications for prevention and management. J Thromb Thrombolysis 2006;21:23-9.

10.   The general prevalences of diseases in the total population of Russia in 2012. Statistical Materials, Part II 2013 (In Russ.). 2013. (Accessed 11.02, 2020, at http://www.rosminzdrav.ru/documents/8029-statisticheskaya-informatsiya-2012.)

11.   The prevalences of diseases in the total population of Russia in 2014. Statistical Materials, Part II 2015 (In Russ.). 2015. (Accessed 11.02, 2020, at https://www.rosminzdrav.ru/documents/9479-statisticheskaya-informatsiya-za-2014.)

12.   Heit JA, Melton III LJ, Lohse CM, et al. Incidence of venous thromboembolism in hospitalized patients vs community residents. Mayo Clin Proc; 2001: Elsevier. p. 1102-10.

13.   Stein PD, Beemath A, Olson RE. Trends in the incidence of pulmonary embolism and deep venous thrombosis in hospitalized patients. Am J Cardiol 2005;95:1525-6.

14.   Sasahara AA, Sharma G, Barsamian EM, Schoolman M, Cella G. Pulmonary thromboembolism: diagnosis and treatment. Jama 1983;249:2945-50.

15.   Sandler D, Martin J. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? J Journal of the Royal Society of Medicine 1989;82:203-5.

16.   Lindblad B, Sternby NH, Bergqvist D. Incidence of venous thromboembolism verified by necropsy over 30 years. Bmj 1991;302:709-11.

17.   Dismuke SE, Wagner EH. Pulmonary embolism as a cause of death. The changing mortality in hospitalized patients. Jama 1986;255:2039-42.

18.   Zhan C, Miller MR. Excess length of stay, charges, and mortality attributable to medical injuries during hospitalization. Jama 2003;290:1868-74.

19.	Sweetland S, Green J, Liu B, et al. Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. Bmj 2009;339:b4583.

20.	Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ. Venous thromboembolism in the outpatient setting. Arch Intern Med 2007;167:1471-5.

21.	Allaert F, Quantin C, Benzenine M. Venous thromboembolism prevalence in French and US hospitals: comparison on the basis of the national data bases. 15th Meeting of the European Venous Forum. Paris, France: Edizioni minevra medica; 2014:16.

22.	Stein PD, Matta F, Dalen JE. Is the campaign to prevent VTE in hospitalized patients working? Chest 2011;139:1317-21.

23.	Amin AN, Varker H, Princic N, Lin J, Thompson S, Johnston S. Duration of venous thromboembolism risk across a continuum in medically ill hospitalized patients. Hosp Med 2012;7:231-8.

24.	Nicolaides AN, Fareed J, Kakkar AK, et al. Prevention and treatment of venous thromboembolism--International Consensus Statement. Int Angiol 2013;32:111-260.

25.	Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:7S-47S.

26.	Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e227S-e77S.

27.	Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell DA, Jr., Caprini JA. A validation study of a retrospective venous thromboembolism risk scoring method. Ann Surg 2010;251:344-50.

28.	Lobastov K, Barinov V, Schastlivtsev I, Laberko L, Rodoman G, Boyarintsev V. Validation of the Caprini risk assessment model for venous thromboembolism in high-risk surgical patients in the background of standard prophylaxis. Journal of Vascular Surgery: Venous and Lymphatic Disorders 2016 (In Press).

29.	Ho KM, Tan JA. Stratified meta-analysis of intermittent pneumatic compression of the lower limbs to prevent venous thromboembolism in hospitalized patients. Circulation 2013;128:1003-20.

30.	Kakkos SK, Caprini JA, Geroulakos G, et al. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism. Cochrane Database Syst Rev 2016 (In Press).

31.	Morris RJ, Woodcock JP. Evidence-based compression: prevention of stasis and deep vein thrombosis. Ann Surg 2004;239:162-71.

32.	MacLellan DG, Fletcher JP. Mechanical compression in the prophylaxis of venous thromboembolism. ANZ J Surg 2007;77:418-23.

33.	Proctor MC, Greenfield LJ, Wakefield TW, Zajkowski PJ. A clinical comparison of pneumatic compression devices: the basis for selection. J Vasc Surg 2001;34:459-63; discussion 63-4.

34.	Comerota AJ, Katz ML, White JV. Why does prophylaxis with external pneumatic compression for deep vein thrombosis fail? Am J Surg 1992;164:265-8.

35.	Cornwell EE, 3rd, Chang D, Velmahos G, et al. Compliance with sequential compression device prophylaxis in at-risk trauma patients: a prospective analysis. Am Surg 2002;68:470-3.

36.   Froimson MI, Murray TG, Fazekas AF. Venous thromboembolic disease reduction with a portable pneumatic compression device. J Arthroplasty 2009;24:310-6.

37.   Bockheim HM, McAllen KJ, Baker R, Barletta JF. Mechanical prophylaxis to prevent venous thromboembolism in surgical patients: a prospective trial evaluating compliance. J Crit Care 2009;24:192-6.

38.   Pavon JM, Adam SS, Razouki ZA, et al. Effectiveness of Intermittent Pneumatic Compression Devices for Venous Thromboembolism Prophylaxis in High-Risk Surgical Patients: A Systematic Review. J Arthroplasty 2016;31:524-32.

39.   Eisele R, Kinzl L, Koelsch T. Rapid-inflation intermittent pneumatic compression for prevention of deep venous thrombosis. J Bone Joint Surg Am 2007;89:1050-6.

40.   Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e278S-e325S.

41.   Bokerija LA, Zatevahin II, Kirienko AI, et al. Russian clinical guidelines for the diagnosis, treatment and prevention of venous thromboembolism (In Russ.). Phlebologiya 2015:1-52.

42.   Schulman S, Angeras U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010;8:202-4.

43.   Lobastov KV, Barinov VE, Schastlivtsev IV, Laberko LA. [Caprini score as individual risk assessment model of postoperative venous thromboembolism in patients with high surgical risk]. Khirurgiia (Mosk) 2014:16-23.

44.   Aboyans V, Criqui MH, Abraham P, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation 2012;126:2890-909.

45.   Lobastov K, Barinov V, Laberko L, Obolensky V, Boyarintsev V, Rodoman G. Electrical calf muscle stimulation with Veinoplus device in postoperative venous thromboembolism prevention. Int Angiol 2014;33:42-9.