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Effect on thromboprophylaxis among hospitalized patients using a system-wide multifaceted quality improvement intervention: Rationale and design for a multicenter cluster randomized clinical trial in China

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Background Venous thromboembolism (VTE) is a life-threatening disease that can affect each hospitalized patient. But the current in-hospital thromboprophylaxis remains suboptimal and there exists a large gap between clinical practice and guideline-recommended care in China.

Methods To facilitate implementation of guideline recommendations, we conduct a multicenter, adjudicator-blinded, cluster-randomized clinical trial, aiming to assess the effectiveness of a system-wide multifaceted quality improvement (QI) strategy on VTE prophylaxis improvement and thromboembolism reduction in clinical setting. Hospitals are randomized into intervention or control group. In intervention group, hospitals receive the concept of appropriate in-hospital thromboprophylaxis plus a multifaceted QI which encompasses four components: (1) an electronic alert combining computer-based clinical decision support system and electronic reminders, (2) appropriate prophylaxis based on dynamic VTE and bleeding risk assessments, (3) periodical audit and interactive feedback on performance, (4) strengthened training and patient education. In control, hospitals receive the concept of recommended prophylaxis alone without QI. Thromboprophylaxis will be at the discretion of hospitals and conducted as usual. With a final sample size of 5760 hospitalized patients in 32 hospitals on mainland China, this trial will examine the effect of QI on improvement in thromboprophylaxis and patient-centered outcomes. This is an open-label trial that patients and healthcare professionals will know group allocation after enrollment, but endpoint adjudicators and statisticians will be blinded. RCT# NCT04211181

Conclusions The system-wide multifaceted QI intervention is expected to facilitate implementation of recommended VTE prophylaxis in hospital, thereafter reducing VTE incidence and relevant adverse events among hospitalized patients in China. (Am Heart J 2020;225:44-54.)

Venous thromboembolism (VTE) is an emerging health threat affecting hospitalized patients. Approximately 55% to 60% VTE are hospital-associated VTE (HA-VTE) that occur during hospitalization or within 90 days

after discharge,¹ underlying more than 50% of VTE burden on population.² It is a global problem faced across countries.¹ In US, deep-vein thrombosis (DVT) and pulmonary embolism (PE), two main clinical

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manifestations of VTE, occurred in 1.3% and 0.4% of hospital admissions, respectively.^{2,3} Similarly, HA-VTE occurs in 0.3% Chinese inpatients.⁴ Albeit the VTE risk in hospital, thromboprophylaxis was pervasively underused and less than 15% Chinese patients receive prophylactic interventions after admission. Moreover, VTE hospitalization rate among Chinese population keeps rising over recent years, which has been up to 15.8/100000 in 2016.⁵ The increasing VTE hospitalization and substantial room for improvement in thromboprophylaxis underscore the necessity of effective thromboprophylaxis to prevent VTE.

Based on newly updated guidelines, existing clinical evidence and institution regulations,⁶⁻¹¹ China Venous Thromboembolism Study Group has issued several thromboprophylaxis guidelines¹²⁻¹⁴ and strongly advocate appropriate in-hospital thromboprophylaxis, including VTE risk assessment for each admitted patient by the use of validated prediction models, continuously monitoring VTE and bleeding risk during the whole hospital stay, uptake of risk-stratification prophylactic interventions, and switching pharmaceutical and mechanical interventions to promptly adjust prophylactic interventions. Some basic interventions are also recommended, e.g., patient education on VTE and encouragement of early mobilization. Despite this, there still exists a large gap between clinical practice and the recommended care. In the VTE prophylaxis survey among 6986 surgical and 6623 medical inpatients, only 14.3% received prophylaxis and 10.3% underwent appropriate prophylactic interventions.⁴ The dearth of enforcement makes VTE one of high priority unsolved clinical problems.

To enhance healthcare providers' adherence to recommended care and facilitate implementation of appropriate thromboprophylaxis, we develop a system-wide multifaceted quality improvement (QI) strategy. A multidisciplinary group of hospital staff (doctors, nurses, administrators, pharmacists, etc) from a wide range of departments will be engaged to carry out the QI. Given that each inpatient has at least one VTE risk factor during hospital stay,^{2,15} QI strategy needs to be comprehensive and systematic for the delivery of thromboprophylaxis to all patients. To examine its effectiveness on VTE reduction and determine how best to implement the recommended prophylaxis, we conduct a multicenter cluster randomized trial. Eligible hospitals will be selected from *Chinese Prevention Strategy for Venous Thromboembolism* (CHIPS-VTE) study network.

CHIPS-VTE is aimed to promote in-hospital thromboprophylaxis in the country. It has been launched in 2018 and a pilot study was performed to test the feasibility of QI intervention for implementing recommendations. Based on the pilot study, we conduct this multicenter trial to assess effect of QI on thromboprophylaxis in a large-scale patient population. Initially, this trial was scheduled to start in February but delayed due to COVID-19 outbreak. Currently, the epidemic is under control and

hospitals are returning to normal work. We will continue to perform this study with a baseline survey to assess hospital eligibility in April and complete hospital randomization in the following month.

Methods

Study objective

The primary objective of this study is to determine whether the system-wide multifaceted intervention increases appropriate VTE prophylaxis rate in hospitalized patients and decreases incidence of any hospital-associated VTE within 90 days after hospital admission. The secondary objective is to reduce safety events, including death incidence (i.e. all-cause mortality, VTE-related mortality) and complications related to prophylactic interventions (e.g. major and clinically relevant non-major bleeding, thrombocytopenia) during the 90-day follow up.

Study design

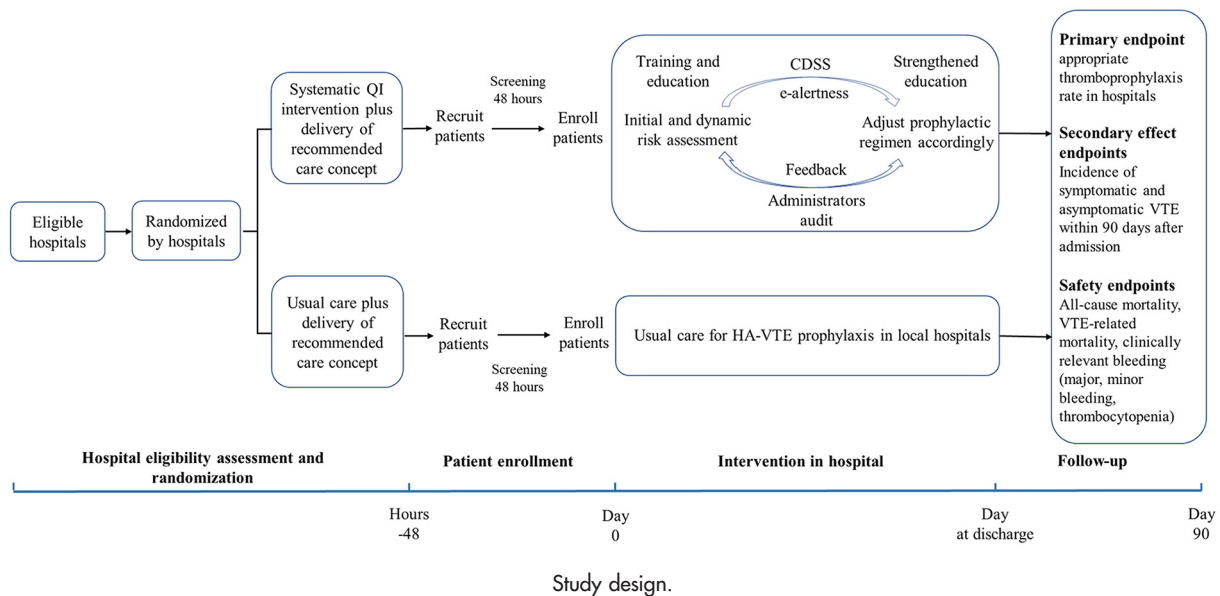
In this multicenter two-armed adjudicator-blinded cluster randomized trial, 32 eligible hospitals are selected from CHIPS-VTE study network, which includes 558 secondary and tertiary hospitals across mainland China. Randomization and interventions are convened at hospital level. During the study period, hospitals in both arms will receive the concept of appropriate VTE prophylaxis. In QI group, a multifaceted intervention will be delivered systematically to facilitate implementation of the recommended care while hospitals in control just receive the concept without QI. In-hospital thromboprophylaxis will be at the discretion of hospitals according to usual care. This is an open-label trial that group allocation will not be blinded to either patients or healthcare professionals. To objectively assess outcomes, adjudicators not involving in study design will assess outcomes. The study is anticipated to be completed in 12 months, starting from hospital selection, patient enrollment, intervention in hospital, 90-day follow up after admission, and data collection of the last patient (Figure 1).

Study hospitals and patients

To ensure implementation of quality improvement intervention during study period, participating hospitals will be selected from tertiary hospitals where electronic information systems are accessible and computer-based clinical decision support system (CDSS) can be embedded. The eligible hospitals will be determined within Chips-VTE network (Figure S1). We plan to select 32 hospitals fulfilling eligible criteria and enroll 180 patients consecutively at each hospital (Table D). See Statistical Analysis Plan section for details on sample size estimation. The enrollment is expected to be completed within the first 1-2 months.

The study population comprises patients admitted to nine high-risk departments (Table I) in which VTE risk

Figure 1



increases during process of care provided in daily practice. Patients fulfilling the inclusion and exclusion criteria (Table 1) will be enrolled consecutively until the sample size is met. Intervention is applied to all inpatients admitted to the target departments.

Baseline assessment and hospital selection

We will conduct a baseline survey for hospital eligibility assessment, including hospital characteristics (hospital grade, availability of HIS, medical and surgical departments, etc.), hospital directors' willingness to participate in the study, and current status of in-hospital thromboprophylaxis. There are 558 tertiary and secondary hospitals in CHIPS-VTE network. We deploy a stratified sampling method to select hospitals from the network (Figure S1 for details).

Cluster randomization and concealment

Stratified permuted block randomization will be adopted to assign hospitals into either QI or usual care group. Hospitals are units for randomization with group allocated at hospital level. By stratifying hospitals into those above or under the median prophylaxis rate obtained in baseline survey, hospitals alphabetically ordered by names will be randomized into each group with a varying block size of 2 or 4 within strata. The randomization procedures will be organized centrally by statisticians in the randomization center. To guarantee blindness to group allocation, hospital identification code and de-identified stratification details will be offered to an independent statistician unaware of the study design. Pre-generated hospital assignment will be concealed until

administration of intervention. In patient enrolment phase, an independent recruiter responsible for enrollment will be masked to hospital allocation. They will not know the allocation sequence until eligible patients are enrolled. Afterwards, interventions assigned to the hospital will be delivered to individual patients by doctors.

Patient enrollment

At each hospital, we schedule to enroll 180 eligible patients consecutively with an average number of 20 hospitalized patients enrolled from 9 departments. Patients admitted to the targeted departments and signing informed consent will undergo assessment for eligibility in screening phase. The enrolled patients and those with screen failure will be compared to evaluate potential selection bias. After enrollment, patients receive interventions assigned to hospitals.

Recommended in-hospital thromboprophylaxis

In the newly issued guidelines,¹²⁻¹⁴ risk stratification is recommended to guide appropriate thromboprophylaxis. Each patient needs to undergo VTE and bleeding risk assessments, particularly when they are admitted, transferred to another department, or their disease conditions change greatly. Validated risk score toolkits are utilized for this dynamic risk monitoring. Identifying patients at diverse risk for VTE and bleeding helps determine appropriate prophylactic interventions. If patients are at risk of VTE and have bleeding risk factors (eg, recent bleed, thrombocytopenia, active bleeding),¹⁶ mechanical intervention, eg, graduated compression

Table 1. Eligibility for hospitals and patients

Hospitals

Inclusion criteria

- (1) Tertiary hospitals with >500 beds that provide VTE diagnosis and care, deliver medical education, and conduct research.
- (2) Have departments in which admitted patients are at increased risk for VTE and thrombotic events can easily occur in routine procedures. The departments that typically have high VTE incidence are Respiriology, ICU, Neurology, Orthopedics, General Surgery, Vascular Surgery, Neurosurgery, Oncology, and Gynecology.
- (3) Hospital electronic information system is accessible and CDSS can be embedded for real-time monitoring and mandatory implementing QI intervention during the study;
- (4) Directors of hospitals wish to improve in-hospital VTE prophylaxis and are willing to conduct multifaceted QI intervention systematically.

Exclusion criteria

- (1) Hospitals that have already conducted QI intervention systematically
- (2) Specialized hospitals, e.g., pediatric, maternal and infants, surgery hospitals or traditional Chinese medicine hospitals
- (3) Electronic medical system is not available

Patients

Inclusion criteria

- (1) Aged ≥ 18 years
- (2) Have an expected hospital stay ≥ 72 hours for medical and/or surgical treatment
- (3) Medical patients admitted for a serious acute medical illness listed in ACCP 8th and 9th Edition (American College of Chest Physicians)^{9,31}; surgical patients undergoing surgical operations listed in ACCP 9th Edition⁸ or having a major traumatic event that do not require an operation, including closed head injury.
- (5) Written informed consent

Exclusion criteria

- (1) Admitted solely for diagnostic testing or hemodialysis
- (2) Admitted for same-day surgery for which surgical procedures not requiring an overnight hospital stay
- (3) Admitted for treatment of VTE (began within 24 hours of admission)
- (4) Incidental VTE identified at or any time before enrolment
- (5) Hospitalized for a chronic condition rather than an acute medical illness
- (6) Patients whose primary reason for hospitalization would have qualified them to be admitted in the following wards: Psychiatric, Pediatric, Palliative care, Maternity, Ear, nose and throat units, Burn units, Dermatological, ophthalmologic services, Alcohol/drug treatment wards, Rehabilitation units/wards
- (7) Pregnancy or breastfeeding
- (8) Inability to be followed-up until 90 days after enrolment
- (9) Have participated in similar trials or are undergoing other clinical trials
- (10) Refuse or are unable to give informed consent

stockings, intermittent pneumatic compression, and venous foot pumps, is the appropriate prophylaxis approach. It is an alternative for patients contraindicated to anticoagulant prophylaxis, the use of which could lead to bleeding and safety events. If patients have low bleeding risk, pharmacological prophylaxis is preferred over mechanical ones. Overall, both thrombosis and bleeding risk assessments are recommended for an optimal decision-making in clinic practice. Thromboprophylaxis approaches may need adjustment accordingly due to patients' changing risk during hospital stay (Figure 2, Figure 3).

System-wide multifaceted QI intervention

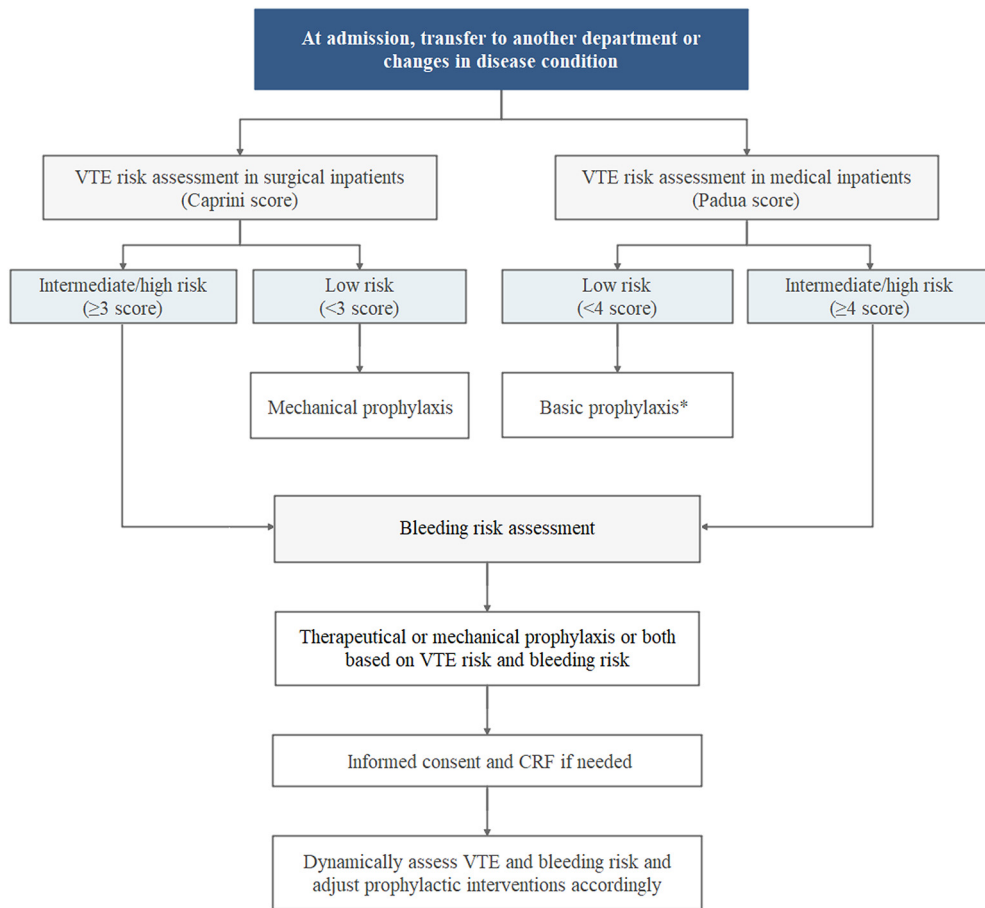
To implement the aforementioned recommendations, we design a multifaceted QI intervention, which entails four components that interact mutually. It is applied in a wide variety of inpatient settings, including surgical and medical patients.

- (1) Integration of computer-based CDSS and e-alertness for thromboprophylaxis.

The CDSS and electronic alerts are linked to the recommended thromboprophylaxis intervention. Doctors and nurses will perform the recommended care

mandatorily with the deployment of CDSS and e-alertness. Doctors in charge have to acknowledge the alert on computer, perform risk assessment as required, and provide appropriate prophylaxis prompted by the system. CDSS is installed in hospital information system (HIS) and connects electronic medical record (EMR), laboratory and imaging testing systems, aiming to help care providers with clinical decision-making. It plays a key role in enhancing appropriate thromboprophylaxis in clinical practice. E-alert on computer reminds doctors or nurses of risk assessment and appropriate thromboprophylaxis. The alerts are set in several core procedures within the electronic system in order to remind medical staff of the recommended prophylaxis. To real-time monitor risk assessment and prophylaxis, doctors are reminded to perform risk assessment and thromboprophylaxis at important time points, including 24 hours after admission, pre and post-surgery, changes in disease conditions, transfer to another department and discharge. Data in EMR will be captured to ascertain the implementation of risk assessment and appropriateness of prophylactic prescriptions. In case of uncompleted risk assessment or improper prophylaxis intervention, medical records submitted by medical staff will be blocked and an e-alert will be sent to remind the staff to correct.

Figure 2



Process for thromboprophylaxis in hospital.

Figure 3

Bleeding risk	VTE risk		
	Low	Intermediate	High
Low	Basic prophylaxis* Performers: patients and/or family care givers	Therapeutical or mechanical prophylaxis Performers: doctors and/or nurses	Therapeutical or therapeutical combined with mechanical prophylaxis Performers: doctors and/or nurses
High		Mechanical prophylaxis Performers: doctors and/or nurses	Mechanical prophylaxis Performers: doctors and/or nurses

* Basic prophylaxis includes patient education, early mobilization, functional exercise, and avoiding dehydration or unnecessary immobilization

Principles of VTE prophylaxis based on VTE and bleeding risk.* Basic prophylaxis includes patient education, early mobilization, functional exercise, and avoiding dehydration or unnecessary immobilization.

Table II. VTE and bleeding risk assessment recommended for surgical and medical inpatients

Inpatients	VTE risk assessment				Bleeding risk assessment
Surgical	Total points: low risk 0–2 points, intermediate risk 3–4 points, high risk ≥ 5 points ⁸				Risk factors for high bleeding risk ⁸
	<p>1 Point</p> <ul style="list-style-type: none"> (1) age 41–60 years (2) BMI >25 kg/m² (3) history of unexplained still infant recurrent spontaneous abortion (≥ 3) (4) pregnancy or postpartum (5) oral contraceptives or hormone replacement therapy (6) medical patient currently at bed rest (7) current swollen legs (8) varicose veins of lower limbs (9) history of inflammatory bowel disease (ulcerative colitis Crohn disease) (10) serious lung diseases including pneumonia (<1 month) (11) abnormal pulmonary function (FEV1% <50%) (12) acute myocardial infarction (13) congestive heart failure (<1 month) (14) sepsis (<1 month) (15) minor surgery planned (<45 minutes) 	<p>2 Points</p> <ul style="list-style-type: none"> (1) age 61–74 years (2) confined to bed (>3 days) (3) malignancy (4) Laparoscopic surgery (> 45 minutes) (5) Arthroscopic surgery (> 45 minutes) (7) Immobilizing plaster cast (8) Central venous access 	<p>3 Points</p> <ul style="list-style-type: none"> (1) Age 75 years (2) History of VTE (3) Family history of VTE (4) Factor V Leiden (5) Prothrombin 20210A (6) Lupus anticoagulant (7) Anticardiolipin antibodies (8) Elevated serum homocysteine (9) Heparin-induced thrombocytopenia (10) Other congenital or acquired thrombophilia 	<p>5 Points</p> <ul style="list-style-type: none"> (1) Stroke (<1 month) (2) Elective arthroplasty (3) Hip, pelvis, or leg fracture (<1 month) (4) Acute spinal cord injury (<1 month) 	<p>General risk factors:</p> <ul style="list-style-type: none"> (1) Active bleeding (2) Bleeding in 3 months before admission (3) Severe renal or hepatic failure (4) Thrombocytopenia (5) Uncontrolled systemic hypertension (6) Lumbar puncture, epidural, or spinal anesthesia within previous 4 h or next 12 h (8) Concomitant use of anticoagulants, antiplatelet therapy, or thrombolytic drugs (9) Coagulation disorders (10) Active gastroduodenal ulcer (11) Known, untreated bleeding disorder <p>Procedure-specific risk factors:</p> <ul style="list-style-type: none"> (1) Abdominal surgery: preoperative hemoglobin level < 13 g/dL, complex surgery defined as two or more procedures, difficult dissection, or more than one anastomosis (2) Pancreaticoduodenectomy: Sepsis, pancreatic leak, sentinel bleed (3) Hepatic resection: primary liver malignancy, lower preoperative hemoglobin level, and platelet counts (4) Cardiac surgery: longer bypass time (5) Thoracic surgery: Pneumonectomy or extended resection (6) Craniotomy, Spinal surgery, Spinal trauma, Reconstructive procedures involving free flap <p>Risk factors for high bleeding risk⁹</p> <p>One of the following factors:</p> <ul style="list-style-type: none"> (1) Active gastroduodenal ulcer (2) Bleeding in 3 months before admission (3) Platelet count <50 × 10⁹/L <p>Meeting three or more of the following factors:</p> <ul style="list-style-type: none"> (1) Age ≥ 85 year (2) Hepatic failure (INR>1.5) (3) Severe renal failure (GFR< 30 ml·min⁻¹·m⁻²) (4) ICU or CCU admission (5) Central venous catheter (6) Rheumatic disease (7) Current cancer (8) Male sex
Medical	Total points: low risk 0–3 points, high risk ≥ 4 points ¹⁷				
	<p>1 Point</p> <ul style="list-style-type: none"> (1) age ≥ 70 years (2) Heart and/or respiratory failure (3) Acute myocardial infarction or ischemic stroke (4) Acute infection and/or rheumatologic disorder (5) Obesity (BMI ≥30) kg/m² (6) Ongoing hormonal treatment 	<p>2 Points</p> <ul style="list-style-type: none"> (1) Recent (≤1 month) trauma and/or surgery 	<p>3 Points</p> <ul style="list-style-type: none"> (1) Active cancer (patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 months) <ul style="list-style-type: none"> (2) Previous VTE (with the exclusion of superficial vein thrombosis) (3) Reduced mobility (Bedrest with bathroom privileges for at least 3 days, either due to patients limitations or on physicians order) (4) Already known thrombophilic condition (Carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome) 		

Abbreviations: INR: International normalized ratio; GFR: glomerular filtration rate.

Performance adjustments are needed until requirements are met. All the computer programs and e-alertness will be well designed and tested in the hospitals assigned to QI group.

Simultaneously, real-time data monitoring and feedback will be accomplished via the electronic system. A cyclical model of predefined performance measures is designed to automatically analyze and provide feedback on quality of prophylaxis. When administering QI intervention, doctors and nurses' behaviors will be reviewed and audited by health administrators. Some in-process metrics (VTE and bleeding risk assessments within 24 hours after admission, dynamic risk assessment, appropriate VTE prophylaxis) and outcome metrics (HA-VTE incidence, clinically relevant bleeding and mortality) will be calculated and sent to medical staff and health administrators via CDSS for audit.

(2) Dynamic VTE/bleeding risk assessments.

Risk factors for hospital-associated VTE are well characterized, enabling the use of VTE risk assessment to identify high-risk population for early and appropriate prophylaxis. According to existing evidence,^{17,18} we recommend the use of Caprini risk score for VTE risk assessment in surgical patients while Padua risk score be used to assess VTE risk in medical patients (Table II). All admitted patients undergo VTE assessment. Nurses perform the initial assessment and doctors confirm the results. Meantime, patients' age, comorbidities, trauma history, medications, invasive procedures and other factors are assessed for bleeding risk by doctors. As disease conditions change during hospital stay, patients need to be assessed for VTE and bleeding risk repeatedly. Dynamic assessments are scheduled to be done at admission, transfer to another department, a significant change in disease conditions, and at discharge.

(3) Regular audit and interactive feedback on performance.

Performances of medical staff (doctors and nurses) are audited monthly by VTE prevention committee, which comprises hospital directors, medical and nursing directors, and health administrators. Using the audited data, the committee sends reports to medical staff, including the overall thromboprophylaxis, in-process and outcome metrics, root-cause analysis of VTE safety events, and measures for quality improvement. In the context of missed risk assessments or inappropriate prophylaxis delivered, an electronic alert will remind health administrators, who in return send feedback to responsible medical staff and urge them to administer interventions in accordance with the recommended care. The initial feedback will be followed by an electronic reminder. Medical staff's performances may need to be adjusted until the expected prophylaxis is delivered properly.

(4) Strengthened hospital staff training and patient education on VTE.

Hospital directors and health administrators will receive trainings on the concept of HA-VTE prevention, overall goal and operation mechanisms, and challenges that need to be tackled with. The trainings will be provided within 30 days after hospital randomization. Medical education focusing on VTE risk assessment, prevention, diagnosis and treatment will be convened to doctors, nurses, pharmacists and other medical staff per quarter. The knowledge of VTE are based on newly published guidelines and consensus.^{6-9,12-14} Likewise, education sessions will be offered to patients and family caregivers to increase their awareness on VTE general knowledge. Doctors or nurses provide the education when patients are admitted and discharged. During hospitalization, nurses will also instruct patients on the use of graduated compression stockings (GCS) or intermittent pneumatic compression (IPC). If not using correctly, patients will receive strengthened education until using these devices correctly. At discharge, guidance on thromboprophylaxis or anticoagulant regimen will be provided for patients or those remaining at high risk of VTE.

Routine VTE prophylaxis

In hospitals allocated to control group, patients will undergo usual care at the discretion of hospitals. VTE risk assessment and prophylactic interventions will be performed according to existing practice in hospitals.

With respect to usual care for VTE prevention, two surveys have been conducted in hospitalized patients and thoracic surgeons in China, respectively,^{4,19} demonstrating the scenario of in-hospital prophylaxis in China. The survey involving nearly 14,000 inpatients nationwide demonstrated a pervasively low rate of CHEST-recommended prophylaxis across China.⁴ Less than 15% patients at risk of VTE received thrombosis prophylactic intervention during their hospital stay. Appropriate VTE prophylaxis was just administered to 10% patients. Another survey was aimed to investigate thromboprophylaxis decision-making among thoracic surgeons.¹⁹ It showed a higher prophylaxis rate in the subgroup of patients undergoing lung resection in China. Nearly 70% surgeons responding to the survey routinely prescribed LMWH for patients with lung resection during hospitalization. Acetylsalicylic acid was still used as a prophylaxis approach in common practice. Time for starting VTE prophylaxis was usually 1 day after operation. The two surveys display current prophylaxis for HA-VTE in China. To better understand usual care in control group in this study, we will conduct a baseline survey in recruited hospitals before cluster randomization, collecting information on VTE and bleeding risk

assessment, prophylactic approaches, initiating time for prophylaxis, etc.

As our study population are medical or surgical patients admitted to the nine departments with high VTE incidence, patients in both arms will receive treatments targeted to diseases responsible for the admission. The treatment patterns and disease management will be at the discretion of doctors. Additionally, VTE incidence and bleeding events within 90 days are important outcomes for effect and safety assessment. To enhance patients' self-reported outcomes, education on signs and symptoms of VTE and bleeding will be delivered to patients during hospitalization in both groups.

Blinding and adjudication

Due to the nature of interventions, both doctors administering interventions and patients will know group allocation after enrollment. To ensure equal attention to two arms, data collectors, endpoint adjudicators, and statisticians will be blinded to group allocations. Before intervention, a randomization schedule for hospitals will be pre-generated by an independent statistician unaware of hospital identity. During the intervention period, data managers and statisticians remain blinded to group assignment in data collection and monitoring. An independent data monitoring board will evaluate the trial data and safety. In order to objectively evaluate outcomes, adjudicators assessing thromboprophylaxis implemented in hospitalized patients, imaging results for VTE diagnosis and other endpoints will be blinded.

Endpoints

The primary endpoint is appropriate prophylaxis rate in hospitalized patients, defined as percentage of patients receiving appropriate thromboprophylaxis during hospitalization. Appropriate prophylaxis is mechanical or pharmaceutical intervention administered based on individuals' VTE and bleeding risk in accordance with the recommendations.

The secondary effect endpoint includes HA-VTE incidence within 90 days after hospital admission. The incidence of HA-VTE is defined as the proportion of patients who develop VTE, including symptomatic and asymptomatic objectively proven DVT and/or PE. Patients presenting symptoms such as lower limb swelling, dyspnea or hemoptysis will undergo ultrasound test for symptomatic DVT diagnosis or CT pulmonary angiogram (CTPA) for PE diagnosis. Patients having no symptoms will undergo bilateral lower extremity duplex ultrasound and CTPA at day 90 for asymptomatic DVT/PE diagnoses. Moreover, incidental DVT/PE identified in routine care during hospitalization will be regarded as asymptomatic DVT/PE events as well. To ensure accuracy of diagnoses, the positive CTPA-grams will be evaluated by experts blinded to allocation group.

Safety endpoints include in-hospital mortality and clinically relevant bleeding within 90 days after hospital admission. Death causes will be ascertained by medical records to adjudicate VTE-related or other deaths. Clinically relevant bleeding are complications to prophylactic intervention, including major bleeding, clinically relevant non-major bleeding (CRNMB) and heparin induced thrombocytopenia (HIT). Major bleeding is a reduction in hemoglobin of ≥ 2 g/dL, or a transfusion of 2 or more units of packed red blood cells/whole blood, or bleeding at a critical site like intracranial, intra-spinal, intraocular, et al., or fatal bleeding.²⁰ CRNMB is an overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, temporary cessation of study treatment, or discomfort of pain or impairment of activities of daily life.²¹ HIT is a fall in platelet count of $>50\%$ from the highest platelet count after the start of heparin use with a positive laboratory test.²² Safety events will be collected by phone visits at day 60 and 90 after admission. Any endpoint or adverse events occurring during study period will be recorded.

Data collection and quality monitoring

During study period, some key in-process and outcome metrics will be regularly monitored (Table S1). Caprini or Padua scores, begun with the initial assessment within 24 hours at admission until the last one at discharge, will be recorded in medical records. Bleeding assessments are recorded simultaneously. Appropriate prophylaxis is determined by VTE and bleeding risk. Mechanical or pharmaceutical interventions are adopted accordingly. To enhance medical staff's awareness on appropriate prophylaxis, trainings on indications and contraindications to mechanical prophylaxis or therapeutic anticoagulation treatment will be delivered per quarter. For patients indicated for anticoagulant use, the dosage, starting time and duration of anticoagulant therapy may need to be adjusted when the risk of bleeding and VTE change. In order to administer prophylaxis properly, indications and contraindications to mechanical or therapeutic treatment are embedded into CDSS system to prompt doctors while prescribing prophylactic regimen. In this study, data collection starts from patient enrollment and continues until completion of the last patient follow up. Figure S2 demonstrates the process of data management and quality control.

Statistical analysis plan

Sample size is estimated based on the primary analysis of group difference in VTE prophylaxis rate among hospitalized patients. The nationwide survey on thromboprophylaxis in China demonstrates an appropriate prophylaxis rate of 10.3% in hospitalized patients.⁴ Assuming a target clinical difference of 5% absolute increase through QI intervention, we anticipate an

appropriate prophylaxis rate of 15.3% in QI group. In this cluster trial with hospitals as unit of randomization, between-cluster variation is indicated by intra-cluster correlation coefficient (ICC), one typically used index for such variation.²³ ICC is determined as 0.01 according to prior studies.^{24,25} Given the same cluster size with an equal number of patients per hospital (cluster), we plan to enroll 180 patients from each hospital and approximately 20 patients from each of the nine target departments. To compare between-group prophylaxis rates with 1:1 allocation, 90% power, 5% significance level, a cluster size of 180, 0.01 ICC and 10% attrition, the sample size is calculated as 5722 patients according to formulae.²⁶ We finally determine to enroll 5760 patients from 32 hospitals. An estimated number of 180 patients will be recruited from each hospital during the first 1–2 months of the study.

Patients who are screened and enrolled into study will be summarized by numbers and percentages. Baseline characteristics of hospitals and patients will be analyzed to assess cluster differences between intervention and control group. Categorical variables are summarized as number (proportion). Continuous variables are expressed as mean and standard deviation (SD) or median (interquartile ranges [IQR]) where appropriate.

Intention-to-treat (ITT) analysis will be conducted to evaluate the effect of QI interventions on enhancing appropriate prophylaxis and reducing HA-VTE in hospitalized patients. ITT principle applies to individual patients, aimed at maintaining comparability of two arms at the beginning of study. To account for intra-cluster correlation, generalized estimation equation will be modeled to estimate the effect of QI interventions on appropriate prophylaxis in hospitalized patients. The effect will be expressed as a population averaged odds ratio for qualitative outcome and mean difference for quantitative outcomes. To analyze secondary outcomes, Cox hazard model will be deployed to analyze time to VTE incidence events within 90 day follow up. Bleeding and death events will be compared using chi-square. The analyses above will be performed in subgroups of medical and surgical patients, respectively. Statistical significance will be established at 2-tailed *P* value <.05. All statistical analyses will be performed in SAS 9.4 (SAS Institute Inc. Cary, NC, USA).

Confidentiality

Patients' anonymity will be maintained by depersonalized data. Documents are only accessible to study investigators or authorized personnel. To comply with data safety regulations, only staff at the study center have access to patients' information.

Ethics and informed consent

This study is approved by ethics committee in China-Japan Friendship Hospital (approval number 2016-SSW-7)

and will be approved by ethnic committee in each hospital. It has been registered at www.clinicaltrials.gov (NCT04211181).

In this multicenter cluster randomization trial, intervention is applied at hospital level. Written consent will be obtained from directors at hospital level with agreement for participation and randomization, avoiding selection bias potentially induced by differences in consent refusal between hospitals.²⁷⁻²⁹ QI intervention is supposed to be beneficial in HA-VTE prevention among hospitalized patients through effective implementation of recommended prophylaxis. Each participating hospital prefers to receive the QI interventions. To reduce hospital withdrawal, the QI interventions, if proven effective, will be delivered to all hospitals randomized to control group after completion of this study.

In patient enrollment process, informed consent will be obtained from patients as well. Written consent includes consent for information routinely collected in hospital, willingness to provide complementary data specific to this study, and permission for 90-day follow up. Due to chronology of individual patient recruitment after hospital randomization in clustered randomization trial,²⁸ this study is prone to selection bias induced by unblinded recruiters or patients who are informed or aware of hospital allocation. To prevent such bias, recruiters in each hospital will be blinded to group allocation and enroll patients independently. Partial information rather than full information will be provided to patients in enrollment process to avoid opt-out option in patients. The hospital allocation will not be specified to patients until they are enrolled and undergo intervention.

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Discussion

To our knowledge, this is the first pragmatic trial to facilitate implementation of recommended thromboprophylaxis and prevent HA-VTE via quality improvement intervention in China. It has clinical and public health implications and can offer real-world evidence on healthcare improvement. If proven effective, QI intervention in this study will help address the pervasively

inadequate prophylaxis therapy in Chinese hospitalized patients and their unmet need in thromboprophylaxis.⁴ The QI can also be introduced into routine clinical practice to enhance care quality and reduce VTE-related safety events. A systematic approach for HA-VTE prevention in NHS England has been demonstrated to be effective in reducing post-discharge deaths with a 15.4% reduction in 90-day mortality,¹ indicating importance of a system-wide and multifaceted intervention for effective prevention of HA-VTE and its related deaths. Given the great disparities in health care systems, hospital protocols and structures across nations and cultures, CHIPS-VTE study will provide data on systematic and multifaceted implementation's effect on patient outcomes in developing countries.

The present study has the following unique features: (1) a multi-center cluster randomized trial is designed to minimize contamination across groups; (2) uses of CDSS and e-alertness in a wide variety of inpatient settings increase their applicability in daily practice. Application of CDSSs in this study will meet the increasing demand for health information technology regarding the growing concerns about quality of medical care in hospital; (3) real-time and mutually interactive quality control via CDSS enable QI intervention implemented properly among multidisciplinary hospital staff; (4) a pilot study has been done to test the feasibility of multifaceted QI in clinical setting, enhancing feasibility of this multi-center trial; (5) behavioral intervention in healthcare professionals through QI and usual practice in control will provide real-world evidence on effectiveness of QI on thromboprophylaxis improvement. The pragmatic design increases generalizability of the findings.

Meanwhile, there are several inherent limitations in this study. First, this is a cluster randomization trial with hospitals being randomized as clusters. Hospital randomization occurs before patient enrollment, making allocation concealment difficult. Selection bias may arise when unblinded recruiters don't enroll patients because their hospitals are not allocated to the group they expect to be in, which may also lead to hospital withdrawal.³⁰ In addition, consent bias could be induced by patients who have been informed of or get known the group allocation before enrollment.^{28,30} To minimize these bias inherent in methodology, informed consent needs to be handled differently from traditional randomized trials, in which randomization and intervention are administered at individual level. We will obtain well-informed written consent from hospital directors and agree to provide QI intervention to hospitals in control group after completion of the study. In patient enrollment phase, information on group allocation will not be provided to patients until they are enrolled. A blinded recruiter unaware of hospital allocation will recruit patients independently. With respect to effectiveness evaluation in this study, QI intervention is a composite of multiple interventions that interact with each

other. It's difficult to analyze the separate effect of each component on enhancing the uptake of recommended thromboprophylaxis in hospital. Despite this, pragmatic clinical evidence on the overall effect of a system-wide QI strategy for optimized VTE prevention in hospital and strengthening adherence to recommendations in daily clinical practice will be provided in our study.

Summary

In this multicenter cluster randomized pragmatic trial, the system-wide multifaceted QI intervention is anticipated to facilitate implementation of recommended thromboprophylaxis in hospitals, thereafter reducing HA-VTE incidence and relevant safety events in Chinese hospitalized patients.

Author contributions

Fen Dong: Formal analysis, Writing - Original Draft, Visualization. Kaiyuan Zhen: Investigation, Writing - Original Draft, Visualization. Zhu Zhang: Investigation, Writing - Review & Editing. Chaozeng Si: Software, Jiefeng Xia: Software, Resources. Tieshan Zhang: Software, Resources. Lei Xia: Investigation, Resources. Wei Wang: Investigation, Resources. Cunbo Jia: Resources. Guangliang Shan: Methodology. Zhenguo Zhai: Conceptualization, Methodology, Project administration. Chen Wang: Supervision.

Declarations of competing interest

None.

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Appendix. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ahj.2020.04.020>.

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