

BRIEF REPORT

Statins for venous event reduction in patients with venous thromboembolism: A multicenter randomized controlled pilot trial assessing feasibility

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Funding Information

This study was funded by the Canadian Institutes of Health Research (CIHR # PJT 148716) and the Southern and Eastern Norway Regional Health Authority (Grant # 2015112).

Abstract

Background: Statins may reduce the risk for recurrent venous thromboembolism (VTE); however, no randomized trials have explored this hypothesis. We performed a pilot randomized trial to determine feasibility of recruitment for a larger trial of secondary VTE prevention with rosuvastatin.

Methods: Patients with a newly diagnosed symptomatic proximal deep vein thrombosis and/or pulmonary embolism, receiving standard anticoagulation, were randomly allocated to adjuvant rosuvastatin 20 mg once daily for 180 days or no rosuvastatin for 6 months.

Results: Between November 2016 and December 2019, 3391 patients were assessed for eligibility in six centers. Of these patients, 1347 (39.7%) were eligible and approached for participation in the trial and 312 (23.1%) were randomized. The mean rate of randomization was 8.2 ± 4.3 patients per month. During follow-up, five recurrent VTE events were observed, three (1.9%) in the rosuvastatin group (two pulmonary embolism, one deep vein thrombosis), and two (1.3%) in the control group (two pulmonary embolism; $P = 0.68$). One major arterial event occurred in the rosuvastatin arm and none in the control arm (0.6% vs. 0%, $P = 0.50$).

Conclusion: This pilot trial supports the feasibility of a larger scale randomized controlled trial to determine the efficacy of adjuvant rosuvastatin for the secondary prevention of VTE.

KEYWORDS

pilot trial, statins, venous thromboembolism

1 | INTRODUCTION

Statins, or HMG-CoA reductase inhibitors, are hypolipidemic drugs that lower blood cholesterol levels and are widely used in the primary and secondary prevention of arteriosclerotic cardiovascular disease (ASCVD). However, statins' properties go beyond lowering blood cholesterol and there is now a large body of evidence to indicate a potential beneficial effect of statins on venous thromboembolism (VTE) risk. Case-controlled and cohort studies suggested statins could prevent first occurrence of VTE,¹ which was subsequently confirmed by the JUPITER placebo-controlled randomized trial.² In secondary prevention, observational data from cohort studies suggest a 30% reduction in risk for recurrent VTE associated with statin exposure,³⁻⁵ which is appealing as statins do not increase bleeding risk and can be used either as an adjuvant to anticoagulation or alone. To date, no randomized controlled trial (RCT) focusing on the role of statins in the secondary prevention of VTE has been published. Such a trial would need to enroll approximately 2700 participants and follow them for a median of 3.5 years to demonstrate a 33% risk reduction in the rate of recurrent VTE.

Herein, we report on a pilot randomized trial designed to assess the feasibility of conducting a larger trial to determine whether adjuvant rosuvastatin reduces the risk of recurrent VTE in patients with symptomatic major VTE.

2 | METHODS

2.1 | Study design and oversight

The Statins for Venous Event Reduction in Patients with Venous Thromboembolism (SAVER) pilot study was a randomized open-label pilot trial to assess the feasibility of a larger randomized trial designed to evaluate if adjuvant rosuvastatin can reduce the risk of recurrent VTE in patients with symptomatic major VTE. The trial was run in five Canadian centers by members of the CanVECTOR network (Ottawa, London, Hamilton, Montreal, Halifax) and one center in Norway.

Patients were eligible to participate if they had a symptomatic objectively confirmed proximal leg deep vein thrombosis (DVT; above the trifurcation of the popliteal vein) and/or pulmonary embolism (PE; segmental or greater) diagnosed in the last 30 days. Exclusion criteria are listed in Table 1.

ESSENTIALS

- Statins may reduce the risk for recurrent venous thromboembolism.
- We conducted a randomized controlled trial to assess feasibility of a larger trial.
- The mean rate of randomization was 8.2 ± 4.3 patients per month in a total of six sites.
- This pilot trial supports the feasibility of a larger scale trial.

TABLE 1 Inclusion and exclusion criteria of the trial

Inclusion criteria	1. Symptomatic objectively confirmed proximal leg DVT (above the trifurcation of the popliteal vein) and/or PE (segmental or greater) diagnosed in the last 30 days
Exclusion criteria	1. Patients unable or unwilling to provide written informed consent; 2. < 18 years of age; 3. Currently prescribed a statin; 4. A medical history or current diagnosis of any of the following (indicated for statin use): abdominal aortic aneurysm, peripheral arterial disease presumed to be of atherosclerotic origin, stroke, TIA, MI, acute coronary syndromes, stable angina, coronary or other arterial revascularization; 5. LDL-C >4.9 mM (indication for statin use); 6. LDL-C between 1.81 mM to 4.9 mM and ASCVD risk score >10% (indication for statin use); 7. Diabetes mellitus or prediabetes; 8. Contraindication to rosuvastatin

Abbreviations: ASCVD, arteriosclerotic cardiovascular disease; DVT, deep vein thrombosis; LDL, low-density lipoprotein; MI, myocardial infarction; PE, pulmonary embolism; TIA, transient ischemic attack.

Research coordinators at each pilot site screened patients for eligibility and completed detailed logs of all patients meeting inclusion criteria (both enrolled and excluded). After providing informed consent, eligibility was confirmed after completing the following tests: a lipid profile, hemoglobin (Hgb) A1C test, complete blood

count (CBC), transaminase (ALT) levels, creatinine, and pregnancy test (if a female of childbearing potential). Hgb A1C and lipid profiles completed in the past year and CBC, creatinine, and ALT completed within the past 30 days were accepted for study screening. ASCVD risk was calculated in patients between the ages of 40 and 79 using the pooled cohort equations by entering the following variables: sex, age, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, treatment for high blood pressure, diabetes, aspirin use, and smoker into the current Prevention Guidelines ASCVD Risk Estimator.

Eligible consenting patients were randomized to one of two trial arms, the treatment group (20 mg rosuvastatin, one oral daily tablet for 180 days [\pm 21 days]), or the control group (no rosuvastatin, standard care). Baseline assessments and randomization were performed within 30 days of VTE diagnosis. The study consisted of four periods: screening, randomization, telephone/email follow-up (90 days [\pm 21 days]), and final visit (180 days [\pm 21 days]).

A stratified randomization list with variable and permuted blocks was generated by an independent statistician prior to the start of the study. Randomized treatment was allocated through a centralized randomization system in a 1:1 ratio for treatment or control. Patients were stratified by center. All patients enrolled in the pilot trial were followed for 6 months.

2.2 | Study outcomes

The primary feasibility outcome measure was the number of subjects randomized per month as an indicator of feasibility of recruitment. A priori indicators of the feasibility of our study design included: (1) recruitment rates average: three per center per month at a minimum; (2) proportion of screened patients who meet eligibility criteria: more than 20%; (3) proportion of eligible patients who provide consent: more than 30%; (4) withdrawals/losses to follow-up among randomized patients: less than 10%; (5) proportion of patients evaluable for compliance with study drug: more than 60% of participants.

Secondary clinical outcomes consisted of recurrent major VTE (proximal DVT, PE) and arterial events (lower limb ischemia, stroke/transient ischemic attack, myocardial infarction). All suspected outcome events were classified by a central adjudication committee whose members were unaware of treatment assignments.

Safety outcomes comprised bleeding complications, development of glucose intolerance (pre-diabetes/diabetes), muscle toxicity (creatinine kinase $>10N$), and muscle-related symptoms (muscle weakness, aching, pain, tenderness, cramps, or stiffness). The central adjudication committee classified bleeding outcomes as major, clinically relevant non-major, or minor as per the ISTH definitions.^{6,7}

2.3 | Statistical analysis

We hypothesized a recruitment rate of an average of 8 per center per month and a range of 2 to 24 per center per month. Assuming

that recruitment rates would be roughly normally distributed, we estimate that the coefficient of variation of the mean intensity would be one half. Thus, under the assumption that the actual mean global recruitment rate will be 32 patients per month (8 per center \times 4 centers) we were able to randomly generate seven normally distributed true recruitment rates with expected value 32 and minimum possible value 0.1. We then used these rates to randomly generate seven Poisson realizations (for a 26-month observation period) and used those Poisson realizations to estimate a mean rate along with a 95% confidence interval. Repeating this process 10,000 times, we observed that we had greater than 90% power to demonstrate that the true mean rate among our centers was greater than three patients per center per month (12 patients per month overall). Thus, our sample size of 312 subjects recruited at more than four centers observed for 26 months each will give us $>90\%$ power to demonstrate that the average monthly recruitment rate is at least 12 patients per month (i.e., 3 patients per center per month).

The protocol was approved by the institutional review board at each center; written informed consent was obtained from all patients. The trial was registered on ClinicalTrials.gov (NCT02679664).

3 | RESULTS AND DISCUSSION

The study flowchart is shown in Figure 1. Between November 2016 and December 2019, 3391 patients were assessed for eligibility in six centers. Of these patients, 1347 (39.7%; 95% confidence interval [CI]: 39.7–41.4) were eligible and approached for participation in the trial; 434 patients consented (32.2%; 95% CI: 29.8–34.8), but 122 (9.1%; 95% CI: 7.6–10.7) could not be randomized as they met one of the exclusion criteria after lipid and glucose screening. In total, 312 patients (23.1%; 95% CI: 20.1–25.5% of eligible patients), or 8.0 ± 4.3 patients per month, were randomized: 155 in the adjuvant rosuvastatin arm and 157 in the control arm. The average monthly enrolment rate was 1.5 ± 1.0 per center.

Mean age of participants was 46.7 ± 10.8 years and 55.8% were women (Table 2). Symptomatic DVT of the lower limbs, with or without PE, was diagnosed in 181 patients (58.0%); the remainder had an isolated symptomatic PE. Seven patients (2.2%) had active cancer at the time of inclusion, 74 (23.7%) were exposed to a minor or major transient risk factor for VTE, and 231 (74.0%) had an unprovoked VTE. One patient died during follow-up (0.3%), four withdrew consent (1.3%), and eight were lost to follow-up (2.6%). Out of 145 patients randomized to the rosuvastatin arm, 112 (77.2%) were evaluable for compliance with study drug. In these patients, mean pill count adherence for rosuvastatin was 81.9%.

During follow-up, five recurrent VTE events were observed, three (1.9%) in the rosuvastatin group (two PE, one DVT) and two (1.3%) in the control group (two PE; $P = 0.68$; Table 2). One major arterial event occurred in the rosuvastatin arm and none in the control arm (0.6% vs. 0%, $P = 0.50$) (Table 2).

Safety analysis showed no major bleeding event in the rosuvastatin arm versus one in the control arm; muscle symptoms with no

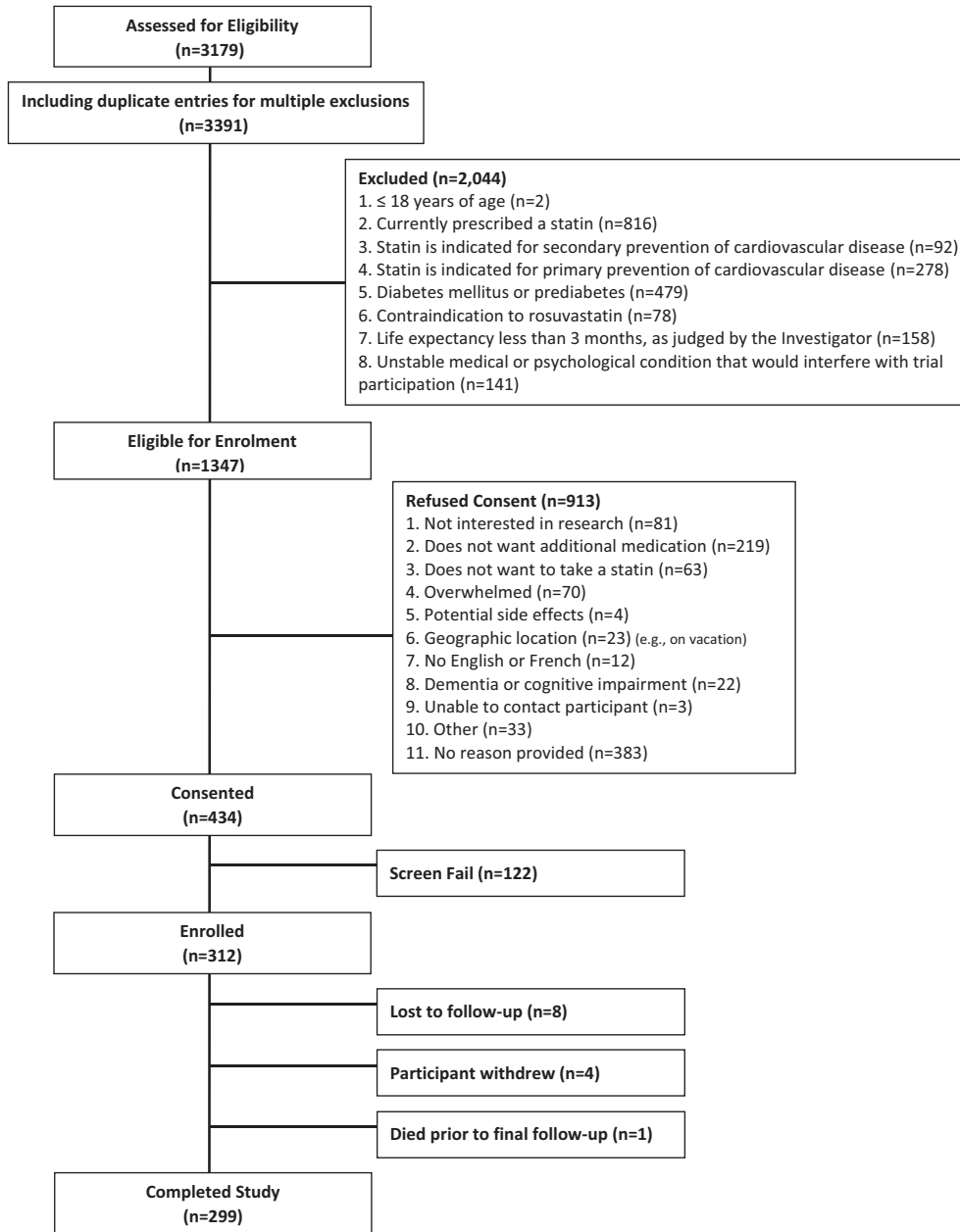
SAVER Pilot Screening & Enrolment Summary

FIGURE 1 Study flowchart

muscle toxicity were reported in eleven (7.1%) versus one (0.6%) of the rosuvastatin and control arms, respectively ($P = 0.01$; Table 3).

Pilot trials are crucial in the development of research programs. Prior to embarking on a costly and time-consuming RCT on generic rosuvastatin for secondary VTE prevention, we undertook the SAVER pilot trial to support feasibility of a large-scale trial. We demonstrated ability to recruit and retain patients, and we found an encouraging consent rate. Most of our a priori indicators of feasibility were met: (1) 39.7% of screened patients met eligibility (aim >20%); (2) 32.2% of eligible patients provided consent (aim >30%); (3) 4.2% of randomized patients were not evaluable due to loss to follow-up, withdrawal, or death (aim <10%); and (4) 77.2% of patients

from rosuvastatin arm were evaluable for compliance (aim >60%) of which mean pill count adherence was 81.9%.

The mean monthly rate of randomization did not meet our expectations for feasibility (1.5 per month per center observed, 3 per month per center expected). To increase overall recruitment rate and ensure timely completion of the trial, we plan to expand recruitment to a larger number of centers. We will engage the members of the International Network of Venous Thromboembolism Clinical Research Networks (www.invent-VTE.com) to double the number of initially planned recruiting centers.⁸

We included patients whose mean age was ~10 years younger than in the most recent RCTs assessing treatment of acute VTE.⁹⁻¹² It

TABLE 2 Baseline characteristics of randomized patients

Characteristics	Total (n = 312)	Rosuvastatin (n = 155)	Control (n = 157)
Age, years (mean ± SD)	46.7 ± 10.8	46.0 ± 10.8	47.3 ± 10.4
Female sex n (%)	138 (44.2)	62 (40.0)	76 (48.4)
Prior VTE n (%)	68 (21.8)	29 (18.7)	39 (24.8)
Weight, kg (mean ± SD)	94.9 ± 24.1	96.9 ± 25.1	92.9 ± 23.0
Total cholesterol, mM mean ± SD	4.87 ± 0.94	4.86 ± 0.86	4.89 ± 1.01
LDL-cholesterol, mM mean ± SD	2.83 ± 0.81	2.81 ± 0.79	2.58 ± 0.82
HDL-cholesterol, mM mean ± SD	1.36 ± 0.44	1.36 ± 0.46	1.35 ± 0.43
Glycemia, mM mean ± SD	5.33±0.32	5.35 ± 0.30	5.31 ± 0.35
VTE risk factors n (%)			
Active cancer	7 (2.2%)	2 (1.3)	5 (3.2)
Inflammatory bowel disease	3 (2.0)	0	3 (1.9)
Leg fracture/lower extremity plaster cast	14 (4.5)	6 (3.9)	8 (5.1)
Immobilization for greater than 3 days	11 (3.5)	8 (5.2)	3 (1.9)
Surgery under an anesthetic >30 min	31 (9.9)	14 (9.0)	17 (10.8)
Surgery with anesthetic ≤30 min	6 (1.9)	3 (1.9)	3 (1.9)
Hospitalized for 3 days or less	9 (2.9)	4 (2.5)	5 (3.2)
Exogenous estrogen therapy	25 (18.1) ^a	12 (19.3) ^a	13 (17.1) ^a
Pregnancy/puerperium	1 (0.7) ^a	1 (1.6) ^a	0 ^a
Leg injury with reduced mobility for at least 3 days	18 (5.8)	11 (7.1)	7 (4.4)
No clinical risk factors identified	231 (74.0)	116 (74.8)	115 (73.2)
VTE presentation n (%)			
Isolated DVT	151 (48.4)	75 (48.4)	76 (48.4)
DVT and PE	30 (9.6)	13 (8.4)	17 (10.8)
Isolated PE	131 (42.0)	67 (43.2)	64 (40.8)

Note: Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

^aAmong women.

seems plausible that excluding patients already receiving a statin or having an indication for a statin from this pilot trial would select for a younger population given that myocardial infarction, stroke, or type 2 diabetes are conditions most likely to occur after the fifth or sixth decade. However, we do not believe there was any inclusion bias as it helped us identify the population we would ultimately target with this intervention (i.e., patients not already taking statins for arterial prevention). We took this observation as valuable information for the larger trial when considering sample size calculations based on an expected recurrence rate that may be lower in the younger population.

Muscle-related adverse events were observed in 7.1% of patients in the rosuvastatin arm compared to 0.6% in the control arm, consistent with other trials.^{2,13} An illustration of the nocebo effect of statins was previously reported among participants of the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm) trial: an excess rate of muscle-related adverse event was reported only when patients and their doctors were aware that statin therapy was being used and not when its use was blinded.¹³

As we planned a placebo-controlled trial for the larger study, we do not expect that muscle-related adverse events will be a hurdle to successfully conducting the trial.

This pilot trial is the largest randomized trial assessing use of a statin after an acute VTE event. However, sample size was insufficient to detect a difference in efficacy for VTE recurrence. Pilot trials are typically not powered to evaluate the primary outcome of the larger study per se. The primary objective of the SAVER pilot trial was to assess feasibility of the larger trial, which after modifications to trial design (more centers) should result in a feasible definitive RCT. The absence of reduction in the rate of recurrent VTE in patients allocated to the rosuvastatin arm should not detract from conducting the larger trial, as our pilot trial was not adequately powered to detect important reductions in risk of recurrent VTE. In the larger SAVER trial, patients will be followed for 6 to 60 months (expected median 3.5 years). Although the SAVER pilot was an open label trial, clinical outcomes of interest (i.e., recurrent VTE) were blindly adjudicated. Nevertheless, to reduce the potential bias of open-label trials, the larger SAVER trial will be placebo controlled and double blinded.

Outcomes	Rosuvastatin (n = 155)	Control (n = 157)	P-value
Thrombotic events, n (%)			
Recurrent major VTE (total)	3 (1.9)	2 (1.3)	0.68
Recurrent DVT	1 (0.6)	0	0.50
Recurrent PE	2 (1.3)	2 (1.3)	1
Recurrent non-major VTE	1 (0.6)	0	0.50
Arterial events (total)	1 (0.6)	0	0.50
Myocardial infarction	0	0	1
Stroke/TIA	1 (0.6)	0	0.50
Acute limb ischemia	0	0	1
Death from any cause, n (%)	0	1 (0.6)	1
Major bleed, n (%)	0	1 (0.6)	1
Clinically relevant nonmajor bleeding, n (%)	2 (1.3)	1 (0.6)	1
Major muscle toxicity (CK>10ULN), n (%)	0	0	1
Muscle-related symptoms, n (%)	11 (7.1)	1 (0.6)	0.01

Abbreviations: CK, creatinine kinase; DVT, deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation; TIA, transient ischemic attack; ULN, upper limit of normal; VTE, venous thromboembolism.

In conclusion, this pilot trial supports feasibility of a larger scale RCT to determine the efficacy of adjuvant rosuvastatin for secondary prevention of VTE. The full SAVER trial (NCT04319627) has received public funding and will definitively answer this important clinical question.

ACKNOWLEDGMENTS

Dr. Aurélien Delluc is the recipient of a University of Ottawa Department of Medicine Research Salary Award. Dr. Susan Kahn holds a Tier 1 Canada Research Chair in Venous Thromboembolism. Dr. Marc Rodger is the McGill University Harry Webster Thorp Professor of Medicine. Aurélien Delluc, Michael J. Kovacs, Sudeep Shivakumar, Susan R. Kahn, Clive Kearon, and Marc A. Rodger are investigators of the CanVECTOR network, which received funding from the Canadian Institutes of Health Research (CDT-142654). The authors would like to thank Megan Inskip and Veronica Bates for their help in managing the trial. We are also grateful to Dr. Francis Couturaud, Dr. Walter Ageno, Dr. Michiel Coppens, Dr. Stefano Barco, Dr. Stavros Konstantinides, Dr. Fionnuala Ni Ainle, and Dr. Sara Ng for their efforts in launching the SAVER Trial (NCT04319627) in their countries.

CONFLICTS OF INTEREST

The authors have no conflicts to declare.

AUTHOR CONTRIBUTIONS

AD performed research, collected data, analyzed and interpreted data, performed statistical analysis, and wrote the manuscript; WD, MJK, SS, SRK, PMS, and CK performed research, collected data, analyzed and interpreted data, and wrote the manuscript; RM designed research and performed statistical analysis; MAR designed research,

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How to cite this article: Delluc A, Ghanima W, Kovacs MJ, et al. Statins for venous event reduction in patients with venous thromboembolism: A multicenter randomized controlled pilot trial assessing feasibility. *J Thromb Haemost.* 2021;00:1-7. doi:[10.1111/jth.15537](https://doi.org/10.1111/jth.15537)