STUDY PROTOCOL
May 2022

Main sponsor:	**Lithuanian University of Health Sciences**
Funders:	
Study coordination centre:	**Lithuanian University of Health Sciences**
NRES reference:	
Principal Investigators:	**Ayman Haq MD, Ali Aldujeli MD, PhD**

Study management group

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Study coordination centre: Lithuanian University of Health Sciences

For general queries, supply of study documentation, and collection of data, please contact:

Study coordinator: **Ali Aldujeli MD**
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Clinical Queries:
Clinical queries should be directed to Ali Aldujeli or Ayman Haq who will direct the query to the appropriate person.

Sponsor:
Lithuanian University of Health Sciences is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder: NA

This protocol describes the Red Yeast Extract study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study.

Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the Lithuanian ministry of health Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

This protocol is strictly confidential and not for public distribution.

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1. Study overview

1.1. Study summary

Design
Patients will be randomized to receive either 30mg of atorvastatin or be presented with a choice of receiving either a “natural” statin (red yeast rice extract) or 30mg of atorvastatin.
In the intervention arm, a goal of either LDL-C reduction of at least 50% or an LDL-C < 100 mg/dl will be discussed on the initial visit. Goals will be re-assessed at 2 months, if goals are not met, patients will be given 30mg of atorvastatin.

Aims
To assess if introducing greater patient autonomy increases patient compliance with statin therapy.

Outcome measures
The primary endpoint will be 6-month compliance of statin therapy, after the initiation of atorvastatin.

Secondary endpoints will be rates of perceived side effects from statin use, including myalgias, fatigue, mental fog and GI upset.

Population
This will be a multi-center study of 300 pts, 150 in each arm.

Eligibility
Primary prevention (no history of CAD, MI, or stroke) patients with a moderate 10-year ASCVD risk who decline statin therapy.

Duration
Anticipated recruitment is 6 months. Follow-up will be performed at 6 months in the control arm and 2 and 8 months in the intervention arm, for a total study duration of 14 months.

1.2. Glossary of abbreviations

ALT	Alanine aminotransferase
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BMI	Body mass index
CAD	Coronary artery disease
CVD	Cardiovascular disease
EAS	European atherosclerosis society
ESC	European society of cardiology
HDL	high-density lipoprotein
LDL	low-density lipoprotein
MI	Myocardial infarction
PCE	Pooled cohorts equation

1.3. Keywords

Statin Intolerance
Autonomy
Therapeutic Relationship

2. Introduction

2.1. Background

Statin therapy is an integral tool in the primary and secondary prevention of ASCVD. Higher compliance with their statin therapy is associated with a lower risk of mortality in a step-wise manner (1). Despite this, rates of statin compliance are abysmally low. Prior studies suggest that less than 40% of primary prevention patients are compliant with their prescribed statin therapy. Individuals who have suffered a prior MI have an incremental improvement in compliance to around 60%. Younger individuals and women appear to have exceptionally low rates of compliance to statin therapy (2). Low rates of compliance remains a significant barrier to reducing the burden of ASCVD, with some suggesting efforts to increase compliance can have an oversized impact on reducing rates of ASCVD (3).

On the other hand, patients often prefer “natural” therapies over conventional medicine for a variety of reasons (6). Monacolin-K is a naturally occurring molecule in red yeast-rice extract, a commonly used health supplement. It is structurally identical to lovastatin and has been shown to reduce LDL-C levels and ASCVD events in randomized placebo controlled trials (7, 8).

Patient autonomy is a core bioethical principle affirming the right of the patient to determine the trajectory of their health care at times. This bioethical principle has been referred to as “first among equals”, implying that it is the most important bioethical principle (4). The role of autonomy in patient compliance is not entirely clear, but there is evidence that suggests that increased patient autonomy in the decision-making process can result in higher rates of long term compliance (5).

3. Study objectives

Primary Objective

The objective of this study is to determine if introducing autonomy in the decision-making process will increase statin compliance and reduce the rate of perceived side effects from statin use.

Rationale for the study

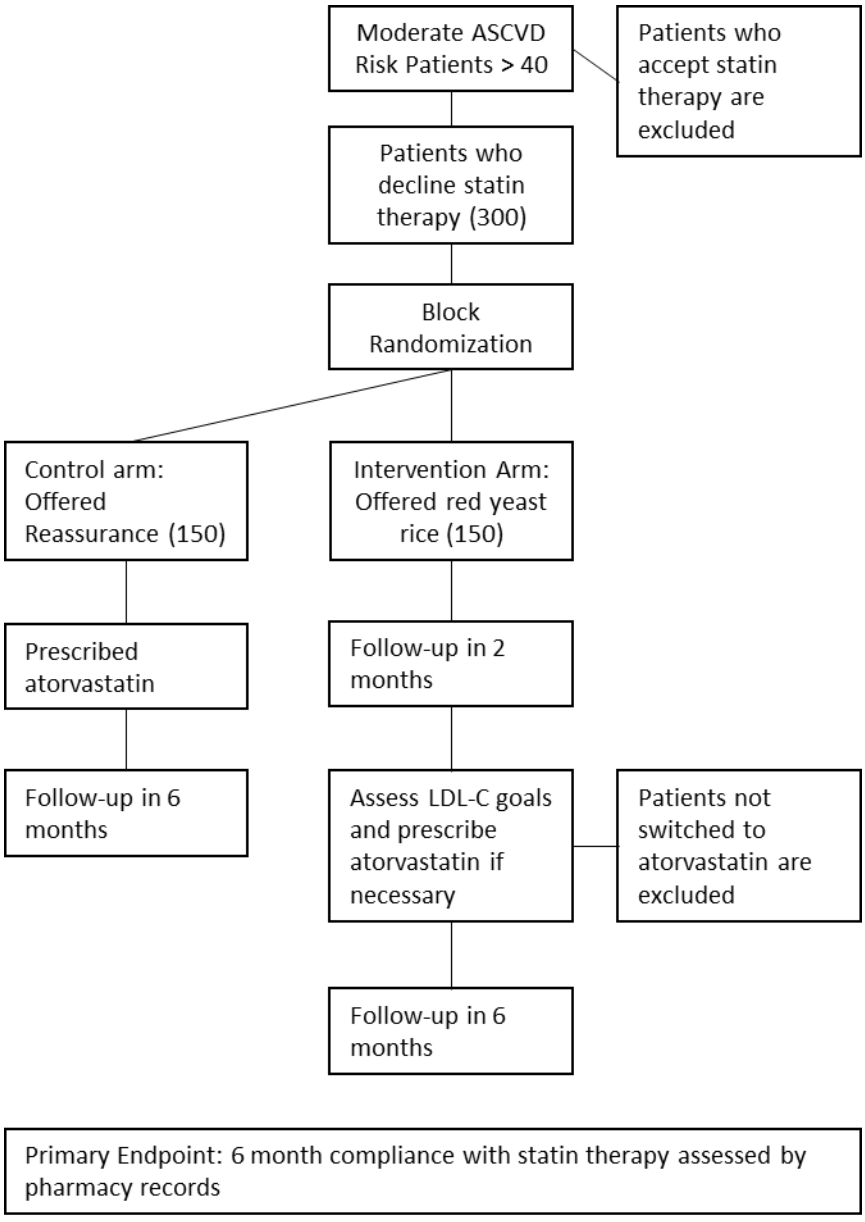
1) Statin use has been repeatedly shown to reduce the risk of ASCVD events
2) Patient compliance is a significant and often insurmountable barrier to statin therapy
3) Increased patient autonomy may be associated with greater rates of long-term compliance and warrants further investigation

Study hypotheses

Patients who perceive a higher degree of autonomy in the decision-making process are more likely to be compliant with statin therapy and less likely to perceive side effects from statin therapy.

4. Study design

1.1. Study overview diagram



4.2 Study protocol:

Patients meeting the study criteria will be enrolled at outpatient cardiology clinics at four centers: Lithuanian University of Health Sciences, Northway Medical Centre, Prienu Hospital, and Unomeda Medical Centre. The enrolment period will last six months, with an estimated 50 patients per month enrolled into the study, for a total of 300 patients.

Patients will be randomized to either the control group or the intervention group. Baseline variables will include demographic variables (age, gender, BMI, blood pressure, heart rate), medical history (hypertension, hyperlipidaemia, type 2 diabetes mellitus, tobacco use), laboratory variables (total cholesterol, HDL, LDL, triglycerides, AST, ALT, creatine kinase, and, vitamin D levels) and socioeconomic variables (education level, income level, rural or urban, and marriage status).

The control group will be provided reassurance through a short, semi-structured discussion on the excellent safety profile of statins, similar to a typical interaction between a clinician and patient. They will then be prescribed 30mg atorvastatin daily as a 30 tablets supply with five patient-initiated re-fills for 30 tablets each. Final follow-up in this group will occur at 6 months.

The intervention group will be offered a red yeast rice extract 20mg nightly to achieve a goal LDL-cholesterol of <2.6 mmol/L (100 mg/dL) in accordance with the 2019 ESC/EAS guidelines (9). Initial follow-up will take place in 2 months to assess the efficacy of their treatment. Patients who are not at the goal LDL-cholesterol will be prescribed 30mg atorvastatin nightly as a 30 tablets supply with five patient-initiated re-fills for 30 tablets each, with final follow-up after 6 additional months. Patients who are at goal on the red yeast rice extract will be recommended to switch to lovastatin 20mg nightly as a bio-identical substitute, but they will be excluded from further analysis.

In both groups, statin adherence will be assessed by pharmacy refill records at the final follow-up. A short, four question questionnaire (Appendix A) will be administered at this point as well. Final follow-up laboratory variables collected will include total cholesterol, HDL, LDL, triglycerides, AST, ALT, creatine kinase, and vitamin D levels.

Conversation guidelines for each clinical encounter in the intervention group are included in Appendix B.

Randomisation
Patients will be randomized by block randomization. On the first week of enrollment, the clinician will only enroll patients into the control arm. On the subsequent week, the clinician will only enroll patients into the intervention arm.

4.3. Study outcome measures

Primary Endpoint

Rate of statin compliance, based on pharmacy refill records. Values per patient can range from 0-6 according to the number of refills.

Secondary Endpoints:

Rate of perceived side-effects from statin use, including muscle aches, fatigue, mental fog, and gastrointestinal upset.

4.4. Relevance and implications of the trial results

1. Low compliance with statin therapy is widely observed and limits the preventative potential of the therapy and results in increased ASCVD events
2. Empowering patients by allowing autonomy in clinical decision making may be an effective tool to increase long term compliance.

4.5. Sample size/Power calculation

This study is designed as a superiority trial. Based on prior literature, we estimate a 50% statin compliance rate with a standard deviation of 10% (2). We will set the minimal detectable effect at a 5% increase in statin compliance, with an $\alpha < 0.05$ and power of 0.9. Based on case-to-control ratio of 1:1, our total minimum sample size for the primary endpoint is 138. However, we will plan on a total sample size of 300 patients, to account for patients who drop out of the study as well as patients who will be excluded due to attaining an LDL-cholesterol of <2.6 mmol/L (100 mg/dL) on red yeast rice extract.

5. Participant entry

5.1. Pre-registration evaluation

Recruitment

Primary prevention patients with a moderate ASCVD risk.

5.2. Inclusion criteria

1. Over 40
2. Moderate ASCVD risk
3. Decline statin therapy

5.3. Exclusion criteria

1. Dementia
2. Severe Mental Illness
3. History of statin intolerance
4. High-risk for ASCVD
5. Currently on lipid lowering therapy
6. Currently taking red yeast rice extract
7. Pregnant or breast feeding
8. Concomitant use of the following drugs: anti-retroviral therapy, niacin, calcineurin inhibitors, mTOR inhibitors, amiodarone, and fibrates

5.4. Withdrawal criteria

Patients will be able to withdraw from the study at any time at their request.

Patient who develop statin intolerance will be withdrawn from the study.

5.5. Screening record

Any patient initially considered suitable, but then found inappropriate due to study exclusion criteria will be recorded into the screening record.

6. Clinical events

6.1. Definitions

The following definitions will be employed in this study.

Statin intolerance

Development of an increase in creatine kinase OR AST/ALT elevation> 3x upper limit of normal OR rhabdomyolysis with statin initiation during the study period.

History of statin intolerance

History of an increase in creatine kinase OR AST/ALT elevation> 3x upper limit of normal OR rhabdomyolysis with statin initiation, prior to enrollment in this study

Moderate risk for ASCVD

7.5%-20% 10-year ASCVD risk by the Pooled Cohorts Equation

Severe Mental Illness

History of schizophrenia or another mental illness with psychotic features

6.2 Reporting procedures

Clinical Events Committee

The CEC is made up of cardiologists who are not participants in the trial. The CEC is charged with the development of specific criteria used for the adjudication of clinical events and clinical endpoints in the trial which are based on protocol.

The Clinical Events Committee will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. All members of the Clinical Events Committee will be blinded to the treatment arm and the primary results of the trial.

The Clinical Events Committee will meet regularly to review and adjudicate all clinical events in which the required minimum data is available. The Committee will also review and rule on all deaths that occur throughout the trial.

Reports of clinical events should be submitted within 15 days of the Chief Investigator becoming aware of the event.

Local investigators should report any clinical events as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact for reporting clinical events: Ramunas Unikas
Email: ramunas.unikas@kaunoklinikos.lt

Case report form
An online CRF form will be used throughout the study. This will be secure, and compatible with currently guidelines to ensure security of patient data. It will be managed via the Lithuanian University of Health Sciences Clinical Trials Unit , and data achieved securely.

7. Assessment and follow-up

Routine follow-up will be performed with a clinic visit at 6 months in the control group and at 2 months and 8 months in the intervention group. The CRF should be completed.

8. Statistics and data analysis

Data will be summarised as mean (SD) or median (interquartile range) for skewed data. Statistical comparisons will be undertaken using a paired Student's t-test (after log transformation if necessary) or nonparametric alternative if data are not normalised by log transformation. Kaplan-Meier survival analysis curves will be used to assess clinical event timelines.

9. Regulatory issues

9.1. Ethics approval

The Chief Investigator will obtain approval from the TBC Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

9.2. Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

9.3. Risks of procedure

No procedures are involved in this study

9.4. Confidentiality
The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

9.5. Indemnity
Lithuanian University of Health Sciences holds negligent harm and non-negligent harm insurance policies which apply to this study.

9.6. Sponsor
Lithuanian University of Health Sciences will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

9.7. Funding
This study is not funded

9.8. Audits
The study may be subject to inspection and audit by Lithuanian University of Health Sciences under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

10. Study management

The day-to-day management of the study will be co-ordinated through **Lithuanian University of Health Sciences**.

10.1. Study reporting
We anticipate that it will take 6 months to complete patient recruitment and another 8 months to complete follow-up. We will aim to begin recruitment after Ethics review approval with first results available for presentation in late 2023

10.2. Study sites and enrolment
We anticipate the study enrolling patients through up to 10 large high volume CABG centres with interventional experience in all of the physiological techniques proposed in this study. We envisage enrolment would take place within 12 months.

10.3. Documentation
All documentation will be collected electronically using ICTU. The ICTU has a track record for running large multi-centre international (e.g. ASCOT study). Clinical, and physiological records will be saved to DVD and then to a central server within ICTU in accordance with GCP guidelines.

11. Publication policy

Publication and future studies committee
A publication committee, consisting of member of the steering committee and study principal investigators will meet to formulate a publication plan to disseminate the principal findings of the study, and the primary and secondary endpoints.

Future studies, and sub-studies will be actively encouraged, by investigators and other interested parties. These will be assessed via the formal application process, and the committee will decide on the applicability and suitability of the study request. Sub-study proposals which aim to look at subset analyses of the primary and secondary endpoints will be underpowered and in general discouraged.

12. References

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13. Appendices

Appendix A
Final Follow-up questionnaire

Have you had any of the following symptoms from atorvastatin over the past 6 months?			
Myalgias (muscle aches)	☐ Yes	☐ No	☐ Not Sure
Fatigue	☐ Yes	☐ No	☐ Not Sure
Mental fog (slow thinking or memory issues)	☐ Yes	☐ No	☐ Not Sure
Gastrointestinal upset	☐ Yes	☐ No	☐ Not Sure

Appendix B

Clinical Encounter Conversation Guidelines

Control Group Initial Encounter

Point(s) to discuss

1. Acknowledge the patient's reluctance to start statin therapy
2. Reassure the patient that long term data supports the safety of statins
3. Reassure the patient that long term data supports the efficacy of statins

Sample Conversation(s):

"I understand that you are hesitant to start statin therapy. We over two decades of long-term follow-up data regarding statin use. The data clearly shows that statins are extremely safe and patients who stay on statins live longer and healthier lives."

Intervention Group Initial Encounter

Point(s) to discuss

1. Acknowledge the patient's reluctance to start statin therapy

2. ESC/EAS 2019 guidelines recommend an LDL-cholesterol < 2.6 mmol/L (100 mg/dL)
3. Present the option of a natural supplement as an open-ended question
4. The impact of the therapy will be assessed in two months

Sample Conversation(s):

"I understand that you are hesitant to start statin therapy. According to European guidelines, your LDL-cholesterol should be less than 2.6 mmol/L (100 mg/dL)to reduce your risk of a cardiovascular event. What is your opinion on trying a natural supplement to reduce your cholesterol?"

If the patient agrees to red yeast rice extract

"Let's follow up in two months to see if our LDL-cholesterol goals have been met"

Intervention Group Initial Follow-up

If LDL-cholesterol > 2.6 mmol/L (100 mg/dL)

Point(s) to discuss

1. Since the natural remedy did not work, we should switch to the statin to reduce cardiovascular events

Sample Conversation(s):

"Unfortunately, we were not able to meet our goals with the natural supplement. Because of this, let's try the prescription medicine instead (atorvastatin 30mg nightly)"

If LDL-cholesterol < 2.6 mmol/L (100 mg/dL)

Point(s) to discuss

1. The natural remedy did reduce your LDL-cholesterol to our original goal
2. However, the effect of the natural remedy is unreliable over time due to lack of regulation

3. Let’s switch to a bio-identical prescription medicine for reliability

“Congratulations, we were able to meet our goal using a natural supplement. This supplement contains naturally occurring lovastatin; however it is difficult to predict the dose that you are receiving since supplements are not regulated. Let’s try a medium dose of lovastatin instead (20mg lovastatin nightly)”