**EMERALD (Emergency Medicine Cardiovascular Risk Assessment for Lipid Disorders)**

**IRB00091989**

**NCT05742841**

**07JUN2023**

**Study Title: EMERALD (Emergency Medicine Cardiovascular Risk Assessment for Lipid Disorders**

**Principal Investigator, Co-investigator(s):** Dr. Nicklaus Ashburn, Dr. Simon Mahler

**Sponsor or funding source:** Atrium Health Wake Forest Baptist

## Background, Rationale and Context

EMERALD (Emergency Medicine Cardiovascular Risk Assessment for Lipid Disorders) is a pilot study seeking to determine the feasibility of initiating medical therapy for hyperlipidemia (HLD) in the Emergency Department (ED) and will collect data essential to inform a future randomized controlled trial comparing ED HLD treatment to usual care (future NHLBI submission). HLD is a key cardiovascular disease (CVD) risk factor that is causally associated with atherosclerotic cardiovascular disease (ASCVD), the leading cause of US mortality and morbidity. [1–3] It is estimated that almost 40% of ED patients with chest pain have poorly managed or unrecognized HLD.[4] However, patients are rarely screened for HLD in the ED and ED initiation medical therapy for HLD is exceedingly uncommon. Because HLD is rarely screened for, prescribing a statin is not the standard of care in the Emergency Department. Therefore, the current ED care paradigm, which does not address HLD, represents a missed opportunity to prevent ASCVD events. Every 38.7 mg/dL reduction in low-density lipoprotein-cholesterol (LDL-C) is associated with a 21% decrease in ASCVD events and a 24% decrease in mortality. [5,6] Thus, there is a clear opportunity to improve health for the millions of patients who present to the ED each year with undiagnosed and/or unmanaged HLD. [7,8] Diagnosing and managing a CVD risk factor such as HLD in the ED would be innovative and paradigm shifting.

To address this gap in ASCVD prevention we have developed a novel ED-based HLD screening and treatment program: EMERALD (Emergency Medicine Cardiovascular Risk Assessment for Lipid Disorders). This program adapts HLD recommendations from the 2013 AHA/ACC and 2022 US Preventive Services Task Force guidelines to the ED setting. The EMERALD intervention involves 1) ordering an ED lipid panel, 2) calculating 10-year ASCVD risk using the Pooled Cohort Equations[9], 3) prescribing a moderate- or high-intensity statin if applicable, and 4) referring patients to outpatient care (primary care, preventive cardiology, or general cardiology, depending on risk level). [10–12] Our preliminary data demonstrate that >90% of ED patients with acute chest pain believe the ED is an appropriate place to evaluate for HLD and >80% believe it is a reasonable place to start medical therapy for HLD. However, the feasibility of screening for HLD and initiating treatment in the ED setting is unclear. It is unknown whether patients prescribed HLD treatment will fill these prescriptions, take their medication, and complete scheduled follow-ups. In addition, it is not clear whether busy Emergency Physicians will adopt and follow the steps of a preventative HLD care program.

## Objectives

What is needed now is a pilot study examining if the ED can screen for HLD and estimate the anticipated effect size of EMERALD in lowering LDL-C. We propose a pilot study with 20 patients designed to assess the feasibility of EMERALD and to explore changes in LDL-C by initiating medical therapy in the ED. The specific aims of this study are:

**Aim 1: Test the feasibility of EMERALD**. We will determine the proportion of patients who receive a complete EMERALD assessment (ED lipid panel drawn, 10-year ASCVD risk

calculated with the Pooled Cohort Equations, and prescribed a statin), fill their prescription within 7-days of the ED encounter, and follow-up at 30-days for a repeat lipid panel.

**Aim 2: Explore changes in LDL-C after initiating preventive care with statin therapy in the ED.** The primary outcome will be change in LDL-C at 30-days. The secondary outcome will be change at 30-days in non-high-density lipoprotein-cholesterol (non-HDL-C).

Our experienced team is well-equipped to conduct this pilot study. This innovative proposal is a key step for determining if EMERALD is feasible and estimating its impact on LDL-C at 30-days. Our team consists of experts in emergency medicine, preventive cardiology, lipid disorders, and biostatistics. There is strong potential that the EMERALD concept could improve care for millions of ED patients across the US who have undiagnosed and/or unmanaged HLD. The concept could be expanded to other modifiable CVD risk factors, including diabetes, hypertension, obesity, and smoking.

## Methods:

### Overview and Design

We propose a pilot study with 20 patients designed to assess the feasibility of EMERALD and to explore changes in LDL-C by initiating medical therapy in the ED.

Subjects will be screened for Emerald in the Emergency Department. Research staff and investigators will screen for subjects in the Emergency Departments with the electric screening "track boards". We will then screen patient health records and speak to their ED providers about EMERALD. Labs will be ordered so that we can either rule in or out a patient for research.

If they meet inclusion and no exclusion criteria, their treating Emergency Physician will be asked to initiate the EMERALD protocol, including: 1) ordering a lipid panel during the index ED encounter and 30-days after ED discharge, 2) completion of the Pooled Cohort Equations, and 3) starting medical therapy (moderate- or high-intensity statin, if appropriate) in the ED.

The research will take place in the Emergency Department at Wake Forest Baptist Medical Center. Follow-ups will occur in the CTSI CRU space, Emergency Medicine CRU, or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) for the 30 day follow-ups.

## Subjects selection criteria

Treatments for Hyperlipidemia in ED settings:

### Inclusion Criteria

- ED patients with chest pain
- 40-75 years old
- An LDL-C ≥70 mg/dL on an ED lipid panel or have known diabetes or ASCVD
- Negative standard of care pregnancy test or documented inability to bear children for female participants

Exclusion Criteria

- Subject unwilling to take study medication
- Pregnancy or breastfeeding
- Inability to take study medication or, in the opinion of the Investigators/subject's doctors unsuitable for study participation
- ST-Segment Elevation Myocardial Infarction (STEMI) Activation
- ST-Segment Depression >1 mm
- On a Lipid Lowering Agent (Statin, PCSK9 Inhibitor, Bempedoic Acid, Ezetimibe, Inclisiran)
- Unstable Vitals (BP <90, HR >120 or <50, O2 sat <90%)
- Statin Intolerance
- High-sensitivity Troponin I ≥100 ng/L
- ESRD and/or GFR <30 mL/min/1.73 m2
- Liver Cirrhosis
- Hospitalization
- Life Expectancy <1 Year
- Transfer from Another Hospital
- Prisoner
- Non-English Speaking

**Intervention and Procedure**

This program adapts HLD recommendations from the 2013 AHA/ACC and 2022 US Preventive Services Task Force guidelines to the ED setting.

To close this critical evidence gap, we propose a pilot study, which will test the feasibility of EMERALD and explore changes in LDL-C concentrations using 20 ED patients with chest pain who are 40-75 years old with an LDL-C ≥70 mg/dL on an ED lipid panel or have known diabetes or ASCVD. For patients enrolled, their treating Emergency Physician will be asked to initiate the EMERALD protocol, including: 1) ordering a lipid panel during the index ED encounter and 30-days (+/- 5 business days) after ED discharge, 2) completion of the Pooled Cohort Equations by the patient's ED provider at the index visit, 3) starting medical therapy (moderate- or high-intensity statin/ rosuvastin) in the ED, if applicable, and 4) having subjects complete a drug diary documenting drug usage. This pilot will provide critical data regarding the feasibility of the EMERALD intervention and its estimated effect size on LDL-C concentration, which are needed to inform a future randomized trial (future NHLBI submission). Ignition funds will be used to pay for lipid measures, support statistical analysis, and provide patient compensation. This pilot project is essential for providing preliminary data for a future randomized controlled trial of EMERALD (future NHLBI submission).

The EMERALD procedure involves

1) Ordering an ED lipid panel
2) The subject's ED provider calculating the 10-year ASCVD risk using the Pooled Cohort Equations[9] at the index visit,
3) Based on the trial diagram, prescribing a moderate- or high-intensity statin (either rosuvastatin 10mg daily or rosuvastatin 40 mg daily) if applicable,

4) Have subjects complete a drug diary during the 30 days before their follow-up, and
5) Bring subjects back 30-days (+/- 5 business days) after ED discharge to retest their Lipid Panel

**Outcome**

This pilot study will provide preliminary data regarding the feasibility of EMERALD and estimate its impact on LDL-C and non-HDL-C. We anticipate the pilot data will demonstrate that implementation of EMERALD is feasible in an ED setting (ED lipid panel drawn, 10-year ASCVD risk assessment performed, and statin therapy initiated) and will result in a trend towards reduced LDL-C among participants.

**Analytical Plan**

This pilot study will provide preliminary data regarding the feasibility of EMERALD and estimate its impact on LDL-C and non-HDL-C. We anticipate the pilot data will demonstrate that implementation of EMERALD is feasible in an ED setting (ED lipid panel drawn, 10-year ASCVD risk assessment performed, and statin therapy initiated) and will result in a trend towards reduced LDL-C among participants. These data will support a future NHLBI submission (likely K23 award for Dr. Nicklaus Ashburn with Dr. Mahler as mentor), which will use a randomized controlled trial design to examine the efficacy and patient adherence to EMERALD on a larger scale. If the pilot data are not supportive of the EMERALD concept, then the investigative team will reconsider the EMERALD program design before pursuing NIH funding. In either case, the data from this pilot will be essential for future proposals and used to produce the first publication regarding ED-initiated medical therapy for HLD.

**Human Subjects Protection**

General requirements: The study will be conducted in compliance to this study protocol, the current version of the Declaration of Helsinki, ICH GCP, and applicable local legal and regulatory requirements.

Submission of study documents: Before study start, the study protocol, and subject information / informed consent and any other study-related document as required by applicable laws and regulations will be submitted to the Ethics Committee and regulatory authorities for written approval. Any protocol amendments or new or amended information that requires ethical consideration will be submitted for written approval, too. In addition, a study report (interim and /or full report) will be submitted to regulatory authorities in line with applicable timelines.

Subject information and informed consent: Participation in this study will include a written informed consent, which will be collected in the ED. All subjects or legal representatives will be informed orally and in writing about the objectives of the study, its procedures, potential risks, and about the fact that to some extent data will be accessible for third parties - provided that data confidentiality is ensured at any time. The participation in this study will be entirely voluntary. Subjects will have the right to withdraw their willingness to participate in the trial at any time without affecting their future medical care in any way. Informed consent will be obtained from both the investigators and from the study coordinators

Clinical study results and publication: The results of the clinical study will be documented in a clinical study report and will be published (e.g. in a journal or presented in a scientific meeting).

Data confidentiality: Auditors, Ethics Committee, and the regulatory authorities will be granted direct access to the subject's medical records to the extent permitted by the applicable law and regulation for verification of clinical study procedures, and/or data control, ensuring subject data confidentiality. The subject's file and the source data will be archived in line with national and international legal requirements.

Data and Safety Monitoring
The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations
Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

**References**


1. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38(32):2459-2472.

2. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation*. 2021;143(8):e254-e743.

3. Vassy JL, Lu B, Ho YL, et al. Estimation of Atherosclerotic Cardiovascular Disease Risk Among Patients in the Veterans Affairs Health Care System. *JAMA Netw Open*. 2020;3(7):e208236.

4. Blomkalns AL, O'Connell EM, Eady CE, Lindsell CJ, Gibler WB. Evaluation of dyslipidemia in the emergency department: impact of cholesterol testing on subsequent therapy. *Am Heart J*. 2006;152(6):1182-1186.

5. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681.

6. Ross SD, Allen IE, Connelly JE, et al. Clinical outcomes in statin treatment trials: a meta-analysis. *Arch Intern Med*. 1999;159(15):1793-1802.

7. Owens PL, Barrett ML, Gibson TB, Andrews RM, Weinick RM, Mutter RL. Emergency department care in the United States: a profile of national data sources. *Ann Emerg Med*. 2010;56(2):150-165.

8. Hooker EA, Mallow PJ, Oglesby MM. Characteristics and Trends of Emergency Department Visits in the United States (2010-2014). *J Emerg Med*. 2019;56(3):344-351.

9. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S49-73.

10. Gulati Martha, Levy Phillip D., Mukherjee Debabrata, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain. *J Am Coll Cardiol*. 2021;78(22):e187-e285.

11. Whelton Paul K., Carey Robert M., Aronow Wilbert S., et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *J Am Coll Cardiol*. 2018;71(19):e127-e248.

12. US Preventive Services Task Force, Mangione CM, Barry MJ, et al. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2022;328(8):746-753.

**Appendix**

1. Data collection form
2. Copies of each questionnaires or surveys that will be used
3. Consent form if one will be used
4. Other Appendix items as appropriate