The US Dept. of Justice

Community Oriented Policing Services

Community Policing Development

CFDA 16.710 Program Application

Topic Area: Open Category

Title:

Law Enforcement Officer

Cardiovascular Screening Initiative (LEO-CSI)

Law Enforcement Officer Cardiovascular Screening Initiative (LEO-CSI)

1. TOPIC SELECTION AND OUTCOME IDENTIFICATION AND JUSTIFICATION

One of the leading causes of death in law enforcement officers (LEOs) is atherosclerotic cardiovascular disease (ASCVD) including myocardial infarction (MI), stroke and peripheral arterial disease (PAD).[1] Compared with civilians, the average age myocardial infarction in LEOs is 49 years compared to age 65 (table 1). Limited data suggest that Law Enforcement Officers (LEOs) have a life expectancy more than twenty years less than their civilian counterparts and the years of potential life lost *was* 21 times larger than among the general population and this discrepancy disproportionally affects younger age groups increasing to 60 times larger for those ages 35-39 years in a study of Buffalo, New York LEOs.[2] As summarized in Table 1, the average age for MI among LEOs may be as young as 49 years compared to 65 years of age in the civilian sector. The cause is unclear but may be related not only to an increased prevalence of known classic ASCVD risk factors (hypertension, hyperlipidemia, diabetes) but also to factors such as mental stress induced by work schedules, shift work, and traumatic events.[2,3,4] **At the present time there is no approach to adequately assess the risk for ASCVD in LEOs.** As in other special populations,[5] standard approaches to ASCVD risk assessment such as a Framingham or Pooled Cohort Equation Risk Score will vastly underestimate the risk of ASCVD in LEOs as these omit LEO-specific factors. The small number of published studies in LEOs have also only looked ASCVD deaths and not morbidity. No data exist on the prevalence of LEOs living with ASCVD, and many are unaware of their risk. In fact, <5% of heart attacks are fatal,[6] and most heart attacks occur in individuals who would be classified as low or intermediate risk based on their known risk factors. Line of Duty death from MI is consistently the second or third leading cause of officer mortality however, this data tracks only officers who suffer their MI during duty hours.[7,8] When extrapolated from a ten- or twelve-hour shift to a twenty-four-hour day, death from cardiac disease easily becomes the number one killer of LEOs. To date, there has only been a single published study attempting to develop an early detection strategy for LEOs with undiagnosed subclinical coronary heart disease (CHD) using coronary artery calcium (CAC) scoring and that study failed to find increased CAC in LEOs compared to the general population[9] although other studies have found that shift workers (including the majority of LEOs) did have significantly higher CAC scores.[10] The knowledge gap addressed by and purpose of our proposed study, based on robust pilot data, is how to better detect ASCVD in LEOs in the early, asymptomatic and modifiable stage *before* death and disability from a cardiac event occurs. The outcome and rationale for our study is to improve LEO health extending their working years while also decreasing the prevalence of ASCVD in retirement. **The potential impact of this study on officer safety, health and departmental costs, immediate and long-term is enormous. Earlier detection of CHD and subsequent intervention will save lives and reduce the devastating impact of ASCVD on fellow LEOs, families and communities.**

Table 1: Comparison between LEOs and civilians for heart attacks and life expectancy. From Violanti et al[2]

	Law Enforcement Officers	Civilians
Average age of a patient with heart attack	**49 yrs**	**65 yrs**
Heart attacks under age 45	**45%**	**7%**
Fatal heart attacks age 55-59	**1.7%**	**56%**
Average life expectancy	**57 yrs**	**79 yrs**

In addition to our supportive preliminary data described below, we are well prepared to carry out the proposed study because of our multidisciplinary team. Dr. Sheinberg is a cardiologist and active LEO. Dr. McNeal is a cardiovascular researcher and specialist in preventive cardiology. Drs. Jack Tubbs and James Stamey are statisticians who have focused on the analysis of complex medical data to identify disease causes using advanced statistical methods. Dr. Copeland has expertise studying the adverse effects of mental health in U.S. veterans. This project has received enthusiastic and broad support from the Baylor Scott & White Health Care System.

2. STRATEGY TO ACHIEVE PROGRAM OUTCOMES AND GOALS

Goal 1: Incorporate a multimodal approach descried below to identify 400 LEOs, men and women, age > 35 years without symptoms or diagnosis of ASCVD from four police departments representing ~ 2,000 LEOs in urban and rural communities plus the Texas Department of Public Safety (DPS) comprising ~5000 sworn and ~5000 civilians. We will develop a predictive model that will incorporate a composite of classic risk factors, mental stress measures, coronary artery calcium (CAC) scoring and serum biomarkers that have emerged in recent years. A treatment plan will be recommended based upon the risk assessment and risk status will be updated through an annual reassessment questionnaire and where possible, medical records review for a minimum of 5 years.

Outcome: Improve knowledge of ASCVD risk, provide motivation and a treatment plan to reduce future ASCVD risk and track outcomes annually to reassess morbidity and mortality due to all cause and conditions specific to ASCVD.

Goal 2: Compare the composite risk scores in 400 LEOs with those in 100 civilians employed by the same collaborating departments using the same platform of risk markers.

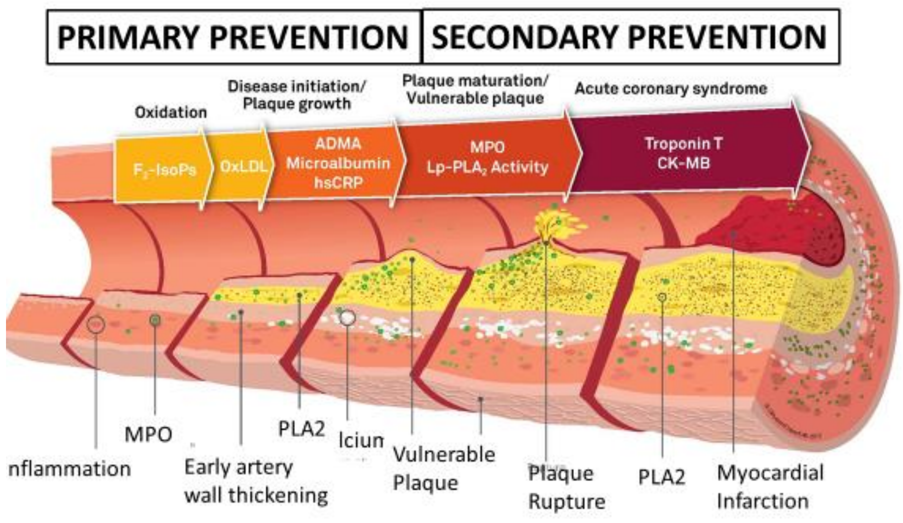

Figure 1. Atherosclerosis is associated with coronary calcium and specific inflammatory biomarkers which can improve identification of high-risk populations such as LEOs.
Source: Cleveland HeartLab

<u>Outcome</u>: Demonstrate that LEOs have a higher burden of ASCVD and through advanced statistical approaches determine the factor(s) that contribute most to the excess risk compared to civilians.

Background: Atherosclerosis begins decades before clinical events occur (Fig. 1). This is a crucial time when the disease is the most susceptible to treatment. Primary prevention through early detection and effective treatment of risk factors has been proven unquestionably to decrease future morbidity and mortality and even reverse the usually relentlessly progressive course of this disease. There is overwhelming evidence from economic evaluations on the cost-effectiveness of interventions for ASCVD prevention versus the cost of treating ASCVD events.[11] These evaluations do not include the broader impact of ASCVD on work productivity and longevity, the cost of replacing workforce personnel, health care costs to employers, or the impact on families and the communities LEOs serve. Classic risk factors for ASCVD are well known: age, gender, family history of premature ASCVD, diabetes mellitus, hypertension, smoking, dyslipidemia, obesity, and physical inactivity. As noted above, primary prevention guidelines rely heavily on population-based 10-year risk prediction models to stratify risk and guide treatment in patients to prevent ASCVD events.[12,13] The data presented in Table 1 underscore the woeful inadequacy of this approach in LEOs. Workplace factors include sudden (and sometimes drastic) elevation in heart rate due to an adrenaline rush (anticipatory, excitation or emotional), physical stress, heat stress, poor dietary or exercise habits in the workplace, poor sleep, restless sleep, disrupted sleep cycles and circadian rhythms, etc., all of which contribute to excess risk in LEOs. **Mental stress-induced MI (MSIMI)**[14,15,16] is an emerging area of research that may help to explain part of the excess risk of mortality and morbidity experienced by LEOs. Greater stress reactivity and poor stress recovery are hypothesized to have an adverse effect on the rates of fatal and nonfatal cardiac events independent of classical risk factors, and even on the severity of coronary artery stenosis as evidenced by angiography in individuals with known CHD however, <u>nothing is known about the impact of MSIMI as an accelerant of atherosclerosis in individuals without diagnosed disease</u>, i.e., in the primary prevention population.

Depression is recognized as a risk factor for ASCVD.[17,18] Antidepressant treatment appears to lessen this effect, as reported in an 8-year follow-up by Lavoie and colleagues.[19] The risk reduction is greater for those *without* ASCVD than for those with ASCVD, underscoring the value of early, preventative treatment. Determining the mechanisms of how mental stress enhances cardiovascular risk is in preliminary stages, and the model will change as more is learned. In some cases, CHD severity has been found to vary by mental stress-induced myocardial ischemia (MSIMI) in men but not women, and MSIMI has a 15% prevalence among men.[20] Thus, the effect of MSIMI on CHD may depend on an interaction with other factors, such as high external stress levels, and the link from mental stress to ASCVD events may be indirect. Accordingly, research into mental stress and cardiovascular health among individuals subject to frequent high stress has unparalleled salience.

Police officers have a **stress pattern** which is often times very different than what is seen in individuals in the civilian sector. In data from more than 4,500 US LEOs from 1984 to 2010, Varvarigou et al reported that the risk of sudden cardiac death was "34-69 times higher during restraints/altercations, 32-51 times higher during pursuits, 20-23 times higher during physical training, and 6-9 times higher during medical/rescue operations."[21] Violanti et al studied the impact of chronic stress on overall health in LEOs and on cardiac vagal control but little is known about the impact of acute stress.[22,23] The inherent nature of policing consists of long periods of routine and sometimes mundane patrol or investigation punctuated by short periods of unexpected rapid elevation in catecholamines and a corresponding increase in heart rate and blood pressure.[14] This is the so-called pattern of policing which is often described as "98% boredom and 2% sheer terror". The episodes of rapid adrenergic surge will occur during and after certain standard police actions to include such events as use of force including the use of non-lethal as well as lethal weapons and high-speed pursuit. During a use of force or high-speed pursuit, several well-defined physiological changes occur in response to the sympathetic activation. There is a rapid increase in heart rate, an increase in blood pressure, repeated Valsalva (increased intrathoracic pressure from breath holding), activation of both the left and right hemispheres of the brain as the officer use both sides of their upper and lower body in offensive and defensive threat mitigation. These intense episodes may go on for several minutes, and in many cases when officers are "fighting for their lives" rapidly convert from aerobic to anaerobic metabolism. This pattern of stress and the resulting catecholamine surge has been well-described. It is also known that MI, which is a result from these described changes in physiology, will often happen hours after the instigating event. Several states recognize this and will consider any firefighter or LEO who suffers a cardiac event while off duty presumptively to have developed the initial stage of their myocardial ischemic event while on duty. We therefore intend to evaluate a subset of officers who have undergone initial baseline screening and who have subsequently been involved in any use of force or high-speed pursuit event. These officers will submit another blood sample within 24 hours of their event.

"Hardening of the arteries" due to **calcification of the coronary arteries** is a term long used to describe progressive atherosclerosis, but only in the past decade has detection of coronary artery calcium (CAC) by CT scanning emerged as a robust predictor of coronary events in primary prevention patients.[24,25] Multiple studies have demonstrated the potential of using CAC in addition to traditional (and nontraditional) risk factors for ASCVD risk prediction.[26] As noted by Greenland et al in their recent review, "coronary artery calcification has emerged as the most predictive single cardiovascular risk marker in asymptomatic persons, capable of adding predictive information beyond the traditional cardiovascular risk factors" noting that it was the most important predictor of CHD and all ASCVD combined outcomes, improving on more than 700 other baseline variables. Recent data from the PESA (Progression of Early Subclinical Atherosclerosis) study reported that half of the subjects with no conventional risk factors had subclinical atherosclerosis as detected by ultrasonography or CAC.[27] The MESA (Multi-Ethnic Study of Atherosclerosis) study demonstrated that a combination of classic risk factor and CAC provided a more accurate estimation of the 10-year CHD risk than either measure alone.[28] CAC has also been shown to be one of several indicators that are elevated in individuals with higher stress responses.[29] Moreover, CAC scanning was cost-effective[30]; it is associated with improved ASCVD risk factor control without increased costs associated with downstream medical testing.[31] The recently released 2019 American College of Cardiology/AHA guidelines on primary prevention of ASCVD incorporate CAC scoring to improve risk stratification.[32,33] CAC screening has been shown not only to facilitate the detection of unknown ASCVD risk but to improve favorable lifestyle changes, medication adherence and is cost-effective (typically less costly than a lipid test).[31] There is no such thing as a “false-positive” CAC score. It is 100% accurate for the presence of coronary atherosclerosis, but the correlation of stenoses detected by using CAC to myocardial ischemia is poor. This is also why a traditional exercise treadmill test is rarely positive in individuals with subclinical CHD – it can only detect coronary artery blockages that are “hemodynamically significant”, i.e., restricting coronary blood flow which typically occurs only in irreversible late-stage disease (Fig. 1). Recently, a method to determine the hemodynamic significance of coronary stenoses has been developed that augments the CAC scan by calculating the coronary artery flow - the fractional flow reserve computerized tomography (FFRCT).[34,35] The addition of FFRCT to CAC scanning allows for a comprehensive anatomic and functional assessment of CHD. FFRCT is comparable in ability to coronary angiography but is noninvasive and like any CAC scan, poses little risk to a patient. This approach will be used in our study if an individual has a CAC score > 75th percentile for age and gender to determine if there is any with hemodynamically significant coronary artery obstructions that would place a LEOs at a much higher risk of non-fatal and fatal ASCVD events.

In addition to blood biomarkers for classic risk factors (diabetes, hyperlipidemia), **blood biomarkers of ASCVD** provide an additional pathway to improve risk-stratification in LEOs. A number of studies have demonstrated that, as with CAC, risk prediction can also be improved by the use of serum biomarkers of atherosclerosis.[36,37] Instead of single biomarkers, a composite risk score may outperform individual ones.[38] We will incorporate a panel of biomarkers[39] which includes: 1) F2-Isoprostanes (F2-IsoPs) which are prostaglandin-like compounds used for measuring oxidative stress; 2) oxidized low density lipoprotein (OxLDL) which is the type of LDL found in plaques; and 3) asymmetric dimethylarginine (ADMA), which is associated with endothelial dysfunction, insulin resistance, hypertension, and subclinical atherosclerosis. We will also incorporate three biomarkers of inflammation including high-Sensitivity C-Reactive Protein (hsCRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), myeloperoxidase (MPO) and high sensitivity cardiac troponin I (hs-cTrI) all of which have has been shown to be predictive of future adverse cardiovascular events in both primary and secondary prevention populations as well as being an indicator of chronic myocardial ischemia in patients with mental stress.[40,41,42,14] HsCRP is a marker of systemic inflammation that can improve risk stratification; however, it is not specific for cardiovascular disease. On the other hand, Lp-PLA2 is a specific marker of vascular inflammation associated with atherosclerosis.[43] A 2008 consensus panel recommended testing Lp-PLA2 as an adjunct to traditional risk factor assessment in individuals with moderate or high risk of cardiovascular disease as defined by Framingham risk scores.[44] The panel found that an Lp-PLA2 level >200 ng/mL indicates an individual's risk is actually higher than that determined using Framingham risk scores, and more intensive therapy is appropriate. While a cardiac troponin level has long been the test used to diagnose a MI, hs-cTrI is also an emerging biomarker for future ASCVD risk and included in our baseline evaluation as well as after use of force or high-speed pursuit event.[41]

3. CAPACITY AND EXPERIENCE:

To date, the authors have collected data on law enforcement officers and civialian in Texas and Colorado with demographics summarized in Table 2:

Table 2: Comparison between LEOs and non-LEOs in pilot data of 2006 subjects (1664 LEOs and 342 non LEOs)

	Law Enforcement Officers	**Non-LEOs**
Male	**1386 (83%)**	**223 (65%)**
Age	**45.8 yrs**	**46.2 yrs**

In addition to classic risk factors were obtained, PLA2, hsCRP and a CAC score. An initial analysis of the pilot data yields several results that motivate our further study. Of the 1664 LEOs in the study, 25.7% had LpPLA2 values out of range while 22.2% of the 342 non-LEOs in the study had values out of range. With respect to the CAC score, 20.6% of the LEOs had a score greater than 0 while 22.5% of non-LEOs had a calcium score over 0. However, the average calcium score for LEOs was 35.1 while non-LEOs had average calcium of 28.1. This indicates that if a LEO has a non-0 score, they are more likely to have a substantially higher score than a non-LEO. A model using a random forest technique was built using the data to predict subjects with PLA2 values that were above normal. Primary variables that were found to be significant James: ?significantly correlated with PLA2?were LDL-C, total cholesterol, small dense LDL-C HDL-C, apolipoprotein-B, triglycerides, and lipoprotein-a. This model had a correct classification of PLA2 Out of Range = “TRUE” 470 times with a misclassification of 122. None of the cases where PLA2 Out of Range = “FALSE” were misclassified. James – not sure what this means and how to express in non stat terms

In summary, our proposed study will encompass a comprehensive approach to identify classic and non-classic risk factors unique to LEOs. The challenge is to identify and treat those individuals at highest risk without incurring excess cost and/or excess treatment in those with minimal risk for future ASCVD. ***When measures of mental stress are coupled with knowledge of lifestyle risk factors, classical risk factors, cardiac calcium scores and biomarker measurements, we believe the combined risk assessment for ASCVD may be superior to all other risk assessments currently in use***. This is a preliminary clinical study to test our hypotheses that: (1) a combined risk score incorporating assessment of lifestyle habits, mental stress, biomarkers and CAC scores (and when elevated, FFRCT) will be more predictive of cardiovascular disease in all types of law enforcement personnel than traditional risk assessments; (2) LEOs have a higher burden of ASCVD than civilians when matched for classic risk factors and this elevation is attributable to mental stress; (3) due to the validity, reliability, specificity, relative cost, and ease of access to these tests, more LEOs will elect to have them done than other tests; and (4) because these tests will identify a disease process sooner than similar (but inferior) tests, life-saving interventions can begin earlier, thus reducing line-of-duty, premature deaths. In addition, when our hypothesis is supported, we may feel that we need additional resources to promote the findings to a wider audience and make strong efforts to encourage changes in procedure and influence a paradigm shift at the national and international levels. If we are unsuccessful in supporting our hypothesis, we will disseminate our "lessons learned" and report the data to further development of the model of how stress impacts cardiovascular health. In either case, we will disseminate our findings in order to improve officer safety, health, and wellness.

4. MANAGEMENT AND IMPLEMENTATION PLAN

We have developed partnerships with four Police Departments in Central Texas (see Letters of Support) and the Texas DPS. We have designed this study to be inclusive. We want every type of police officer involved. We seek to obtain real clinical data (not generated for the purpose of this study) from a variety of subjects and a variety of department types. Although we could compare data from LEOs with normative values from population studies, we have opted to include 100 non-LEOs in the same workplace environment to insure a valid comparison. that there such subjects do represent a typical U.S. population. Our sample size of 400 LEOs was based on CAC distributions in the U.S. population. Based on the excess ASCVD risk in this population, we expect that ~50% of individuals will have a CAC score > 75th percentile for age and gender. If we obtain additional institutional and/or extramural funding, our sample size will be increased. Although the duration of this study is 2 years, we will continue to follow the cohort longitudinally for a minimum of 5 years with the expectation that the program will be sustainable allowing individuals to be followed for up to 10 years or more.

PROJECT MEASUREMENTS

As shown in Fig. 2, demographics, vital signs, blood work and CAC score from a CT scan will be obtained using standardized measurements. If the CAC score is > 75th percentile for age and gender, FFRCT will be obtained to determine if there is an exceedingly high risk of ASCVD mandating evaluation by a Cardiologist. The subject will also complete questionnaires to assess symptoms of depression (PHQ-9), anxiety (Beck Anxiety Inventory), PTSD (PCL-5), alcohol use (AUDIT-C) and general health status (SF-12) on a 10- to 15-minute survey. Every effort will be made to schedule subjects while they are on duty (with the permission of the partner Department). "Patient paperwork" will be limited and/or completed prior to arrival to optimize use of subjects' time which we estimate to be 1-2 hrs. All testing and interpretation will be carried out with strict adherence to equipment, instruments, standards, and procedure requirements.

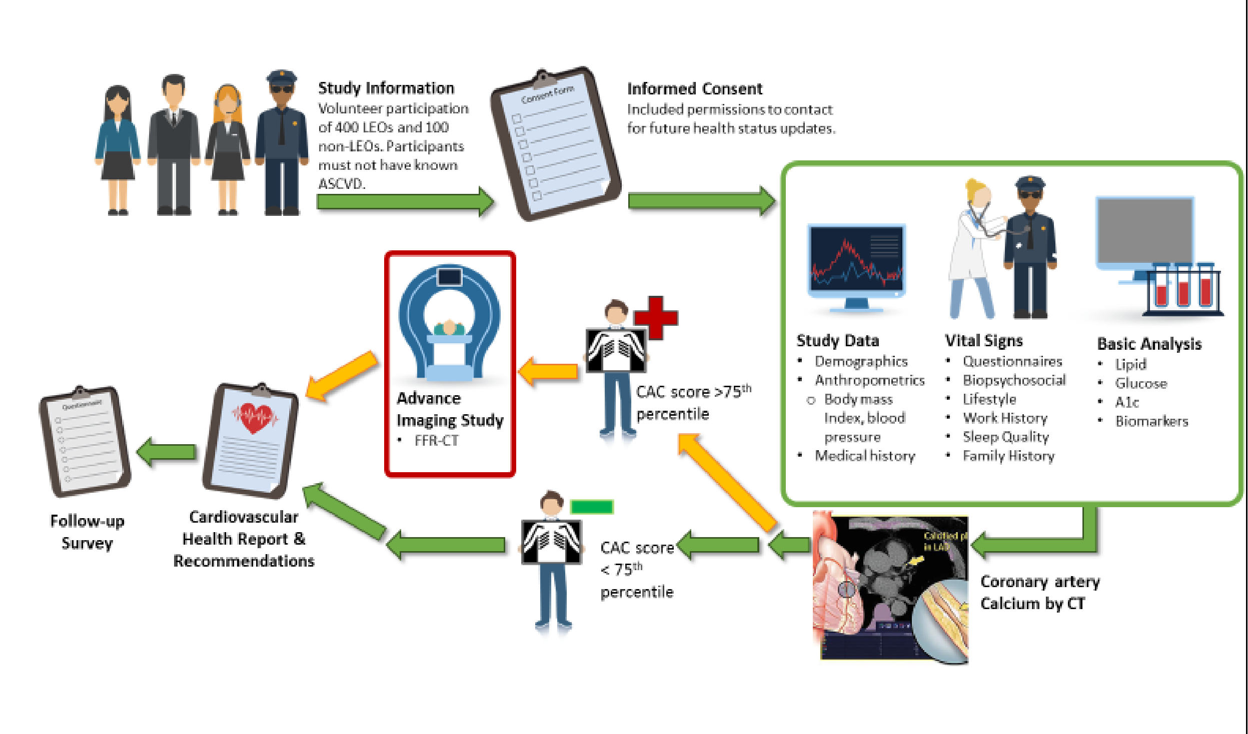

Fig. 2: Schematic of study design. In addition any LEO involved in use of force or high-speed pursuit event will submit a blood sample within 24 hrs to measure biomarkers of stress.

PROJECT ANALYSIS

We intend to compare LEOs risk of coronary artery disease via the combined risk determined by their combined lifestyle score, mental stress score, classic risk factors, CAC score and biomarkers versus civilians in the same workplace. We will survey study subjects annually through questionnaires to assess any self-reported changes in risk factors, overall health and ASASCVD events or death. Although the duration of this study is only 2 years, we expect to obtain internal support to follow the cohort for a minimum of 5 years. A detailed battery of statistical tests will be conducted in consultation with our biostatistician, including factor analysis. ANOVA, MANOVA, and correlation coefficients. Particular attention will be paid to the specificity of Lp-PLA2 and cardiac calcium scores in these occupationally high-risk subjects who > 35 years old. The Principal Investigator (PI) and research team do have the expertise to perform the planned analysis and defend the results in a peer review process. A brief introduction into the capabilities of the research team is provided below, as are biosketches in the appropriate area.

A leading national funding organization for clinical studies, the Patient-Centered Outcomes Research Institute (PCORI) was created by the Affordable Care Act and mandated that all funded research involve patients and other healthcare stakeholders as equitable partners rather than merely research subjects. The PCORI believes that leveraging stakeholder experience and expertise results in research that is more patient-centered, relevant, and useful. PCORI studies have shown that their involvement throughout a study, from planning the study, to conducting the study, and disseminating study findings results in greater use and uptake of research results by patients and other stakeholders within the healthcare community. **Our proposed study therefore will include a stakeholder committee consisting of at least 4 LEOs from each agency participating in the study**.

We propose the following timeline for the study:

STUDY TIMELINE								
Gantt Chart for COPS Study	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8

Complete DUA process	x							
Complete IRB processes	x							
Initiate team meetings schedule	x							
Develop patient education & feedback materials	x	x						
Finalize recruitment plan	x	x						
Semi-monthly team meetings	x	x	x	x	x	x	x	x
Quarterly stakeholder meetings		x		x		x		x
Recruit Subjects, imaging, blood draws, surveys		x	x					
Develop data coding algorithms			x	x	x	x	x	x
Review data for values, missingness and correlations		x	x	x	x	x	x	
Analyze goals 1 and 2						x	x	x
Prepare abstracts and stakeholder reports of progress				x	x	x	x	
Manuscript development						x	x	x
Results dissemination							x	x

5. EFFECTIVENESS, DISSEMINATION AND IMPLEMENTATION

The researchers will work closely with, and frequently update their findings via status reports, to the Federal Emergency Management Agency (FEMA), the International Association of Chiefs of Police, and others. We anticipate using these organizations' existing resources (websites, magazines, and conferences) to support dissemination and implementation throughout the law enforcement community to improve officer safety, awareness, health, and wellness. A final report will be generated and provided to the aforementioned Agencies. In addition, the results will be presented by the researchers at appropriate conferences (both police and medical related). The investigators will also work closely with the national organizations in an effort to disseminate any findings that may result in procedural changes.

REFERENCES

[1] Zimmerman FH. Cardiovascular disease and risk factors in law enforcement personnel: a comprehensive review. Cardiology in review. 2012 Jul 1;20(4):159-66.

[2] Violanti JM, Fekedulegn D, Hartley TA, Andrew ME, Gu JK, Burchfiel CM. Life expectancy in police officers: a comparison with the U.S. general population. Int J Emerg Ment Health. 2013;15(4):217-28.
[3] Ramey SL, Downing NR, Franke WD. Milwaukee police department retirees: cardiovascular disease risk and morbidity among aging law enforcement officers. AAOHN journal. 2009 Nov;57(11):448-53.
[4] Varvarigou V, Farioli A, Korre M, Sato S, Dahabreh IJ, Kales SN. Law enforcement duties and sudden cardiac death among police officers in United States: case distribution study. BMJ. 2014 Nov 18;349:g6534.
[5] Lloyd-Jones DM, Braun LT, Ndumele CE, Smith SC Jr, Sperling LS, Virani SS, Blumenthal RS. Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease. Circulation. 2018 Nov 10.
[6] Myerson M, Coady S, Taylor H, et al. Declining severity of myocardial infarction from 1987 to 2002: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2009; 119:503.
[7] http://www.theiacp.org/Portals/0/documents/pdfs/COSW IACPLineofDutyFactsheet.pdf
[8] https://www.odmp.org/search/year?year=2014
[9] Wanahita N, See JL, Giedd KN, Friedmann P, Somekh NN, Bergmann SR. No evidence of increased prevalence of premature coronary artery disease in New York City police officers as predicted by coronary artery calcium scoring. Journal of occupational and environmental medicine. 2010 Jun 1;52(6):661-5.
[10] Havakuk O, Zukerman N, Flint N, Sadeh B, Margolis G, Konigstein M, Keren G, Aviram G, Shmilovich H. Shift Work and the Risk of Coronary Artery Disease: A Cardiac Computed Tomography Angiography Study. Cardiology. 2018;139(1):11-16.
[11] Barton P, Andronis L, Briggs A, McPherson K, Capewell S. Effectiveness and cost effectiveness of cardiovascular disease prevention in whole populations: modelling study. BMJ. 2011 Jul 28;343:d4044.
[12] Arnett DK, Blumenthal RS, Albert MA, Michos ED, Buroker AB, Miedema MD, Goldberger ZD, Muñoz D, Hahn EJ, Smith SC, Himmelfarb CD. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. Journal of the American College of Cardiology. 2019 Mar 17:26029.
[13] Motamed N, Rabiee B, Perumal D, Poustchi H, Miresmail SJ, Farahani B, Maadi M, Saeedian FS, Ajdarkosh H, Khonsari MR, Hemasi GR, Zamani F. Comparison of cardiovascular risk assessment tools and their guidelines in evaluation of 10-year CVD risk and preventive recommendations: A population based study. Int J Cardiol. 2017 Feb 1;228:52-57.
[14] Hammadah M, Alkhoder A, Al Mheid I, Wilmot K, Isakadze N, Abdulhadi N, Chou D, Obideen M, O'Neal WT, Sullivan S, Tahhan AS, Kelli HM, Ramadan R, Pimple P, Sandesara P, Shah AJ, Ward L, Ko YA, Sun Y, Uphoff I, Pearce B, Garcia EV, Kutner M, Bremner JD, Esteves F, Sheps DS, Raggi P, Vaccarino V, Quyyumi AA. Hemodynamic, catecholamine, vasomotor and vascular responses: Determinants of myocardial ischemia during mental stress. Int J Cardiol. 2017 Sep 15;243:47-53.
[15] Ramadan R, Sheps D, Esteves F, Zafari AM, Bremner JD, Vaccarino V, Quyyumi AA. Myocardial ischemia during mental stress: role of coronary artery disease burden and vasomotion. J Am Heart Assoc. 2013 Oct 21;2(5):e000321.
[16] Wei J, Rooks C, Ramadan R, Shah AJ, Bremner JD, Quyyumi AA, Kutner M, Vaccarino V. Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. Am J Cardiol. 2014 Jul 15;114(2):187-92.

[17] Zhang Z, Jackson S, Merritt R, Gillespie C, Yang Q. Association between cardiovascular health metrics and depression among US adults: National Health and Nutrition Examination Survey, 2007–2014. Annals of epidemiology. 2019 Jan 2.
[18] Penninx BW. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. Neuroscience & Biobehavioral Reviews. 2017 Mar 1;74:277-86.
[19] Lavoie KL, Paine NJ, Pelletier R, Arsenault A, Diodati JG, Campbell TS, Pilote L, Bacon SL. Relationship between antidepressant therapy and risk for cardiovascular events in patients with and without cardiovascular disease. Health Psychology. 2018 Nov;37(11):989.
[20] Almuwaqqat Z, Sullivan S, Hammadah M, Lima BB, Shah AJ, Abdelhadi N, Fang S, Wilmot K, Al Mheid I, Bremner JD, Garcia E, Nye JA, Elon L, Li L, O'Neal WT, Raggi P, Quyyumi AA, Vaccarino V. Sex-Specific Association Between Coronary Artery Disease Severity and Myocardial Ischemia Induced by Mental Stress. Psychosom Med. 2019 Jan;81(1):57-66.
[21] Varvarigou V, Farioli A, Korre M, Sato S, Dahabreh IJ, Kales SN. Law enforcement duties and sudden cardiac death among police officers in United States: case distribution study. Bmj. 2014 Nov 18;349:g6534.
[22] Violanti JM, Ma CC, Mnatsakanova A, Fekedulegn D, Hartley TA, Gu JK, Andrew ME. Associations Between Police Work Stressors and Posttraumatic Stress Disorder Symptoms: Examining the Moderating Effects of Coping. J Police Crim Psychol. 2018 Sep;33(3):271-282.
[23] Andrew ME, Violanti JM, Gu JK, Fekedulegn D, Li S, Hartley TA, Charles LE, Mnatsakanova A, Miller DB, Burchfiel CM. Police work stressors and cardiac vagal control. *Am J Hum Biol*. 2017 Sep 10;29(5):10.
[24] Hecht HS. Coronary Artery Calcium: From the Power of 0 to >1,000. JACC Cardiovasc Imaging. 2019 Apr 10. pii: S1936-878X(19)30276-1.
[25] Hecht HS. Coronary artery calcium scanning: past, present, and future. JACC Cardiovasc Imaging. 2015 May;8(5):579-596.
[26] Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary calcium score and cardiovascular risk. Journal of the American College of Cardiology. 2018 Jul 24;72(4):434-47.
[27] Fernández-Friera L, Fuster V, López-Melgar B,et al. Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. J Am Coll Cardiol 2017;
70:2979–91.
[28] McClelland RL, Jorgensen NW, Budoff M, Blaha MJ, Post WS, Kronmal RA, Bild DE, Shea S, Liu K, Watson KE, Folsom AR, Khera A, Ayers C, Mahabadi AA, Lehmann N, Jöckel KH, Moebus S, Carr JJ, Erbel R, Burke GL. 10-Year Coronary Heart Disease Risk Prediction Using Coronary Artery Calcium and Traditional Risk Factors: Derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) With Validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). J Am Coll Cardiol. 2015 Oct 13;66(15):1643-53.
[29] Chida Y, Steptoe A. Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: a meta-analysis of prospective evidence. Hypertension. 2010 Apr;55(4):1026-32.
[30] Roberts ET, Horne A, Martin SS, Blaha MJ, Blankstein R, Budoff MJ, Sibley C, Polak JF, Frick KD, Blumenthal RS, Nasir K. Cost-effectiveness of coronary artery calcium testing for coronary heart and cardiovascular disease risk prediction to guide statin allocation: the Multi-Ethnic Study of Atherosclerosis (MESA). PLoS One. 2015 Mar 18;10(3):e0116377.
[31] Rozanski A, Gransar H, Shaw LJ, Kim J, Miranda-Peats L, Wong ND, Rana JS, Orakzai R, Hayes SW, Friedman JD, Thomson LE. Impact of coronary artery calcium scanning on coronary

risk factors and downstream testing: the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. Journal of the American College of Cardiology. 2011 Apr 12;57(15):1622-32.
[32] Cardoso R, Nasir K, Blumenthal RS, Blaha MJ. Selective Use of Coronary Artery Calcium Testing for Shared Decision Making: Guideline Endorsed and Ready for Prime Time. Annals of internal medicine. 2019 Feb 19;170(4):262-3.
[33] Arnett DK, Blumenthal RS, Albert MA, Michos ED, Buroker AB, Miedema MD, Goldberger ZD, Muñoz D, Hahn EJ, Smith SC, Himmelfarb CD. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. Journal of the American College of Cardiology. 2019 Mar 17:26029.
[34] Douglas PS, Pontone G, Hlatky MA, Patel MR, Norgaard BL, Byrne RA, Curzen N, Purcell I, Gutberlet M, Rioufol G, Hink U. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFRCT: outcome and resource impacts study. European heart journal. 2015 Sep 1;36(47):3359-67.
[35] Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, Jensen JM, Mauri L, De Bruyne B, Bezerra H, Osawa K. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). Journal of the American College of Cardiology. 2014 Apr 1;63(12):1145-55.
[36] Wang J, Tan GJ, Han LN, Bai YY, He M, Liu HB. Novel biomarkers for cardiovascular risk prediction. J Geriatr Cardiol. 2017 Feb;14(2):135-150.
[37] Agarwala A, Virani S, Couper D, Chambless L, Boerwinkle E, Astor BC, Hoogeveen RC, Coresh J, Sharrett AR, Folsom AR, Mosley T, Ballantyne CM, Nambi V. Biomarkers and degree of atherosclerosis are independently associated with incident atherosclerotic cardiovascular disease in a primary prevention cohort: The ARIC study. Atherosclerosis. 2016 Oct;253:156-163.
[38] Niiranen TJ, Vasan RS. Epidemiology of cardiovascular disease: recent novel outlooks on risk factors and clinical approaches. *Expert Rev Cardiovasc Ther*. 2016 Jul;14(7):855-69. doi: 10.1080/14779072.2016.1176528. Epub 2016 Apr 25.
[39] Agarwala A, Virani S, Couper D, Chambless L, Boerwinkle E, Astor BC, Hoogeveen RC, Coresh J, Sharrett AR, Folsom AR, Mosley T, Ballantyne CM, Nambi V. Biomarkers and degree of atherosclerosis are independently associated with incident atherosclerotic cardiovascular disease in a primary prevention cohort: The ARIC study. *Atherosclerosis*. 2016 Oct;253:156-163.
[40] Jia X, Sun W, Hoogeveen RC, Nambi V, Matsushita K, Folsom AR, Heiss G, Couper DJ, Solomon SD, Boerwinkle E, Shah A, Selvin E, de Lemos JA, Ballantyne CM. High-Sensitivity Troponin I and Incident Coronary Events, Stroke, Heart Failure Hospitalization, and Mortality in the ARIC Study. Circulation. 2019 Apr 29.
[41] Zhu K, Knuiman M, Divitini M, Murray K, Lim EM, St John A, Walsh JP, Hung J. High-sensitivity cardiac troponin I and risk of cardiovascular disease in an Australianpopulation-based cohort. Heart. 2018 Jun;104(11):895-903.
[42] Jansen H, Jänsch A, Breitling LP, Hoppe L, Dallmeier D, Schmucker R, Brenner H, Koenig W, Rothenbacher D. Hs-cTroponins for the prediction of recurrent cardiovascular events in patients with established CHD - A comparative analysis from the KAROLA study. Int J Cardiol. 2018 Jan 1;250:247-252.

[43] Jenny NS, Solomon C, Cushman M, et al. Lipoprotein-associated phospholipase A(2) (Lp-LA(2)) and risk of cardiovascular disease in older adults: Results from the Cardiovascular Health Study. Atherosclerosis. 2010;209:528-532.

[44] Tsimikas S, Willeit J, Knoflach M, et al. Lipoprotein-associated phospholipase A2 activity, ferritin levels, metabolic syndrome, and 10-year cardiovascular and non-cardiovascular mortality: Results from the Bruneck study. Eur Heart J. 2009;30:107-115