Rationale and Design of the Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD (WARRIOR) Trial

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ABSTRACT

BACKGROUND: Approximately half of all women with anginal symptoms and/or signs of ischemia and no obstructive coronary artery disease (INOCA) referred for coronary angiography have elevated risk for major adverse cardiac events (MACE), poor quality of life (QoL) and resource consumption. Yet, guidelines focus on symptom management while clinical practice typically advocates only reassurance. Pilot studies of INOCA subjects suggest benefit with intensive medical therapy (IMT) that includes high-intensity statins and angiotensin converting enzyme inhibitors (ACE-I) or receptor blockers (ARB) to provide the rationale for a randomized pragmatic trial to limit MACE.

METHODS: The Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD (WARRIOR) is a multicenter, prospective, randomized, blinded outcome evaluation (PROBE design) of a pragmatic strategy of IMT vs. usual care (UC) in 4,422 symptomatic women with INOCA (NCT 03417388) in ~70 US sites. The hypothesis is that IMT will reduce the primary outcome of first occurrence of MACE by 20% vs. UC at ~2.5 year followup. Secondary outcomes include QoL, time to return to "duty"/work, healthcare utilization, angina, cardiovascular death and individual primary outcome components over 3 years follow-up. The study utilizes web-based data capture, e-consents, single IRB and centralized pharmacy distribution of strategy medications directly to patients' homes to reduce site and patient burden. A biorepository will collect blood samples to assess potential mechanisms.

CONCLUSIONS: The results of this trial will provide important data necessary to inform guidelines regarding how best to manage this growing and challenging population of women with INOCA.

BACKGROUND

Cardiovascular disease (CVD), the leading cause of death in American women (~400,000 annually), is predominantly ischemic heart disease.[1-3] Risk factors (hypertension, diabetes, dyslipidemia) combined with obesity, overweight and/or low fitness are prevalent in American women.[2] Among women with symptoms and/or signs of ischemia undergoing coronary angiography, ~40-65% of have no obstructive coronary artery disease (CAD), now termed ischemia and no obstructive CAD (INOCA).[4] Previously considered "low risk"[5,6], evidence now documents a higher than expected risk for major adverse cardiac events (MACE, as *death*, *myocardial infarction* [MI], *stroke*, or *hospitalization* for chest pain or heart failure [HF]) vs age and sex-matched asymptomatic subjects.[7-12] Although mechanisms are incompletely understood, coronary endothelial and/or microvascular dysfunction, diffuse non-obstructive atherosclerosis, and myocardial ischemia have each been implicated.[13] Persisting angina, high risk factor burden, and stress testing ischemia identify those at highest MACE risk.[14] Estimates indicate ~4 million Americans (>60% women) have INOCA, with many incurring healthcare costs similar to those of obstructive CAD.[10,15] This preponderance of INOCA burden in women, prior work of the NHLBI-sponsored Women's Ischemia Syndrome Evaluation which specified the exclusive study of women, the Congressionally Directed Medical Research Program "Topic Area" of women's heart disease based on the increasing representation of women in the active duty military (16.5%) and the large number of female military dependents who receive healthcare in the military healthcare system provided the directive for this trial to focus recruitment in women.

Rationale for the WARRIOR Trial

Prior, small sample-size, short-term pilot studies in these subjects suggest that intensive medical therapy (IMT), using high-intensity statins in combination with angiotensin-converting enzyme inhibitors (ACE-Is) or receptor blockers (ARBs) if intolerant, at maximally tolerated doses, improved angina, stress test results, and/or myocardial perfusion with beneficial coronary endothelial and coronary microvascular effects.[16,17] However, appropriately-designed (well-powered, randomized, longer-term) outcome trials, investigating therapeutic strategies, have not been performed and Class I treatment guidelines are lacking for this group.[17] Thus, current management focuses on symptom control and primary risk reduction (e.g., usual care [UC]), while primary prevention risk scores substantially underestimate risk,[18] and prevailing clinical practice centers

largely on reassurance and dismissal from subspecialty care. We believe this is not appropriate because symptoms frequently recur, limiting function, contributing to healthcare resource consumption, with relatively higher MACE rates versus similar asymptomatic subjects.[7,15,19]

METHODS

Trial Overview and Objectives

The Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD (WARRIOR) trial is a multicenter, prospective, randomized, blinded outcome evaluation (PROBE design) using a pragmatic strategy of provision of IMT study drug vs. UC defined as routine clinical care, allocated 1:1, in 4,422 clinically stable women with chest pain but no obstructive CAD (NCT 03417388) to address the lack of Class I treatment guidelines. The hypothesis is an IMT strategy of potent statin plus ACE-I (or ARB) and low dose aspirin will reduce MACE vs. UC. The trial design is illustrated in **Figure 1**.

Support

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The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Patient Identification

Enrolled women will be clinically stable, with angina or equivalent symptoms of sufficient severity to seek, or have sought, referral for cardiac catheterization, or coronary angiography or coronary CT angiogram within the previous 5 years.

Inclusion criteria

- Signs and symptoms of suspected ischemia prompting referral for further evaluation by cardiac catheterization, or coronary angiogram or coronary CT angiogram within 5 years from consent
- Willing to provide written informed consent
- Age ≥18 yrs
- Non-obstructive CAD defined as 0 to 49% diameter reduction of a major epicardial vessel or a FFR>0.80

Exclusion criteria

- History of noncompliance (with medical therapy, protocol, or follow-up)
- History of non-ischemic dilated or hypertrophic cardiomyopathy
- Documented acute coronary syndrome within previous 30 days
- LVEF <40%, NYHA HF class III-IV, or hospitalization for HFrEF within 180 days
- Stroke within previous 180 days or intracranial hemorrhage at any time
- End-stage renal disease, on dialysis, or estimated glomerular filtration rate (eGFR) <30 ml/min
- Severe valvular disease or likely to require surgery/TAVR within 3 years
- Life expectancy <3 yrs. due to non-cardiovascular comorbidity

- Enrolled in a competing clinical trial
- Prior intolerance to both an ACE-I and ARB
- If intolerant to a statin unless taking a PCSK9 as a statin replacement by their clinical provider
- Pregnancy (If they have not gone through menopause, had a hysterectomy, oophorectomy, or sterilization such as tubal ligation procedure, all pre-menopausal females must have negative urine pregnancy test if randomized to IMT before study drugs are prescribed)

A summary of the demographics of the initial 150 women enrolled appears in **Table 1**.

Outcomes

The *primary outcome* is MACE that includes time to first occurrence of all-cause death, non-fatal MI, non-fatal stroke, or hospitalization for chest pain or HF at ~2.5 years. *Secondary outcomes* include: 1) components of the primary outcome, 2) quality of life (QoL) using the following questionnaires: EQ-5D-3L, Duke Activity Status Inventory, Health, KCCQ-English, Modified Morisky Medicine Scale, PACE, Seattle Angina Questionnaire (SAQ)[20,21], PTSD Scale-PCL-5[22], and Beck Depression metrics[23], as well as cardiovascular death; 3) time to return to work/"duty"; and 4) healthcare utilization and cost-effectiveness. Outcomes are ascertained at the site, with source documentation transmitted to and adjudicated by the CEC.

Components (e.g., events) comprising the MACE outcome were selected because these are the events observed most frequently in this population that are clinically important, disabling and costly. All events will be adjudicated by an experienced Clinical Events Committee (CEC) according to objective defined criteria, masked to treatment assignment clues, and not otherwise involved in the trial. A uniform definition of events for use in clinical trials is under development by the FDA. Trial criteria will be consistent with these.

All-cause death will be used, because: 1) cardiovascular death is insensitive in this population with non-obstructive CAD since death is less likely attributed to cardiovascular causes when no obstructive CAD is documented; 2) all-cause death is resistant to ascertainment bias in this unblinded trial. Cardiovascular death will be defined broadly to include both definite and possible cardiovascular death (all deaths except those with definite non-cardiovascular cause, e.g., cancer, witnessed trauma, homicide ,etc.). The MI definition follows the "Fourth Universal Definition of Myocardial Infarction" requiring a rise and/or fall of cardiac biomarker values,

with at least one value >99th percentile upper reference limit, and the preferred biomarker is cardiac troponin. In addition, at least one supportive criterion should be met. Stroke was chosen as part of MACE as WISE documented a relatively high stroke rate in women with ischemia and non-obstructive CAD.[7,10,24,25] Furthermore, stroke is an established part of the "continuum" of atherosclerotic CVD. The stroke definition is new onset neurological defect of central origin confirmed by brain imaging (computed tomography or magnetic resonance imaging) evidence of cerebral infarction or intracerebral hemorrhage.

Selection and definition of hospitalization for chest pain. Because admission for chest pain is frequent in this population due to diagnostic uncertainly and recurrent chest pain with evidence of ischemia, we included any hospitalization for chest pain, rather than an only unstable angina or acute coronary syndrome. There are two reasons for this: 1) hospitalization is burdensome, has a risk of recurrent procedures, consumes healthcare resources, and is relevant to both the physician and patient; 2) implementation of IMT may cause anxiety and trigger chest pain hospitalization in the short-term, therefore inclusion is again relevant for guideline advisement.

Selection and definition of hospitalization for HF. Hospitalization for HF was chosen because we observed a relatively high incidence of new-onset HF in the WISE follow-up[7], a finding confirmed by others[26,27] in larger, independent cohorts with ischemia and non-obstructive CAD. Reports using CTA[28] have also confirmed that adverse outcomes are increased with non-obstructive CAD. We and others observed normal ejection fractions, supporting a link between the growing HF epidemic and preserved systolic function.[27,29] Established objective criteria for angina and HF hospitalizations were used (*Supplement 1*).

QOL and Health-related costs, determined using our prior methods in this population[15], was selected because of the elevated health resource consumption of this population, comparable to obstructive CAD. Details regarding the QoL and Health-related Cost methods are in *Supplement 2*.

Estimated MACE Rates

Multiple reports document elevated MACE rates for subjects with INOCA.[7,9,10,24,25,30-35] Specifically, INOCA patients with ischemia on noninvasive testing[7,9,10,14,26,30,35-38] (**Table 2**) have 3-year MACE rates ranging from 20-34%, predominantly composed of hospitalizations for angina and/or HF, with health resource utilization that rivals many with obstructive CAD.[7,9,10,24,25,31] Hospitalizations for chest pain or HF occur frequently[39], lead

to repeated testing, and are costly. Therefore MACE, including hospitalization for chest pain or HF, is the primary outcome of this trial.

Estimated Risk Reduction

The SPRINT trial observed 25% MACE reduction and 27% all-cause mortality reduction in high-risk patients by targeting a systolic blood pressure (BP) <120 vs. <140 mm Hg[40], although SPRINT used an unattended, automated BP measurement where an SBP ~120 is estimated similar to a usual office SBP of ~130 mm Hg. Protocolized medication with express mail delivery in INVEST achieved superior BP control (~72%,<140/90 mmHg) in obstructive CAD patients (e.g. complicated hypertension)[41] as angina and QoL improved in most patients (>70% of those that used ACE-Is).[42] The Asymptomatic Cardiac Ischemic Pilot also observed angina management efficacy[43], where ~40% of CAD patients randomized to titrated medical anti-anginal arms were "ischemia-free" with improved exercise time to angina and daily-life ischemic electrocardiographic changes and clinical outcomes. Intensive vs. less intensive statin therapy produced 40-50 mg/dl LDL-C group differences[44,45] resulting in ~1% reduction in death/MI for every 2 mg/dl lipid lowering, or 20-25% effect size.[44] In the WISE original cohort we observed ~30% 3-year mortality difference (6 vs 4%) associated with intensive hypertension treatment[46], and improved coronary flow reserve and (SAQ) angina reduction with intensive ACE-I therapy.[47] Drug combinations (e.g., statins plus ACE-I) appear to amplify benefits.[48] These considerations support the proposed MACE reduction of 25% as achievable.

Study Organization

The Data Coordinating Center (DCC) focused initially on OneFlorida Clinical Research Consortium sites, a PCOR.net Clinical Data Research Network (CDRN) housing data from >15 million lives to help identify participants using a computable phenotype, and research-ready practices. Additionally, multiple private and academic institutions from across the US were selected to provide 75-100 clinical sites. All sites are connected via a web-based data capture system and a single IRB and the Statistical Coordinating Center.

Data Capture Platform and IMT Distribution

An integrated web-based, real-time modified REDCap data capture system is used to facilitate recruitment, enrollment, randomization and outcome collection. The system includes an e-prescription/express mail pharmacy[41] that enables rapid prescription of IMT medications (atorvastatin or rosuvastatin) and ACE-I (ramipril) (or ARB [losartan]) delivered in 3-4 days. Providing strategy medication expediently and at no-cost yields superior medication management using structured medication algorithms.[41] (Specific details and algorithms, *Supplement 3*.)

The study was initiated at 10 sites with the first enrollment on February 9, 2018, to test the platform and prescribing system. After enrolling 150 women, modifications were made based on site feedback, the system was finalized and remaining sites were contracted.

There will be 70-100 US sites, including VAMC/military and OneFlorida CDRN, and clinical sites across the US. Web-based real-time data entry and management is used for site selection, screening, patient eligibility confirmation, enrollment and randomization. After randomization, study drugs are delivered by express mail to IMT patients or local pharmacies. Participants are recruited from screened women with clinically stable symptoms suspected to be ischemic in origin with no obstructive CAD (>50% diameter reduction or FFR >0.80) by invasive coronary angiography or coronary computed tomographic angiogram (CTA) within the prior 5 years. They are subsequently randomized to either the IMT or UC strategies (**Figure 2**). The IMT strategy used generic medications previously suggested effective for improving angina, stress test results, myocardial perfusion, and coronary flow reserve in intermediate-size trials in this population.[47,49,50] Aspirin is provided as a component of IMT for women without contraindications. Both strategies receive Lifestyle Counseling (*Supplement 4*), with the same visit schedule and "face-time" with site staff to limit bias. Events are adjudicated by an experienced Clinical Events Committee (CEC) according to objective criteria, and masked to all treatment assignment clues.

Study Follow Up

Participants undergo eligibility screening, informed consent and randomization procedures. Follow-up occurs at 3, 6, and 12 months following randomization and every 6 months thereafter, with clinic visit follow-up and other testing as described below (**Table 3**). Clinic, video or phone visits are required for assessment and

ordering of IMT medications. Information about all healthcare utilization (doctor visits, emergency department, hospitalizations, testing) as well as medical status, medication, and clinically performed blood pressure are collected at baseline and every study visit. Blood lipids are collected annually. The PACE Lifestyle Intervention is initiated at the initial visit and reinforcement provided at each follow up visit.

If a scheduled research visit is not possible, to ensure follow-up, other forms of contact are used (telephone, video, email, communication) from a personal physician, other health professional, and/or review of electronic health record or public records. After the first year, participants are followed every 6 months until the end of the trial, at which time sites will be notified to perform a closeout visit. At these long-term follow-up contacts, information on current health and medications, and interval hospitalizations will be collected. If any adverse events are noted, the participant is asked to complete a release of medical record form so the records can be obtained to accurately record what happened and report the de-identified information to appropriate committees, study sponsor, and IRB.

Impact of COVID-19

During the recruitment phase of the trial, the COVID-19 pandemic resulted in the halt of recruitment at all sites due to social distancing recommendations, and temporary cessation of all non-essential research activities at most clinical sites. On March 26, 2020, sites were advised to temporarily halt clinic visits and to utilize available telephone/video clinic visit option for all visits, and blood draws were deferred. Sites were encouraged to continue screening activity during this period, all patients continued on randomized treatment arms without interruption and the REDCap platform remained open. Recruitment site reopening has varied from site to site/region to region. Because of concern for a possible COVID-19 resurgence, the protocol was modified to allow for virtual enrollment, randomization, and follow up.

Due to the extended length of the pandemic, now approaching a year, short- and long-term impacts of the pandemic on active clinical trials like WARRIOR have yet to be fully realized. The crowding of emergency rooms, the fear of going to a hospital as well the restriction of hospital admissions and semi elective procedures such as cardiac catheterizations are all factors that have resulted in a significant reduction in admissions for acute coronary syndrome of up to 48%[51,52] and at the same time cardiovascular mortality

increased significantly in the early months of the pandemic.[53,54] These changes may have unexpected consequences on adverse event occurrences that are primary outcomes for ongoing clinical trials.

Statistical Considerations

Data Management and Analyses Plan

All major comparisons between randomized groups will be according to "intent-to-treat" (ITT) principle, that is, participants will be analyzed (and outcomes attributed) according to randomized strategy, regardless of subsequent treatment. Statistical comparisons will be performed using two-sided significance tests. Subjects experiencing non-fatal events among those in the primary or secondary outcomes are expected to remain in the trial and in their assigned treatment strategy until the trial ends.

Analysis of Study Primary Outcome: MACE-Rate

Statistical comparison of the randomized treatment strategies, with respect to the primary outcome, will be "time-to-event" analysis based on time from randomization to first occurrence of any of the following: all-cause death, non-fatal MI, non-fatal stroke/transient ischemic attack (TIA), or hospitalization for either angina or HF. The log rank test[55] will be used for this comparison. Although the power analysis required the exponential assumption, the actual statistical test is free of assumptions, as the null hypothesis is that the survival distributions for the two strategies are the same, and therefore the null hazard ratio is 1.00 (proportional hazards). Because of anticipated contamination, proportional hazards will not literally hold under a non-local alternative hypothesis. Hence the descriptive distributions for MACE and other outcomes will utilize Kaplan-Meier analysis with 95% CIs for the difference in event rates, with primary focus on 3-year MACE-rates. To avoid unprovable assumptions, we shall utilize the log rank test to compare MACE outcomes in pre-specified subsets of interest and to compare other outcomes.

Ascertainment of Events

All participants with suspected MACE comprising the primary and secondary outcomes will be reported and classified by site investigator to the DCC with supporting documents. Once complete, event documents

are transmitted for adjudication to the CEC. Only CEC confirmed events will be included in primary and secondary outcomes analysis.

Analysis of Study Secondary Outcomes.

Secondary outcomes include: (1) Health status measured by the SAQ Summary, Angina Frequency, Physical Limitation and QoL Scores; (2) first occurrence of cardiovascular death, non-fatal MI or non-fatal stroke/TIA; (3) first occurrence of cardiovascular death, non-fatal MI, resuscitated cardiac arrest or hospitalization for angina or HF; (4) all-cause mortality; (5) cardiovascular death; (6) total MI [fatal plus non-fatal]; (7) resuscitated cardiac arrest plus all-cause death; (8) hospitalization for angina; (9) hospitalization for HF; (10) total stroke/TIA [fatal plus non-fatal]; (11) first occurrence of cardiovascular death, non-fatal MI, stroke/TIA, resuscitated cardiac arrest, or hospitalization for angina or HF; and (12) health resource utilization, (13) estimated costs, (14) time away from duty/work, and (15) cost effectiveness. Variables (2)-(8), (10), and (11) will be analyzed per MACE.

The total number of hospitalizations for angina (variable 8), as well as HF (variable 9) within each treatment group (as randomized) will be divided by total time at risk for the treatment group to obtain an observed hazard rate for each treatment group. This is a ratio estimate and we employ natural logs and the delta method to provide a standard error in the log scale. The difference between these two estimates in the log scale is then obtained with 95% confidence limits (CIs) in the log scale and a P-value. By exponentiation (antilog) we can obtain a 95% confidence interval for the hazard ratio. This analysis is non-parametric, but subject to slight bias due to competing risks.

The priority QoL analysis will be as follows. Because of variable follow-up time, we shall employ the QoL scores at a fixed times of approximately 6, 12 and 24 months after randomization. We use rank methods as follows: Deaths in the first 2-years will share the worst ranks, those with non-fatal MACE in the first 2-years will share the next to worst, while those MACE-free for 2-years will be ranked according to the QoL scale being evaluated. Comparisons will be made via a Wilcoxon test, while the effect size estimates and CIs will be constructed for the generalized odds ratio (estimated by ratio of concordant to discordant pairs). To avoid use of QoL scores as anything but ordinal, we shall not subtract baseline scores from the 2-year QoL score.

Parametric tertiary QoL comparisons will also adhere to the ITT principle. For each QoL measure examined, data analysis will proceed in several stages. We will examine changes over time from baseline and identify the major determinants of those changes using regression analysis. First, we will pre-specify the angina frequency and QoL scales from the SAQ as the CAD-specific measures of primary interest and assign all other comparisons to a secondary (descriptive) status. Second, we will employ a mixed-model methodology that makes use of all available QoL data at each study assessment to model the time profile (fixed effect). Using the fitted model, we can estimate the overall difference in the QoL measures as well as test the global hypothesis of no difference over time. We can also estimate the difference in the areas under the two QoL treatment curves (and test the hypothesis of no difference, on average).

Unambiguous operational definitions of each study outcome will be documented in the CEC Charter plan before performing unblinded analysis. Data collection instruments and the adjudication process will allow construction of alternative MI definitions, if needed.

Sensitivity Analysis

Although the log rank test is assumption-free for testing the null hypothesis that two survival distributions are the same, the hazard ratio estimates rely on approximate proportional hazards. Therefore, we shall augment the results using 3-year Kaplan-Meier estimates to obtain point and 95% CI estimates for event-free rates and differences between the treatments for all time to event results. Unfortunately, we will not have appropriate data to perform a time-dependent covariate analysis on differences for “as treated”, as time of contamination will not be available in a substantial number of subjects.

Contingency Plan for Insufficient Primary Outcome Events

The projected MACE rate of 25% at 3 years for the primary outcome in UC participants was based on multiple sources. Although we believe the projected rate is reasonably conservative, an acceptably precise estimate of the true event rate of the primary outcome will not be known until substantial participant recruitment and follow-up have accrued. We provided power analysis in **Table 4**, indicating that the study is viable for 3-year UC rates as low as 15% (scenario 3) and conclude that the study is sensitive to reasonably tight, but clinically important effect sizes for this lower rate.

Analysis of accrual and contamination at 6-month intervals will determine if action is needed. Further, if contamination is projected to be >20% at 3 years (7.2%/y actuarial), we will conduct a conditional power analysis to determine if an increase in accrual is indicated. At each DSMB meeting after the study has opened to accrual, we shall monitor actual vs. projected accrual and contamination vs. expected contamination. Should accrual be below projections or contamination be above projections, we shall recruit additional sites (remaining within budget by shifting some resources from low enrolling sites) and report on new projections at the next DSMB meeting, where a recommendation to continue as is, continue with conditions, or terminate the trial would occur.

Contingency Plan for Insufficient Enrollment

Projected enrollment of 4,422 over 2-3 years is based on multiple data sources, including use of the OneFlorida CDRN and electronic health record screening for eligibility. Given that use of CDRNs for large outcome trial recruitment with pragmatic randomization in treating physicians' offices is novel, we have developed contingency plans for insufficient enrollment (*Supplement 5*). With the unanticipated COVID-19 temporary halt, and potential for a secondary rise in cases, these become critically important.

Health Economics Analysis, Life Expectancy Estimation and Cost-Effectiveness

Costs of each treatment arm (IMT vs. UC) will be compared and an incremental cost-effectiveness analysis[56] will be conducted. We are collecting the EQ%D, allowing calculation of utility and thus QALYs. For participants alive at the end of the follow-up period, it will be assumed that the relationship between observed age- and female-specific mortality rates calculated from participants expected corresponding mortality rates from US-Life Table would continue to apply to surviving patients in the future.[57] For participants with non-fatal MI and/or stroke events during the follow-up, additional age- and sex-specific life expectancy will be further adjusted from Framingham Heart Study and added to results obtained in the previous step.[58] Cost-effectiveness is expressed as the incremental cost effectiveness ratio, the difference in costs of the two treatments divided by the difference in QALY adjusted life years gained. QALYs will be measured as the integral sum of utility measured by the EQ-5D and survival. Because the distribution of the differences for cost and effectiveness is typically skewed (non-normally distributed), the distribution of the differences was

estimated by bootstrap analysis.[59] Probabilistic sensitivity analysis will be conducted to assess the impact of the simultaneous changes of all variables involved in the cost and life-years gained.[60] The distribution of the joint bootstrap analysis will be displayed as a cumulative plot in a cost-effectiveness acceptability curve.[61] (*Supplement 2.*).

PROBE Outcomes Statistical Design

WARRIOR is a PROBE design. Compared to classic double-blind design, advantages of PROBE design are lower cost, greater similarity to standard clinical practice which should facilitate translation to routine medical care. Although healthcare costs, related to hospitalization and MACE other than mortality, are subjective, blinded CEC minimizes the difference between a PROBE and blinded design using rigorously standardized definitions and adjudication. While MACE is not a perfect outcome, no ideal outcome exists, and MACE is widely used in CVD and ischemic heart disease trials to inform FDA and guidelines. To reduce any bias due to unblinding, "*hospitalization"* must meet pre-specified objective criteria for hospitalization (e.g., NT-proBNP level, intravenous therapy, etc.) and be reviewed blindly by the CEC. Only those meeting objective criteria and confirmed by the CEC are counted as hospitalizations for the primary analysis. DSMB reports will also provide results with treatments coded. Complete unblinding requests from the DSMB will be honored, however.

Power Considerations

Table 4A lists design assumptions and **Table 4B** summarizes study power considerations. The main hypothesis is the difference between 3-year cumulative incidence of MACE in the UC and IMT assigned groups considering a drop-out 10% rate, probability of lost-to-follow-up within trial duration 2% for both groups and contamination (non-adherence to IMT or UC) rates ranging from 10-30%. All subjects will be randomized within 2 years, with 67% of subjects in the first year. With observed MACE rates in this population of 25% and determining a 20% event rate reduction would be clinically meaningful for practice and guidelines, the estimated total sample size, with powers of 80% and 90%, appear in **Table 4C.** Assumptions: Two-sided log-rank test with alpha = 0.05; survival times follow exponential distribution;1:1 allocation to treatment arms.

Rationale for Contamination Rate (Cross-Over).

Adherence to IMT and UC will be assessed by LDL-C (high intensity statin) and blood pressure (ACEi or ARB). Intensive high risk secondary prevention obstructive CAD trials (COURAGE, BARI-2D, FREEDOM, ISCHEMIA) document low contamination rates with UC (12% overall for 3 major risk factors at entry) and substantial increases with IMT to 55-84% for LDL-C, and 53-71% for BP goal achievement.[62-66] Analysis of high-risk patients in a managed care setting shows that those who were newly prescribed statin therapy were usually started at low-to-moderate doses of simvastatin, and approximately 50% discontinued therapy within 12 months.[67] We and others have documented moderate rates of primary prevention therapy (**Table 5**)[9,33,38,68-76] ranging from 10-56% in non-obstructive CAD populations. An NHANES report documents only 27% intensive lipid management in the community[77], as WISE and other data indicate <10% use of potent statin and ACE-I/ARB combination therapy (unpublished data, WISE-CVD NCT00832720).[68-70,78] Further, maturation contamination from UC to IMT (contamination) or from IMT to UC (non-adherence) will be identified by pharmacy and subject compliance monitoring. Action will be taken to minimize these using the adherence enhancement protocol in the IMT strategy if insufficient group differences are observed in potent statin and ACE-I or ARB use.

Interim Analysis

Enrollment and baseline characteristics of the first 150 women enrolled are shown in **Table 2.** Given that the total trial duration is 3.5 years, all subjects will be randomized in the first 3 years and the main endpoint is 3-year cumulative incidence of MACE, a formal interim analysis for early stopping is not proposed. Instead, we plan to estimate contamination in UC and IMT groups before accrual is completed and, if necessary, increase the total sample size required to assure that the desired power is achieved.

Data Safety Monitoring Board

The DSMB is comprised of content experts (cardiology, neurology, health outcomes, biostatistical) with input from the CDMRP-DoD.

DISCUSSION

The number of patients with INOCA is growing[8], it is an under-represented entity in clinical trials, and such patients are a major concern for physicians worldwide, particularly because they have poor quality of life and consume enormous healthcare resources. Data from large randomized controlled trials dedicated explicitly to INOCA are largely lacking, but there is growing evidence from both invasive[79] and non-invasive[80] assessment of myocardial blood flow reserve that clearly documents that microvascular dysfunction may be present in those without obstructive epicardial CAD and contribute to adverse outcomes. It is certainly plausible that our treatment approach can improve the outcomes of those patients based on observational data and small randomized preliminary studies. They support the hypothesis that statins and renin-angiotensin system inhibitors may be beneficial in mitigating adverse clinical events. Furthermore, INOCA patients are mostly women, with several million women affected nationally; women are well known to be understudied and under-enrolled in randomized trials. Clearly, more prospective data are needed to rigorously assess the effects of these agents on adverse outcomes in this syndrome. The findings from WARRIOR are destined to make a major contribution toward resolving the issue of defining an optimal therapeutic approach in these patients. Finally, data emerging from WARRIOR will likewise determine the safety and costs of an intensive management strategy in INOCA patients.

CONCLUSIONS

The WARRIOR pragmatic randomized trial investigates a strategy of IMT vs UC in women with evidence of INOCA for reduction of MACE. Results will provide the data necessary to inform future guidelines regarding how best to treat this growing population, for the goals of improved cardiovascular health, QOL and healthcare costs.

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Table 1. WARRIOR Enrollment Baseline Demographics (n= initial 150 women)

	Total **(n=150)**
Baseline Variable	
Age ≥65 years	50 (33.3%)
Ethnicity Hispanic/Latina	16 (10.7%)
American Indian or Alaska Native	2 (1.3%)
Asian	3 (2%)
Black or African American	31 (20.7%)
White	110 (73.3%)
Other	4 (2.7%)
Polycystic Ovary Syndrome	8 (5.3%)
Post-menopausal	123 (82%)
Hormone replacement therapy:	
Current	14 (9.3%)
Past	27 (18%)
Current Alcohol Use	36 (24%)
Current Smoking (or Tobacco Use)	24 (16%)
Past smoking	44 (29.3%)
ACE-I	44 (29.3%)
Antiarrhythmic agent	9 (6%)
Anticoagulant	15 (10%)
Antiplatelet agent, other than aspirin	15 (10%)
ARB	28 (18.7%)
Aspirin	79 (52.7%)
Beta blocker	66 (44%)
Calcium channel blocker	24 (16%)
Diuretic	57 (38%)
Nitrate	30 (20%)
Ranolazine	5 (3.3%)
Selective estrogen modulator	1 (0.7%)
Statin	91 (60.7%)
Vasodilators or other antihypertensive	11 (7.3%)
Symptoms/signs of ischemia	150 (100%)
Chest pain above waist	132 (88%)
Shortness of breath/breathlessness	93 (62%)
Invasive coronary angiography-non-obstructive CAD	95 (63.3%)
Noninvasive coronary computed tomographic angiography -non-obstructive CAD	55 (36.7%)
Fraction flow reserve >0.8, n=95	5 (5.3%)

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease

Table 2. Three-year major adverse cardiac event (MACE) in non-obstructive coronary artery disease (CAD)

Source- **Non-Obstructive CAD** **(N= total sample size)** **[n= women]**	**Ischemia**	**Death/MI/ Non-fatal Stroke (%)**	**Angina or HF Hospitalization (%)**	**MACE (%)**
WISE[7] (N/n=540)	Yes	5.0/6.6*	25.5	34.1
Murthy[26] (N=1,218) [n=813]	Yes	N/A	N/A	20.0
Schindler[35] (N=72) [n=28]	Yes	N/A	NA	25.0
Pazhenkottil[30] (n=324)	Yes	8.4	NA	NA
Jespersen[9] (N=11,223) [n=820]	NA	5.5	NA	~25.0 (KM estimate)
Sedlak[38] (N=1,864) [n=482]	NA	7.5*	NA	NA

CAD = coronary artery disease; HF = heart failure; MI = myocardial infarction

Table 3. WARRIOR Schedule of Study Assessments and Procedures

Item	Baseline	3 mos	Follow Up Visits 6,12,18,24,30 mos	Study Exit
Consent	X			
Inclusion/Exclusion	X			
Lipid Panel	X		X**	X
Safety Lab	X^	X^		
Biorepository/GeneticSample	X	X*	X*	
Office Visit	X	X	X	X
QoL Assessment	X		X**	X
PACE Lifestyle Intervention	X		X	
Study Drug Dispensing /Drug Compliance	X	X	X	X
Serious AEs			X	X

*only if not collected at baseline, **annually, ^clinically indicated
AEs = adverse events; QoL = quality of life

Table 4. Power Analysis

A. Power Assumptions

Accrual Rate Years 1-4= 2951, 1475, 0, 0
Total Sample Size n= 4476
Randomized 1:1 IMT vs UC
Drop-out rate 10%
Effective Sample Size 4028
3 Year UC MACE Rate 25%
Contamination UC to IMT 10-30%
Contamination IMT to UC 10-30%
Type I error (2-sided) 0.05
Minimum follow-up 18 months
Enrollment 24 months
Total Follow-up 42 months
Lost to Follow-up 2%

B. Power Calculation

3-year cumulative incidence of MACE		Power				
		Contamination				
UC	**IMT**	**10%**	**15%**	**20%**	**25%**	**30%**
0.15	0.12	68.2	64.5	60.6	56.6	52.6
0.20	0.16	82.5	79.3	75.6	71.7	67.4
0.25	0.20	91.6	89.3	86.5	83.3	79.6
0.30	0.24	96.6	95.3	93.5	91.3	88.6
0.35	0.28	98.9	98.2	97.3	96.1	94.4

C. Total Sample Size*

Contamination	80%	90%
10%	3084	4124
15%	3356	4488
20%	3666	4902
30%	4426	5918

*comparison of 3-year MACE in UC and IMT groups with 10% drop-out and 2% probability of lost-to-follow-up for both groups
IMT = intensive medical therapy; MACE = major adverse cardiac events; UC = usual care;

Table 5. Percent of Patients Continuing or Receiving New Primary Therapy: Non-Obstructive CAD Population

	HTN/Angina (%)	ACE-I/ARB (%)	Any Statin (%)
Johnston[33] (n=5394)	26-56	NA	51
Jespersen[9] (n=3479)	44	NA	50
Beltrame* (n=252)	21	NA	NA
Honigberg[69](n=419)	100	NA	66
Hulten[70](n=2839)	55-92	NA	36-72
Sedlak[38] (n=1864)	34	NA	32
Maddox[71] (237,167)	51	NA	47
Sharaf[74] (n=917)	34	NA	23
Shaw[75] (n=824)	10-18	NA	16
Maddox[72] (n=8384)	NA	45	60
Sedlak[73]	NA	54	11**
WISE-CVD (unpublished data)[76]	NA	40	10**
Bairey Merz[68]	NA	32	58

*J. Beltrame, personal communication; **high dose potent statin

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; HTN = hypertension

Legends

Figure 1. WARRIOR is a multi-site, PROBE design, point-of-care strategy trial.

[1]No unstable angina, acute coronary syndrome, myocardial infarction (MI) etc. [2]Symptoms–angina or equivalent. [3]<50% diameter stenosis. [4]Exclude for history of noncompliance, HIV, hepatitis C, eGFR <30, liver disease, etc. [5]IMT-intensive medical treatment–potent statin (or PCSK9 inhibitor) + ACE-I (or ARB if intolerant). [6]UC–usual clinical care.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; eGFR, estimated glomerular deficiency rate; HF, heart failure; HIV, human immunodeficiency virus.

Figure 2. WARRIOR randomized to intensive medical treatment (IMT) strategy.

ACE Inhibitor, angiotensin-converting enzyme inhibitor; PO QD, by mouth every day; RAS, renin-angiotensin system.