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WARRIOR

Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD

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RATIONALE

- ~ Half of women with symptoms/signs of ischemia referred to coronary angiography have no obstructive CAD (INOCA), elevated major adverse cardiac events (MACE), poor QoL and increased healthcare costs

- Guidelines focus on symptom management - clinical practice advocates risk factor management and reassurance

- Pilot studies suggest benefit with intensive medical therapy (IMT) high-intensity statin, maximally tolerated ACEIs or ARBs

HYPOTHESIS:

IMT reduces primary outcome first occurrence of MACE (all cause death, MI, stroke or hospitalization for worsening angina or HF) by 20% vs. UC at 5 yr follow-up

METHODS

- Multicenter, prospective, randomized, blinded outcome evaluation (PROBE) design
- Pragmatic strategy trial of IMT vs usual care (UC) in symptomatic women with suspected INOCA (NCT 03417388)
- Secondary outcomes include QoL, time to return to work, healthcare utilization, angina, CV death, total events, individual primary outcome components and WIN ratio over 5 yrs F/U
- Web-based data capture, e-consents, single IRB and centralized pharmacy used to reduce burden

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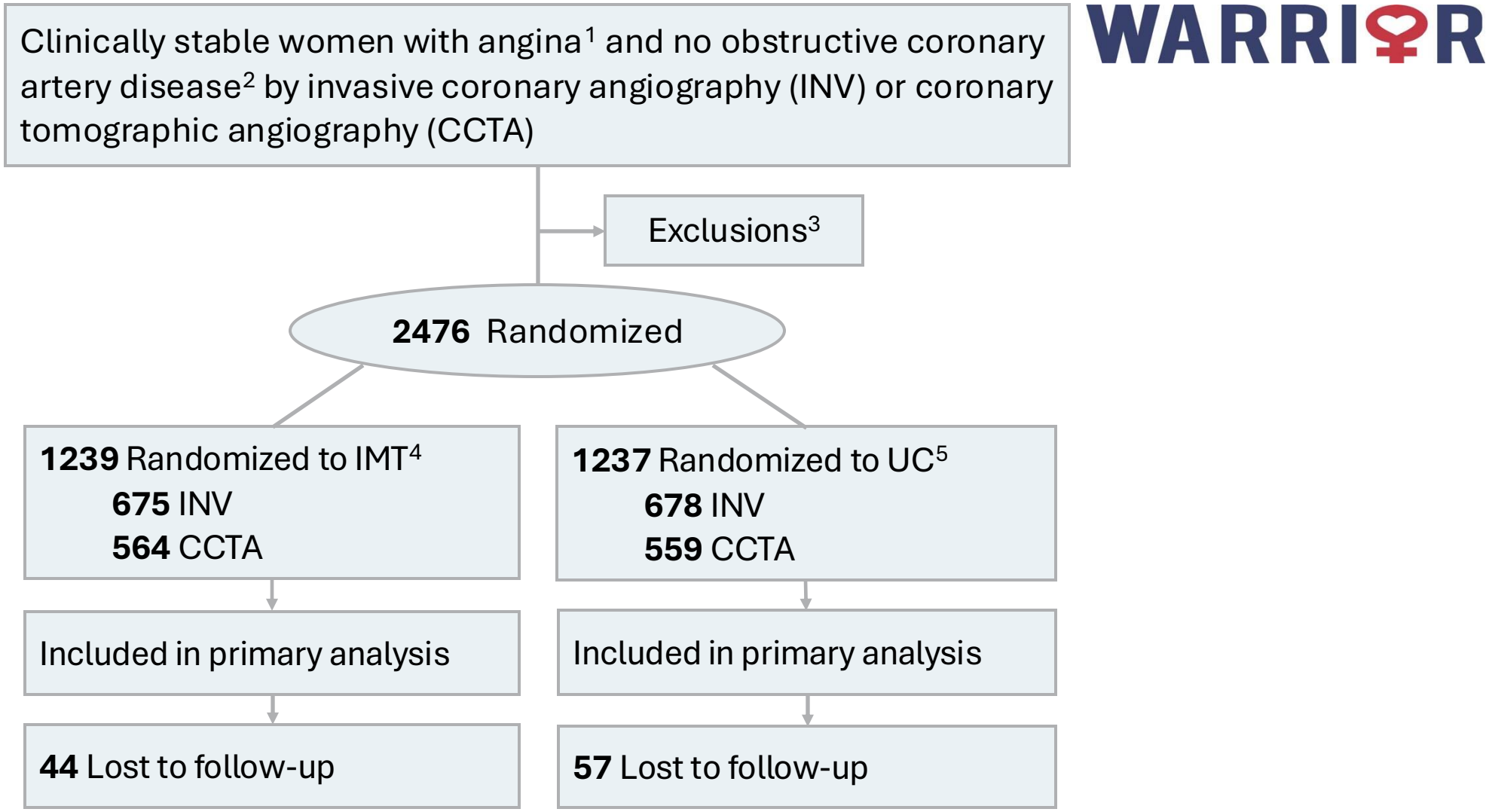


[1] Angina or Angina Equivalent

[2] No coronary artery narrowing ≥50% diameter reduction, UAP, ACS, MI, PCI, or CABG

[3] History of Cardiomyopathy, Significant Valvular or uncorrected Congenital Ht Disease, HIV, HepC, eGFR <30, liver disease, expected survival <2 yrs, or noncompliance

[4] Intensive Medical Therapy = high intensity statin (or PCSK9 i) + ACE-I (or ARB) + low dose aspirin

[5] Usual Care- dictated by treating physician

COVID 19 Pandemic Enrollment Impact:
Nov 14, 2022- WARRIOR DSMB and External Independent Advisory Panel recommendations

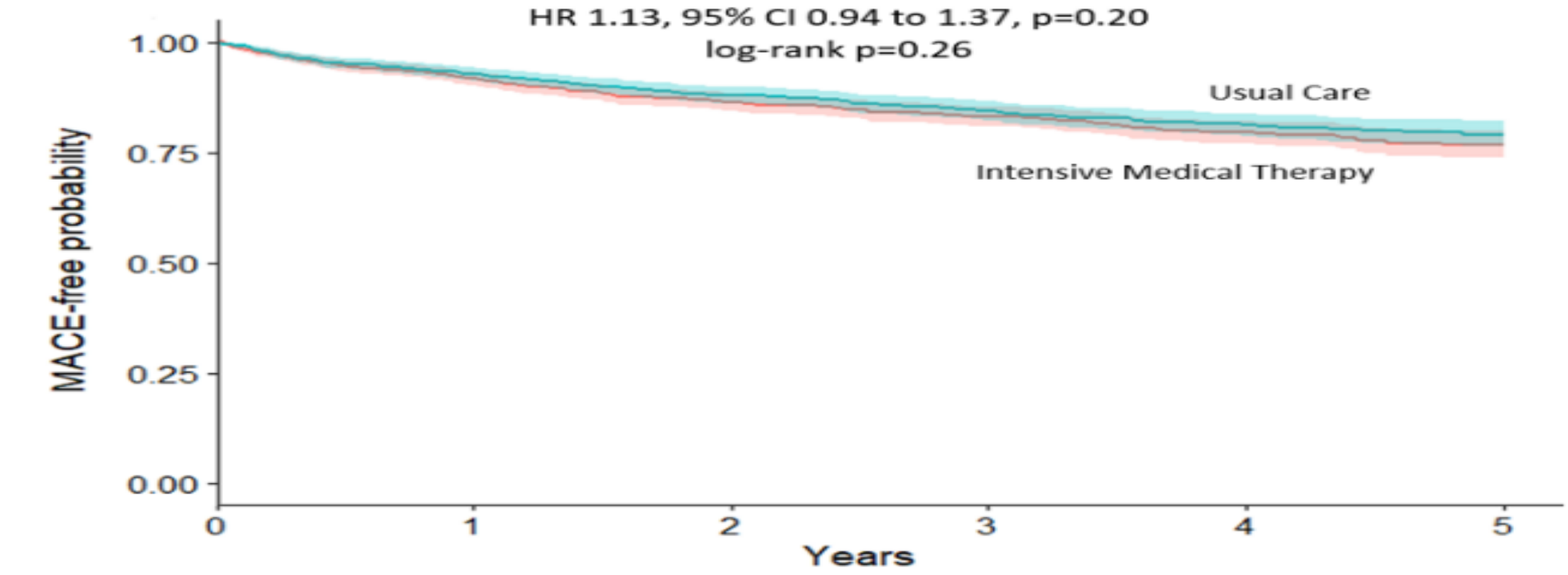
- Continue the trial
- Maximize recruitment efforts (increase sites, reimbursement) to reach original goal of 4,476 and extend follow up.
- Focus on biorepository sample collection for all participants
- Encourage co-enrollment in Ancillary Studies
- External independent advisory panel review – do not change the primary outcome

Baseline WARRIOR Characteristics by Assignment

Characteristic	Intensive Medical Therapy (IMT) (n=1239)	Usual Care (UC) (n=1237)
Demographic		
Age (years), Mean (SD)	64.2 (2.88)	64.1 (2.89)
≥65, n (%)	466 (37.6%)	487 (39.4%)
White, n (%)	1104 (89.2%)	10997 (88.7%)
BMI (kg/m^2), Mean (SD)	32.1 (8.38)	31.7 (7.91)
≥30, n (%)	661 (53.8%)	643 (52.6%)
Condition		
CCTA, n (%)	564 (45.5%)	559 (45.2%)
Invasive Angiography, n (%)	675 (54.5%)	678 (54.8%)
History of:		
Diabetes, n (%)	266 (21.5%)	251 (20.3%)
Myocardial Infarction, n (%)	86 (6.9%)	102 (8.2%)
Hypertension, n (%)	783 (63.2%)	812 (65.6%)
Ever Smoked cigarettes n (%)	427 (36.8%)	436 (37.9%)
Post Menopausal, n (%)	1004 (81.5%)	1010 (82.0%)
SBP (mmHg), Mean (SD)	125.2 (15.45)	125.9 (15.83)
LDL-C (mg/dl), Mean (SD)	93.6 (34.46)	92.7 (34.90)
≥70 mg/dl, n (%)	835 (73.1%)	834 (73.8%)
SAQ7 overall, Mean (SD)	69.7 (20.87)	71.6 (20.45)
COVID-19 infection, ever, n (%)	490 (39.5%)	489 (39.5%)
Medication		
Statin, n (%)	878 (70.9%)	863 (69.9%)
Atorvastatin 40-80 mg	282 (22.8%)	264 (21.3%)
Rosuvastatin 20-40 mg	164 (13.2%)	158 (12.8%)
Other lipid lowering agents, n (%)	389 (31.6%)	385 (31.4%)
ACE-I or ARB, n (%)	658 (53.1%)	596(48.2%)
Beta Blocker, n (%)	454 (36.9%)	493 (40.2%)
Calcium Channel Blocker, n (%)	317 (25.8%)	348 (28.4%)
Aspirin, n (%)	779 (62.9%)	724 (58.5%)

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

Primary Outcome



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MACE	IMT (n=369)	UC (n=354)	Total (n=723)
Death, all cause	27	17	44
CV Death	4	5	9
Hospitalization for Chest Pain	305	298	603
Hospitalization for Heart Failure	7	6	13
Non-Fatal MI	14	14	28
Stroke/TIA	16	19	35

Non-CV Deaths: malignancy 7, sepsis/infection 5, neurologic 1, pulmonary 2, trauma 4, undetermined 16
*p=ns IMT vs UC

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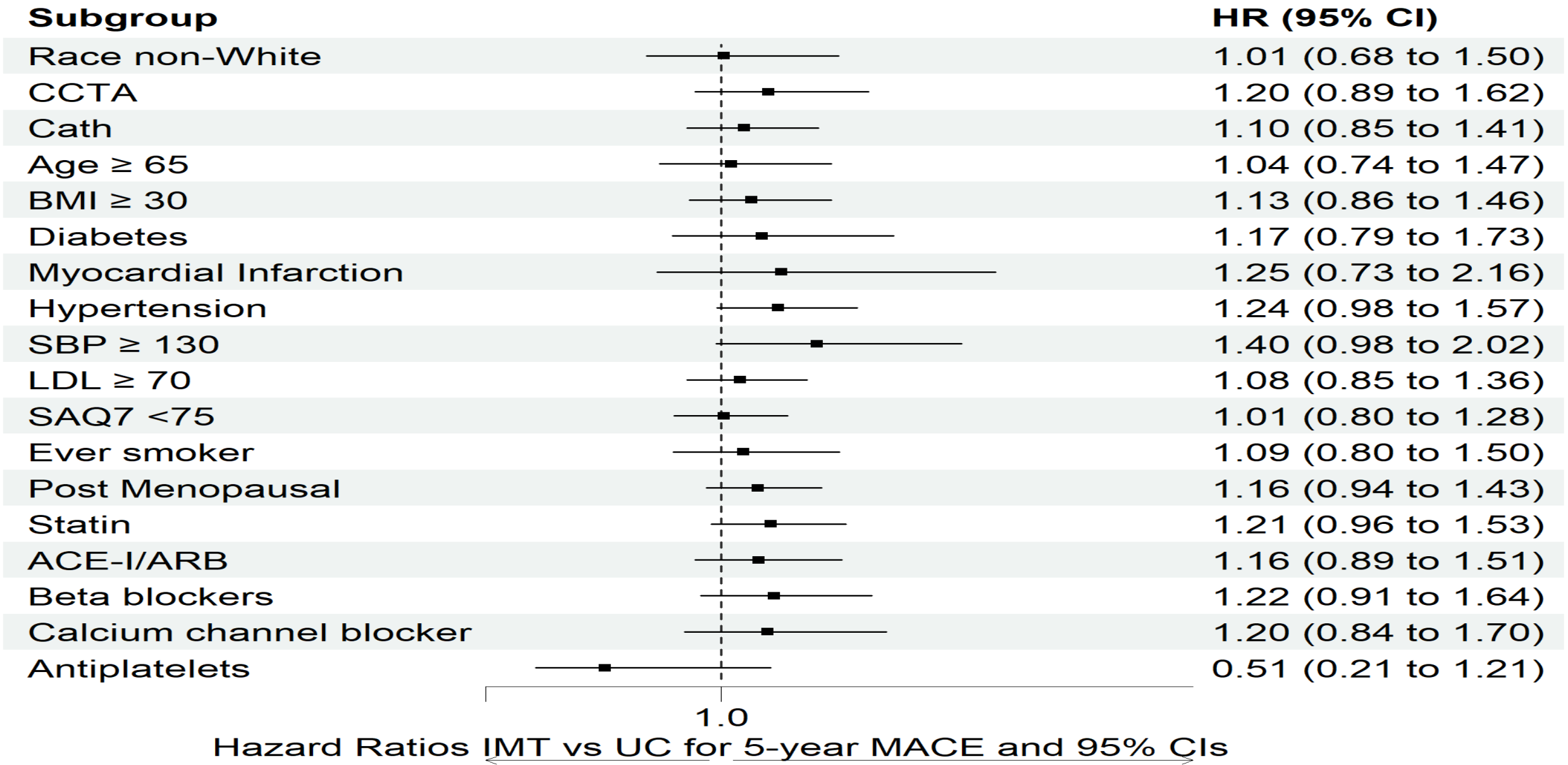
Heterogeneity of Treatment Effect for the Primary Outcome



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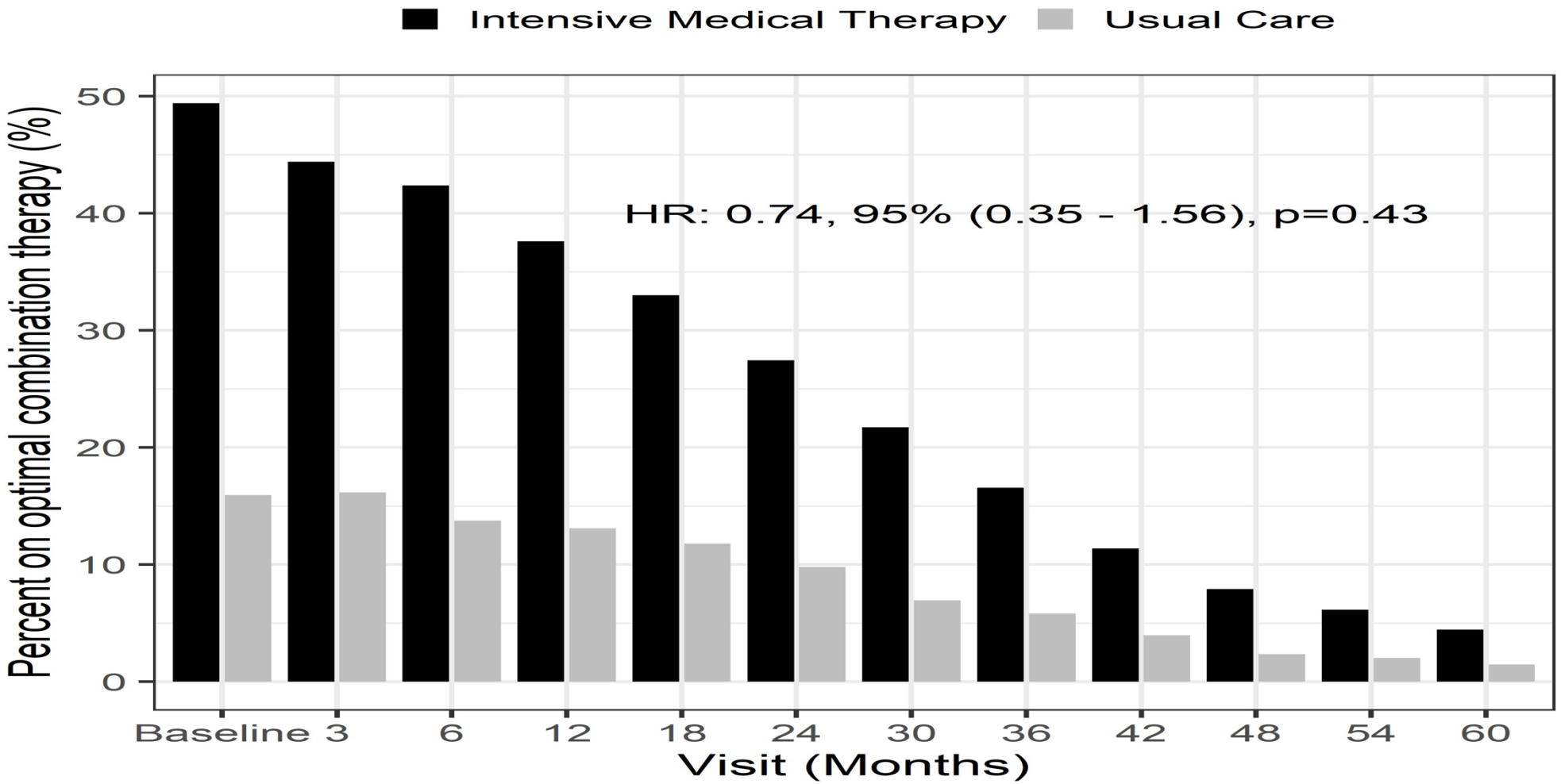
Sensitivity Analysis of Contamination- HR: 0.74, 95% (0.35 – 1.56), p=0.43



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LIMITATIONS

- Under-enrollment limited power
- CCTA inclusion increased enrollment but lowered MACE risk profile
- Open label, pragmatic trial design resulted in higher than anticipated trial contamination in both groups
- High enrolled baseline SAQ reduced capacity to improve angina and angina-related QoL

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SUMMARY

- Largest trial in the INOCA field, documents high burden of recurrent angina hospitalization
- Sensitivity analyses incorporating contamination in both arms demonstrated a non-significant 25% MACE reduction, potentially supportive of an effect had sufficient statin and ACEI/ARB been utilized.
- Results extend prior literature suggesting ACEI/ARB treatment in INOCA to a goal of SBP ≤120 mmHg may be best for SAQ angina reduction

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CONCLUSIONS

- Among women with suspected INOCA, **IMT did not reduce the first occurrence of all cause death, MI, stroke or hospitalization for worsening angina or HF** by 20% vs. UC at 5 yrs
- "Neutral trial result" should **NOT** be:
  - Consider a negative trial, rather insufficient adherence and power to test Ho.
  - Interpreted as endorsing discontinuing statin and ACEI/ARB medications among women with CV risk factors
- Ongoing ancillary imaging and biorepository studies will continue to contribute to improve our understanding of this growing patient population and its' symptom burden

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WARRIOR PORTFOLIO OF FUNDED TRIALS

- WARRIOR Trial – funded by Congressionally Directed Medical Research Program of Department of Defense award (CDMRP-DoD)
- WARRIOR Ancillary Trial (WAT) – funded by NHLBI to interrogate baseline and exit coronary CT angiograms (CCTA) in response to randomization and related to primary and secondary outcomes
- QUIET-WARRIOR ancillary study funded by the CDMRP-DoD will investigate CCTA mechanisms related to outcome
- WARRIOR Biorepository to create more “personalized’ models for risk prediction, outcomes and define new directions for therapy

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