Angina with Unobstructed Coronary Arteries: Leveraging the WISE Study to prove Cardiac Mortality in M.E.

by Anonymous

Today, I'm going to show you why many patients with M.E. are dying from microvascular cardiac disease. And I'm going to introduce you to the Women's Ischemia Syndrome Evaluation (WISE), an NIH initiative which presents a huge opportunity for research synergy *and funding* on cardiac disease in M.E.

First of all, some definitions: The endothelium is the inner lining of the blood vessel. Microvascular circulation represents the smallest vessels. And "ischemia" is when your tissues are oxygen-starved. Persistent undiagnosed chest pain is rampant among ME patients. Yet patients presenting with chest pain receive standard cardiac tests focused on blocked coronary arteries, which *routinely* miss a microvascular diagnosis.

WISE researchers don't fully understand the mechanism of cardiac ischemia in their patients. But they know that many patients with clear-as-a-bell coronary arteries can have deadly cardiac ischemia. They might have coronary artery vasospasm: vascular reactivity, tightening their coronary arteries, blocking off blood-flow to the heart. They might have inflammatory narrowing of the lumen of the microcirculation. What the WISE researchers *do* know is that microvascular and endothelial dysfunctions can and do kill.

If ever there were a research direction for the CFSAC to recommend, it is into the causes of premature death in M.E.. The NIH must learn that M.E., for many, is fatal.

The WISE research is a strategically funded and continuing NIH initiative with which CFSAC-sponsored researchers could dovetail. The profile of WISE patients is uncannily similar to that in M.E.. There are many unanswered questions by the WISE teams, which M.E. researchers could help answer. It's a win/win.

About the Women's Ischemic Syndrome Evaluation (WISE) research The WISE research arose because – contrary to popular opinion – women die *far more* often than men from cardiovascular causes. In a study of 80,000 men and women, the cardiac mortality ratio was *12-fold higher* for middle-aged women, than men. Women with crystal clear coronary arteries are dropping dead – after years of atypical chest pain and neglect.

Crossovers between WISE and M.E. patients

The WISE research aimed to identify "novel risk markers" for womens' cardiovascular risk. And they found a pattern that should be familiar. I submit the WISE researchers are studying a population with *significant* representation by M.E. patients. Here's why:

Findings in W.I.S.E. patients	Associated with M.E.?
Inflammatory cytokine signature, including IL-6 and C-reactive Protein*: generalized inflammation predicts higher CV risk*	✓[i]
Comorbid conditions: *migraine, IBS, FM, interstitial cystitis*	✓

Findings in W.I.S.E. patients	Associated with M.E.?
Other signs of microvascular compromise: *eg. Raynaud's, migraine, retinal artery narrowing*[ii]	✓[iii]
Net lactate production	✓
Abnormal metabolism	✓
Exercise stress shifts reliance to anaerobic metabolism*, consistent with ischemia*	✓[iv]
Abnormal pain perception	✓[v]
Peripheral endothelial dysfunction (eg. abnormal Brachial Artery Flow-Mediated Dilation; abnormal EndoPat, etc)	✓[vi]
Overlap with metabolic syndrome	✓
High oxidative stress*, leads to endothelial dysfunction, & is predictive of prognosis*	✓
Early morbidity/mortality from heart disease	✓[vii]
Low functional capacity *found in 70% of WISE women on Duke Activity Status Index (how many had M.E.?)*	✓
"Harm Avoidance": *Sickest patients are reported high on psychosocial "Harm Avoidance" scales. (Is this an inadvertent euphemism for Post-Exertional Relapse?)*	✓
Abnormal "Autonomic Perception": *Sickest patients are reported high on "Autonomic Perception" (Is this undiagnosed POTS?)*	✓
High incidence of history of past treatment for depressive symptoms *(many M.E. patients are misdiagnosed as depressed)*	✓[viii]

Given the many parallels between the WISE patients and M.E., research into microvascular/ endothelial pathology could prove pivotal for our community. Bottom line, Atypical Angina is a condition which the NIH is pouring money and attention into.

WISE researchers found that smaller anatomy, different hormones, and predisposition to vascular pathology, prime women for microvascular dysfunction. If so, then women with M.E., with their high oxidative & nitrosative stress, inflammatory cytokine cascades, and prevalence of vasculitic symptoms, should be sitting ducks for microvascular dysfunction.

Atypical angina is *not* restricted to women. But as a first step, collaboration with the WISE teams could supercharge funding and foster recognition of the seriousness of M.E.

We could help the WISE researchers differentiate depression & anhedonia from OI and PEM. But this won't happen if the waters are muddied, and magnified "CFS" cohorts such as Fukuda are used. So please: set CFSAC priorities that accelerate recognition that M.E. can and does kill. And use robust M.E. Criteria such as the CCC, that requires PEM.

If you'd like to dig further, I've provided additional information, recommendations, WISE team contact information, and references in the Appendix. Thank you for this opportunity.

Additional Background Information:

Additional Background Information includes:

- Contact Information for the Chair of the WISE studies;
- A list of researchers calling for recognition of the impact of microvascular dysfunction in M.E.;
- Link to prior written testimony
- Recommended Areas for Enquiry with the WISE research
- Hotlinked References to key WISE studies

Key contact for the WISE Study:

Dr C. Noel Bairey Merz. Chair, NIH-sponsored Women's Ischemic Syndrome Evaluation initiative. Women's Heart Center, Cedars-Sinai Medical Center.

Bio: http://www.cedars-sinai.edu/Bios---Physician/H-O/C-Noel-Bairey-Merz-MD-FACC.aspx

Clinical Trial Information: http://clinicaltrials.gov/ct2/show/NCT00832702

Email: merz@cshs.org

I'm not the only one saying we need to look at serious microvascular dysfunction in M.E.

Other voices include the team at the Vascular and Inflammatory Diseases Research Unit at the U. of Dundee; researchers at the U. of Alberta, including Dr Broderick and Dr Mason; Dr Mikovits; Dr Jonathan Kerr; and endothelial specialists such as Dr Merz (Chair of the WISE initiatives), who have noted a high prevalence of pain syndromes such as Raynaud's, migraine, FM, and IBS in WISE-profile patients.

Thank you!

Appendix 1: Areas for Enquiry in Collaboration between M.E. and WISE research:

Below are some research areas which could be addressed by collaborating with WISE researchers. For example, vascular smooth muscle dysfunction such as migraine was linked in the WISE findings with coronary artery spasm (tested with intracoronary adenosine) and with ischemic heart disease (IHD). Similarly, vascular smooth muscle dysfunctions such as migraine and Raynaud's have been connected with M.E. **Link with M.E.**: *Are M.E. patients at serious risk for coronary artery spasm and IHD?*

WISE Findings	Link with M.E.?
Diagnoses of coronary microvascular dysfunction/endothelial dysfunction should be considered *in women with chest pain and unobstructed coronary arteries*	?
Abnormal coronary and peripheral endothelial test results increase coronary risk 10x. *Biomarkers include Brachial Artery Flow-Mediated Dilation; EndoPAT technology; and intracoronary Acetylcholine testing.*	?
Abnormal Magnetic Resonance Spectroscopy *& Phosphocreatine/Adenosine Triphosphate ratio reveals shift to anaerobic metabolism, consistent with myocardial ischemia*	?
MRS Cardiac Stress Test *identifies women more likely to have worsening & persisting angina requiring intensive medical care*	?
Duke Activity Status Inventory: *2/3 of cardiac events in WISE women occurred at less than < 4.7 Duke Activity Status METS*	?
Redox state of thiols such as glutathione *strongly correlate with endothelial dysfunction and in turn cardiac risk*	?
Retinal microvascular abnormalities are linked to inflammation and endothelial dysfunction. *Retinal Artery Narrowing can be captured on non-invasive Retinal photography*	?
Up to 50% of WISE patients (persisting chest pain + non-obstructed coronary arteries) have Microvascular Coronary Dysfunction (MCD)[ix]	?
The most common presentation prior to sudden cardiac death for WISE women is atypical*, with fatigue, shortness of breath, and atypical chest pain*	?
Near-term cardiac prognosis is driven by acuity and comorbidity *(eg. "pain syndromes", etc.)*	?
Inflammatory marker and cytokine levels predict future vascular events *(see Kerr, Broderick, Mikovits' work on cytokines in M.E.)*	?
Polymorphisms in the β_1- and β_3-adrenergic receptors increase cardiovascular risk *in WISE women*	?
Anemia is an important risk *factor for vascular events in WISE women, and postulated to reduce Endothelial Progenitor Cells needed for repair.*	?
"Anhedonia" Predicts Major Adverse Cardiac Events and Mortality *in patients, 1 year after Acute Coronary Syndrome (or is "anhedonia" = M.E.?)*[x]	?
Somatic symptoms of depression predict cardiovascular events and mortality*, but Cognitive/Affective symptoms do not.*[xi] *(When do "somatic symptoms" = undiagnosed M.E.?)*	?

WISE Findings	Link with M.E.?
"Depression refractory to treatment" is associated in the WISE cohort with adverse cardiovascular outcomes. *(or is this misdiagnosed M.E.?)*	?
Self-rated health predicts major cardiovascular disease events; *Poor and Fair self-rated health categories were highly significant predictors of major Cardiovascular Disease (CVD) events and All-Cause Mortality (ACM)*[xii]	?
Brain Naturietic Peptide is predictive of adverse outcomes *for women with Acute Coronary Syndrome*	?
Overall inflammation predicts cardiovascular disease (CVD)*: IL-6, C-Reactive Protein and Serum Amyloid-A all predict cardiovascular disease (CVD) risk in women, but global measures of inflammation and simply counting the number of markers with high levels improves CVD risk stratification.*	?
Stress tests have low diagnostic accuracy for women with low functional status *on DASI. The DASI as a pre-screen, with Dobutamine (pharmacologic) stress test offers an alternative.*	?
AND THE GOOD NEWS: Restoration of endothelial function is associated with improved cardiac outcomes, *specifically a 7.3 fold reduction in Ischemic Heart Disease events compared to untreated patients.*[xiii]	?

Selected References: Women's Ischemia Syndrome Evaluation (W.I.S.E Study):

Prognosis in Women with Myocardial Ischemia in the Absence of Obstructive Coronary Disease: Results from the NIH-NHLBI-Sponsored Women's Ischemia Syndrome (WISE) Evaluation (2004): http://circ.ahajournals.org/content/109/24/2993.full.pdf+html

Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation Study. Part 1: Gender Differences in Traditional and Novel Risk Factors, Symptoms Evaluation, and Gender-Optimized Diagnostic Strategies (2005): http://www.sciencedirect.com/science/article/pii/S0735109705025064#sec3

Global Inflammation Predicts Cardiovascular Risk in Women: A Report from the Women's Ischemia Syndrome Evaluation study (2005): http://www.sciencedirect.com/science/article/pii/S0002870305001201

Multimarker Approach Predicts Adverse Cardiovascular Events in Women Evaluated for Suspected Ischemia: Results from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (2009): http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2811492/?tool=pmcentrez

Anhedonia Predicts Major Adverse Cardiac Events and Mortality in Patients 1 year after Acute Coronary Syndrome (2010): http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3058237/pdf/nihms215930.pdf

Self-Rated Versus Objective Health Indicators as Predictors of Major Cardiovascular Events: The NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (2010): http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3113514/pdf/nihms-294231.pdf

Coronary Microvascular Reactivity to Adenosine Predicts Adverse Outcome in Women Evaluated for Suspected Ischemia: Results from the NHLBI Women's Ischemia Syndrome Evaluation (2010): http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2898523/pdf/nihms-173567.pdf

Effectiveness of cardioprotective medication in women with suspected ischemic heart disease syndrome: the NHLBI-sponsored women's ischemia syndrome evaluation study (2011): http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3106725/?tool=pmcentrez

Endnotes:

[i] See Dr Faisal Khan's work @ the U of Dundee on C-reactive protein, arterial stiffness, inflammation and oxidation in M.E.

[ii] See earlier written testimony: page 3, reference to Dr T.J. Anderson's presentation on Atypical Angina patient profile: Oct 2010 CFSAC: http://www.hhs.gov/advcomcfs/meetings/presentations/pysiotherapistandoccupationaltherapist.pdf

[iii] Eg. Dr Jonathan Kerr's work on Parvovirus B19 M.E., Raynaud's

[iv] Eg. Snell, Stevens research from Pacific Fatigue Lab

[v] Eg. the Light's research

[vi] Eg. See frequent reports by M.E. patients, of icy cold extremities; Raynaud's; fingerprint changes

[vii] See Dr. Jason's work on heart failure: average age for death from heart failure. Normal = 83.1 yrs; "CFS" sample = 58.7 years.

[viii] M.E. is notorious for being misdiagnosed as depression

[ix] Patients with Microvascular Coronary Disease (MCD) face a 2.5% annual adverse cardiac event rate, including myocardial infarction, stroke, hospitalization for congestive heart failure, and sudden cardiac death. What is the event rate for M.E. patients with persisting chest pain and patent coronary arteries?

[x] The WISE researchers found that patients with anhedonia were significantly more likely to have a higher Charlson comorbidity index score. Also, they demonstrated that of the 2 core depression criteria (depressed mood and anhedonia), only anhedonia predicted the risk of Major Adverse Cardiac Events (MACE) and All-Cause Mortality (ACM). Is it possible these patients had M.E. or other chronic illnesses, misdiagnosed as anhedonia? Note also that WISE researchers found that almost half of the patients with severe anhedonia in their sample *did not have* MDE (Major Depressive Episode)! The WISE researchers themselves acknowledge that it is possible that the post-Acute Coronary Syndrome patients with the worst anhedonia may be the ones with the worst heart disease.

[xi] Another red flag: were the WISE researchers mistaking M.E. for somatic symptoms of depression? Interestingly the WISE researchers included antidepressant use as an indication of depressed state. But as many M.E. patients with histamine intolerance know, some antidepressants/anxiolytic agents such as amitryptilline are prescribed in M.E. for their antihistamine properties. Additionally, the research on efficacy of antidepressants does not show significant improvement in cardiac outcomes. Are these WISE patients really depressed, or do they have undiagnosed serious organic illness, such as M.E.?

[xii] M.E. patients are all too familiar with the experience that self-rated health is ignored in M.E. patients. Yet the power of self-rated health for those WISE patients giving a Poor or Fair rating *rivaled effects of established CVD factors* such as diabetes and dyslipidemia in predicting adverse outcomes. The WISE researchers were perceptive in noting that "*impairment secondary to women's medical status explains much of the relationship between self-rated health and CVD outcomes*". In other words, these patients really *are* sick. If M.E. patients are shown to frequently have endothelial/microvascular dysfunction, this dismissal of self-reported health in M.E. patients could change, given the predictive validity of this measure for major cardiovascular events.

[xiii] ***Bottom line: can the CFSAC get M.E. patients into these WISE trials and/or secure NIH funding to conduct our own trials on diagnosis and treatment of endothelial and microvascular dysfunction in M.E.?***