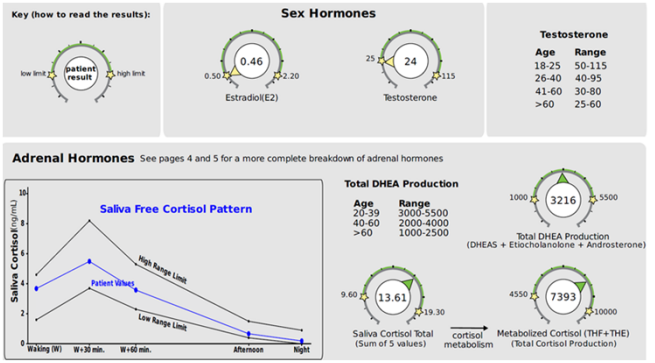
CVD Risk Assessment

Gaining insights from the DUTCH Test



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Disclaimer

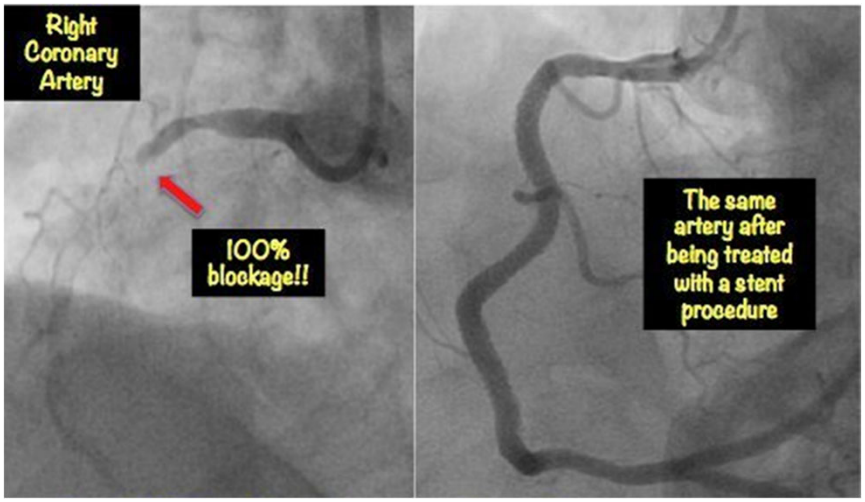
This lecture and the cited scientific literature, when referring to women/females, are referring to individuals born biological females; when referring to men/males, this lecture is referring to individuals born biological males.

Objectives

- **At the end of this presentation, attendees should have a better understanding of, and gain insights into:**
  - The nuances of the CVD patient history and PE
  - The necessary laboratory testing, including the DUTCH test, and cardiac testing
  - Treatments: both non-pharmacological and pharmacological

Goals

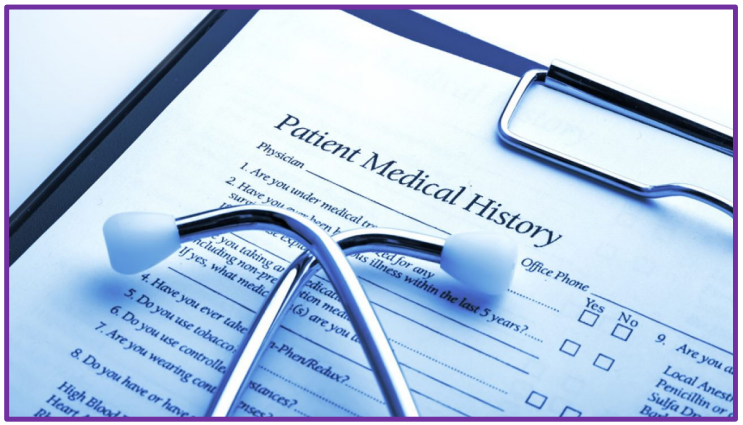
- **Prevent cardiovascular (CV) events in those at risk and in those with subclinical cardiovascular disease: primary prevention**
- **Prevent secondary events in those who have had a prior event: secondary prevention**



Review

- HPA axis dysfunction and its role in CVD events and mortality
- Glucose dysregulation and its effect on the endothelial glycocalyx (EGCX) and the endothelium: 1st steps in the atherosclerotic process
- How sex-hormone deficiencies increase potential for adverse CVD outcomes and how MHT and TTh likely improve CV outcomes
- How gut dysbiosis and a SAD diet increase TMAO, an independent predictor of adverse CV outcomes
- ANS imbalance is associated with increased event rates
- Inability to detoxify, increases inflammation

The Patient History



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History

- A day in the life of …
  - What a typical day looks like
    - Sleep habits: wake up, bedtime, restful sleep, breathing patterns, snoring
    - Daily stressors: work, family, marital
    - Diet, nutrition, and gut health: a Mediterranean diet decreases CV event rates by ~ 30%
    - Exercise history
- Traditional CV risk factors
  - IR/DM, obesity, HTN, HLD, family history of premature CAD, smoking, CKD, OSA
- Non-traditional risk factors
  - Mood, detoxification, heavy metal exposure (lead, cadmium, mercury, arsenic), chronic inflammatory/autoimmune disorders, BMD

Question

In addition to traditional and other functional CV risk factors, what else do we need to ask about?

Females

- Adverse pregnancy outcomes
  - Gestational diabetes, pre-eclampsia, eclampsia, and pre-term deliveries are all associated with increased future heart disease risk
    - Pre-eclampsia doubles the future risk of: DM and stroke
    - Pre-eclampsia quadruples the future risk of HTN
- Chronic inflammatory disorders: autoimmune diseases
  - For example, SLE, psoriasis, and rheumatoid arthritis 2-3 fold higher MI and CVD mortality risk
  - Steroids, which are common treatments, increase risk of MetS and premature atherosclerosis

Mehta PK, et al. trends Cardiovasc Med. 2015; 25(2): 140-151.

Females

- Osteopenia/osteoporosis
  - Osteoporosis severity is associated with cardiac events
  - Low vitamin D (more common in females) associated with a 1.62x increased event rates; vitamin D treatment does not decrease event rates
- Acute mental stress: Takotsubo-cardiomyopathy
  - Highly prevalent in PMP women (80% cases)
- Marital Stress
  - Severe marital stress 3x increased coronary event risk, despite controlling CVD RF

Mehta PK, et al. trends Cardiovasc Med. 2015; 25(2): 140-151.

Females

- Depression in women ≤ 55 years old
  - Increased CV mortality compared to men ≤ 55 years old
- Vasomotor symptoms
  - Frequent or severe VMS can be expected to persist for ~ 7-9 years, while milder forms may last even longer
  - Linked to adverse CVD risk factors:
    - HTN, IR/DM, dyslipidemias
    - Poor endothelial function
    - Autonomic nervous system imbalance with reduced vagal tone
    - More proinflammatory and/or procoagulant profile

Mehta PK, et al. trends Cardiovasc Med. 2015; 25(2): 140-151.
Thurston RC, et al. J Am Heart Assoc. 2021; 10(3): e017416.

Females

Menopausal Vasomotor Symptoms and Risk of Incident Cardiovascular Disease Events in SWAN (Study of Women's Health Across the Nation)

Rebecca C. Thurston, PhD; Helen E. Aslanidou Vlachos, MSc; Carol A. Derby, PhD; Elizabeth A. Jackson, MD, MPH; Maria Mori Brooks, PhD; Karen A. Matthews, PhD; Sioban Harlow, PhD; Hadine Joffe, MD, MSc; Samar R. El Khoudary, PhD, MPH

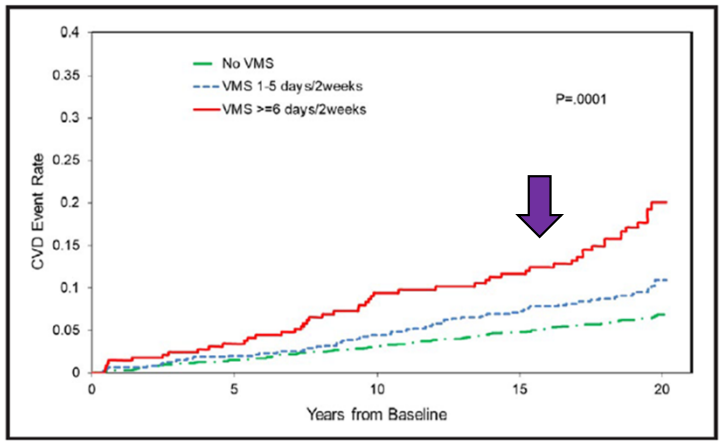

Figure 1. Baseline vasomotor symptoms (VMS) in relation to fatal and nonfatal cardiovascular disease (CVD) events, N=3083, 231 events.

Associations not explained by traditional RF or serum E2 levels

- **Objective:** To determine whether frequent and/or persistent VMS were associated with the risk of increased nonfatal and fatal CVD event
  - Whether women with [1] more frequent VMS at baseline or [2] persistently frequent VMS over time were at increase risk for subsequent CVD events
- **Study:** Longitudinal cohort study, midlife women followed for > 20 years
  - 3083 pre and early perimenopausal women, median age 46 years, followed up to 22 years were included in this analysis
  - VMS categorized as:
    - None; 1-5 days/2 weeks; ≥ 6 days/2 weeks (frequent)
  - Median E2 levels using an immunoassay: 57.7pg/mL (no VMS); 52.1pg/mL (mild VMS); 48.3pg/mL (frequent)
- **Results:**
  - Frequent or persistent VMS were associated with a 50-77% increased risk of future CVD events
- **Conclusions**
  - **Results suggest that frequent VMS early in the MT or persistent VMS over the MT are associated with increased risk of CVD events later in life**
  - **More studies are needed**

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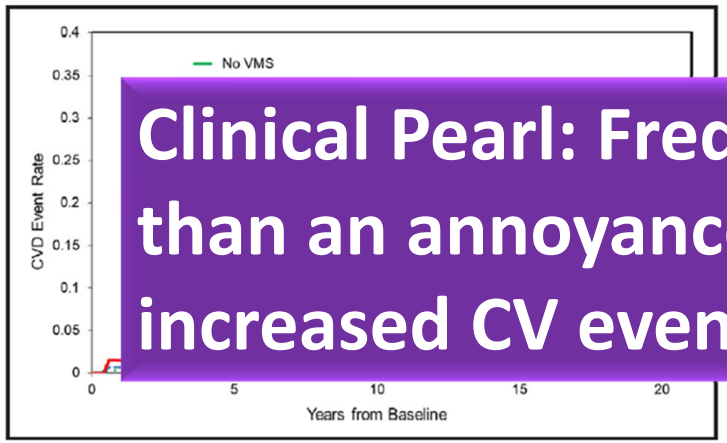

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- **Study:** Longitudinal cohort study, midlife women followed for > 20 years

Clinical Pearl: Frequent/persistent VMS are more than an annoyance, they are associated with increased CV events.

  - Frequent or persistent VMS were associated with a 50-77% increased risk of future CVD events
- **Conclusions**
  - **Results suggest that frequent VMS early in the MT or persistent VMS over the MT are associated with increased risk of CVD events later in life**
  - **More studies are needed**

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Males

"Erectile dysfunction (ED) should be considered a vascular disease until proven otherwise."

Graham Jackson, MD

Jackson G, et al. Int J Clin Pract. 2013; 67(11): 1163-1172.

Males

- EGCX and endothelial dysfunction, a common link between erectile dysfunction (ED) and CVD
  - ED and CVD share the same set of CVD risk factors
  - Vascular ED is an independent CVD risk marker
  - ED may indicate subclinical vascular disease in an otherwise asymptomatic male, especially 40-60 years old
  - CVD patients are more likely to have ED and patients with ED are more likely to develop CVD in the future
- ED symptoms and CVD
  - There is a 2-3 year time interval between ED onset and CVD symptoms
  - ED severity is correlated with coronary disease burden
  - ED has been independently associated with CVD events

Jackson G, et al. Int J Clin Pract. 2013; 67(11): 1163-1172.
Miner M, et al. Sex Med Rev. 2019; 7(3): 455-463.

Males

- ED predicts CV Events
  - Comprehensive literature review and meta-analysis
  - Objective: assess whether ED was an independent risk factor for CV events
  - Study: 154,794 males
  - Results: Severe ED predicted higher CVD and all-cause mortality risk
    - When compared to men without ED, men with ED had a SS increase in: CVD by 43%, CAD by 59%, stroke by 34%, and all-cause mortality by 33%
    - Older males (≥ 55 years old), those with ED for a shorter duration (≤ 7 years), and those men with higher rates of DM and smoking, were more prone to develop CVD
  - **Conclusion: CVD, CAD, stroke, and all-cause mortality may be significantly increased in males with ED, especially severe ED**

Zhao B, et al. J Sex Med. 2019; 16(7): 1005-1017.

Males

- ED predicts CV Events
  - Comprehensive literature review and meta-analysis
  - Objective: assess whether ED was RF for CV events

Clinical Pearl: All men with erectile dysfunction should undergo CV risk stratification

by

  - Older males (≥ 55 years old), those with ED for a shorter duration (≤ 7 years), and those men with higher rates of DM and smoking, were more prone to develop CVD
  - Severe ED predicted higher CVD and all-cause mortality risk
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IIEF-5 Questionnaire

The IIEF-5 Questionnaire (SHIM)

Please encircle the response that best describes you for the following five questions:

Over the past 6 months:					
1. How do you rate your confidence that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never or never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always or always 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?	Almost never of never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always or always 5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never or never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always or always 5

- Scoring
  - Severe ED: 1-7
  - Moderate ED: 8-11
  - Mild-moderate ED: 12-16
  - Mild ED: 17-21
  - No ED: 22-25

Rosen RC, et al. Int J Impot Res. 1999; 11(6): 319-326.

Males: Low T Adam Questionnaire

Check if you have any of the following:

- ❑ *1. Do you have a decrease in libido (sex drive)?*
- ❑ *2. Do you have a lack of energy?*
- ❑ *3. Do you have a decrease in strength and/or endurance?*
- ❑ *4. Have you lost height?*
- ❑ *5. Have you noticed a decreased "enjoyment of life"?*
- ❑ *6. Are you sad and/or grumpy?*
- ❑ *7. Are your erections less strong?*
- ❑ *8. Have you noticed a recent deterioration in your ability to play sports?*
- ❑ *9. Are you falling asleep after dinner?*
- ❑ *10. Has there been a recent deterioration in your work performance?*

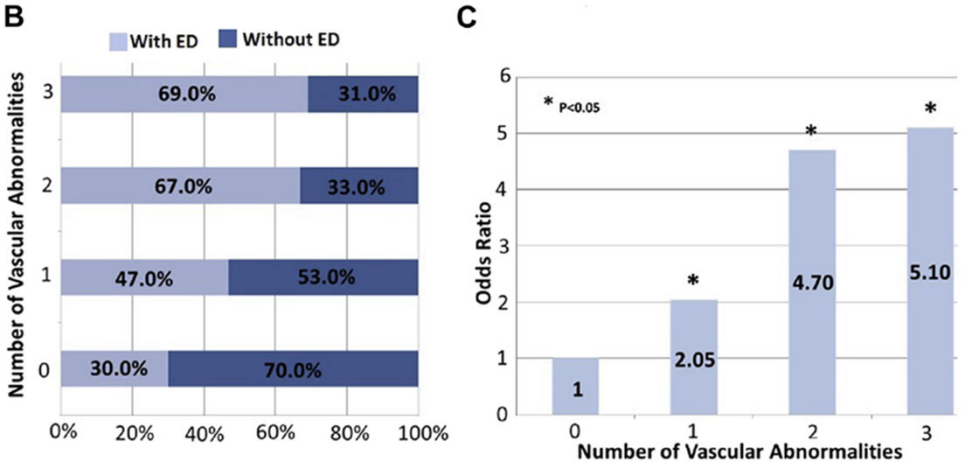
If you checked question **1** or **7** or ***any 3 other questions***, you may have low testosterone. A simple blood test can determine your testosterone level. **Talk with your doctor to see if you should be tested.**

Morley JE, et al. Metabolism. 2000; 49(9): 1239-1242.

Males

Subclinical Vascular Disease and Subsequent Erectile Dysfunction: The Multiethnic Study of Atherosclerosis (MESA)

David I. Feldman, BS; Miguel Cainzos-Achirica, MD; Kevin L. Billups, MD; Andrew P. DeFilippis, MD, MSc; Kanchan Chitaley, PhD; Philip Greenland, MD; James H. Stein, MD; Matthew J. Budoff, MD; Zeina Dardari, MSc; Martin Miner, MD; Roger S. Blumenthal, MD; Khurram Nasir, MD, MPH; Michael J. Blaha, MD, MPH



- **B:** ED frequency among patients with different vascular abnormalities
- **C**: Odds ratio for ED in patients with different numbers of vascular abnormalities

- Vascular studies at baseline: CaC, CIMT, FMD, vascular stiffness, carotid plaque score, ABI, etc.

- **Objective:** Determine the association between baseline subclinical CVD and subsequent ED
- **Study:** first to reveal that subclinical CVD is an ED predictor and to determine the temporal relationship between ED and subclinical CVD
  - 1862 men, mean age 59.5 years, no known CVD
  - Diverse population: Caucasian: 42.8%, African American: 23.5%, Hispanic: 23%, Chinese: 10.6%
  - CV risk stratification at baseline; ED questionnaire ~ 9 years after baseline studies
- **Results:**
  - Men with ED had higher baseline prevalence of every abnormal measurement except ABIs when compared with men w/o ED
  - CaC and carotid plaque score ≥ 2, SS associated with subsequent ED
- Conclusion: Subclinical vascular disease is common in men who later develop ED

Feldman DL, et al. Clin Cardiol. 2016; 39(5): 291-298.

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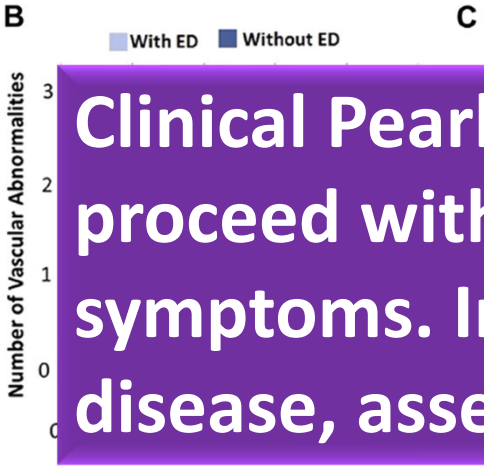

Clinical Pearl: In all males with erectile dysfunction, proceed with CV risk stratification, regardless of symptoms. In all men with subclinical vascular disease, assess for ED

- **B:** ED frequency among patients with different vascular abnormalities
- ***C***: Odds ratio for ED in patients with different numbers of vascular abnormalities

- **Objective:** Determine the association between baseline subclinical CVD and subsequent ED
- **Study:** first to reveal that subclinical CVD is an ED predictor and to determine the temporal relationship between ED

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red

  - CAC and carotid plaque score ≥ 2 SS associated with subsequent ED
- Conclusion: Subclinical vascular disease is common in men who later develop ED

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Males

Five-year prospective study on cardiovascular events, in patients with erectile dysfunction and hypotestosterone

Rosanna Iacona [1], Vito Bonomo [1], Mariaconcetta Di Piazza [1], Angela Sansone [1], Manuela Usala [2], Salvatore Novo [1], Carlo Pavone [3]

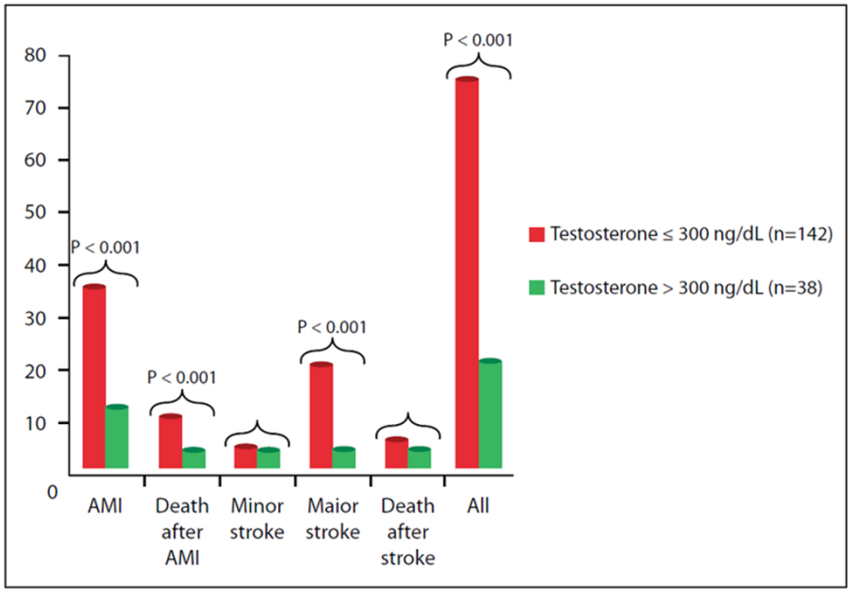

Figure 1.
Major adverse cardiovascular events (MACEs) at mean follow-up of 5.1 years according to testosterone levels.

- **Objective:** Investigated the prognostic significance of testosterone on CV outcomes
- **Study:** 5-year prospective study assessing CVD in men with ED and TD
  - 802 men, 40-80 years old at intermediate CV risk
    - Framingham 10 year CAD event: 10-20%
  - TT levels obtained: > 300ng/dL considered normal
  - FMD obtained and IIEF-5 questionnaire administered
- **Results:**
  - TT < 300ng/dL had SS higher prevalence of:
    - HTN, DM, hyperlipidemia, obesity, endothelial dysfunction
  - TT < 300ng/dL SS more frequent:
    - AMI, death post MI, major stroke, and the composite of all MACE
  - Independent predictors of future CV events were:
    - Dyslipidemia, obesity, TT < 300ng/dL, and erectile dysfunction
- **Conclusion: Men with CVD RFs and ED should have TT levels obtained; TTh may prevent future CV events**

Iacona R, et al. Arch Ital Urol Androl. 2017; 89(4): 313-315.

Males

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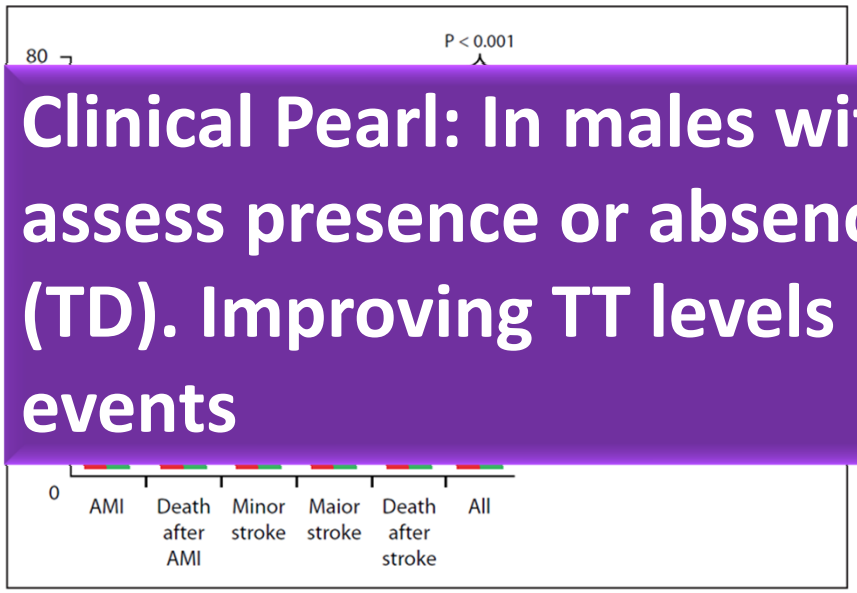

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Major adverse cardiovascular events (MACEs) at mean follow-up of 5.1 years according to testosterone levels.

- Objective: Investigated the prognostic significance of testosterone on CV outcomes
- Study: 5-year prospective study in on CVD in men with ED and TD
  - 892 men, 40-80 years old at intermediate CV risk

Clinical Pearl: In males with ED, check hormone levels to assess presence or absence of testosterone deficiency (TD). Improving TT levels may decrease major adverse CV events

  - all MACE
  - Independent predictors of future CV events were:
    - Dyslipidemia, obesity, TT < 300ng/dL, and erectile dysfunction
- Conclusion: Men with CVD RF and ED should have TT levels obtained; TTh may prevent future CV events

Iacona R, et al. Arch Ital Urol Androl. 2017; 89(4): 313-315.

Key Points

- A complete history provides insight into CV risk and the need for additional risk stratification. In addition to traditional RFs
  - In females, ask about: reproductive history, inflammatory disease history, bone density, mental health struggles, VMS, marital stress
  - In males, ask about: sexual history and in particular ED, work stress, have males proceed with the IIEF-5 and ADAM questionnaires
  - In both, assess: all stressors, sleep (OSA), anxiety, anger, radiation history, alcohol, physical activity, nutrition, socioeconomic status, MetS, gut health, exposures (heavy metals), sexual health

Clinical Pearls

- In females
  - VMS may represent a female-specific CVD risk factor
  - Peri- and PMP females with frequent or persistent VMS warrant CVD risk stratification, CVD risk reduction and prevention
- In males
  - ED is common and share the same risk factors and pathophysiology with CVD
  - ED is commonly associated with TD
  - ED is a marker of general vascular disease and precedes a CVD event by 2-3 years
  - ED is highly prevalent in CAD patients and is associated with increased all-cause mortality
  - ED diagnosis and treatment should include CVD risk stratification and prevention

Physical Exam

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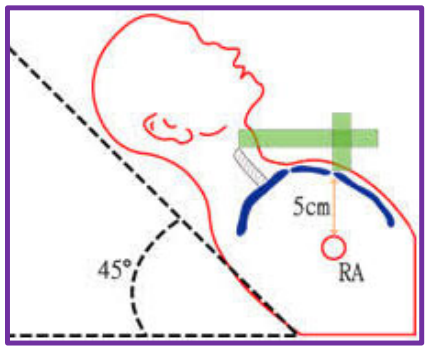
Physical Exam

Please make sure the patient has a yearly complete physical exam. Either you do one and/or the patient has a PCP who will do one.



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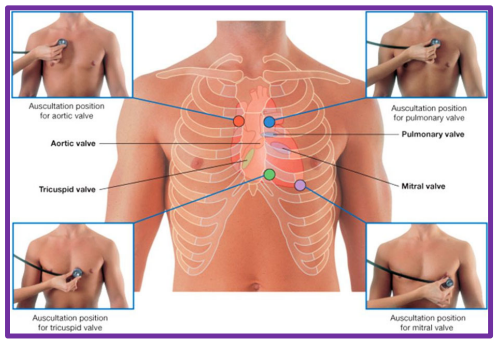

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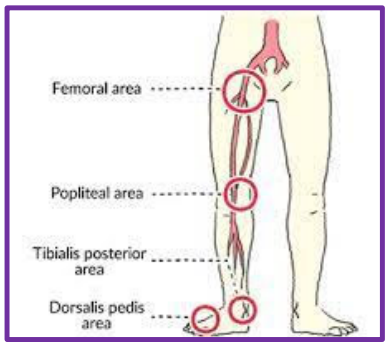

otsuka.co.jp

The Autonomic Nervous System and CVD

Resting Heart Rate

Heart Rate Recovery Time

Each is a strong predictor of CV risk and all-cause mortality

Heart Rate Variability

The Autonomic Nervous System and CVD

- **Resting Heart Rate (RHR)**
  - There is a remarkably strong association between heart rate and survival
  - A normal resting heart rate is 62 beats/min
  - As heart rate ↑ to 75 to 80 b/min, there are marked increases in total mortality and CAD mortality
  - For every increase in HR by 4 beats/minute the CHD risk increases 7-10%

Lauer M. Cleve Clin J Med. 2009; 76 Suppl 2:S18-22.
Wirtz P, von Kanel R. Curr Cardiol Rep. 2017; 19(11): 111.
Kivimaki M, Steptoe A. Nat Rev Cardiol. 2018; 15(4): 215-229.
Fioranelli M, et al. Front Immunol. 2018; 9:2031.

The Autonomic Nervous System and CVD

- **Heart Rate Recovery Time (HRRT)**
  - An optimal HRRT is a decrease in HR from peak exercise to 1 minute by > 12 b/min
    - Peak HR = 160 b/min, an abnormal HRRT at 1 min = HR > 148 b/min
  - Low HRRT strongly predictive of SCD
  - PVC's early in recovery associated with increased mortality
  - The evidence suggests that the link between HRRT and mortality may be a reflection of the PSN system's antiarrhythmic properties
- **HRRT is thought to be a function/measure of PSN activity**

Lauer M. Cleve Clin J Med. 2009; 76 Suppl 2:S18-22.
Wirtz P, von Kanel R. Curr Cardiol Rep. 2017; 19(11): 111.
Fioranelli M, et al. Front Immunol. 2018; 9:2031.
Guan L, et al. Front Neurol. 2018; 9: 90.

The Autonomic Nervous System and CVD

- **Heart Rate Variability (HRV)**
  - HRV is defined as the fluctuations in the intervals between normal heartbeats
  - Just as with RHR, there is robust literature linking decreased HRV (↑ HR) to cardiac events and mortality
  - HRV is an independent predictor of MI and SCD
    - Low HRV: SNS predominance and increased CV events and mortality
    - High HRV: PNS predominance and decreased CV events and mortality
  - Decreased HRV is present in all persons with HTN
- **HRV provides information on the body's adaptability to stress**

Lauer M. Cleve Clin J Med. 2009; 76 Suppl 2:S18-22.
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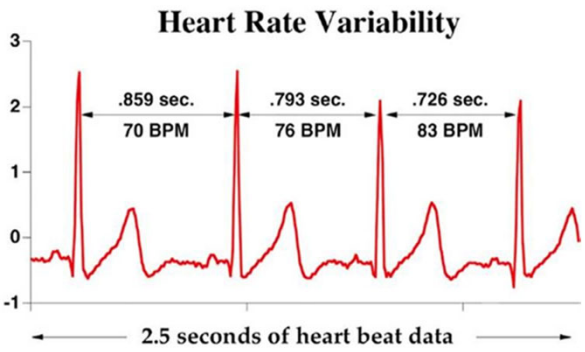
The Autonomic Nervous System and CVD



Low HRV	High HRV
"Fight or Flight"	"Rest & Digest"
Easily exhausted	Improved Performance
Low Adaptability	High Adaptability
Decreased Cognition	Improved Cognition

- **Chronic ds associated with ↓ HRV**
  - Obesity
  - IR and diabetes
  - Borderline HTN and HTN
  - Hyperlipidemia
  - CAD
  - CVD (TIA, stroke, HF)
  - PVD
  - Anxiety and depression

- **Age, fitness, lifestyle dependent**
- **20-25 years old: ~ 55-100msec**
- **60-65 years old: ~ 25-40msec**

Lauer M. Cleve Clin J Med. 2009; 76 Suppl 2:S18-22.
Wirtz P, von Kanel R. Curr Cardiol Rep. 2017; 19(11): 111.
Fioranelli M, et al. Front Immunol. 2018; 9:2031.
Guan L, et al. Front Neurol. 2018; 9: 90.

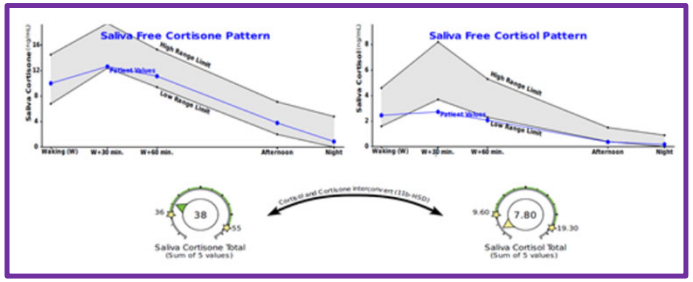
Physical Exam

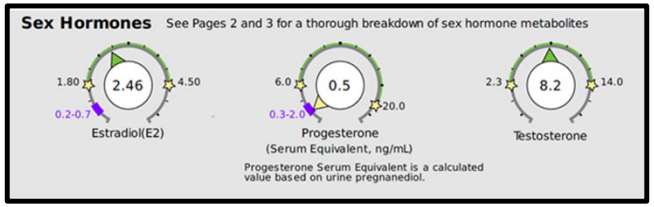
- Females
  - Breast exam and gynecological exam (typically includes a rectal exam)
- Males
  - Breast exam, testicular exam with testicular measurement, and rectal exam
- Males and Females
  - BP, HR, weight, BMI, waist: hip circumference
  - HEENT, thyroid, lung, abdominal exam
  - Take shoes and socks off to assess peripheral circulation, etc.

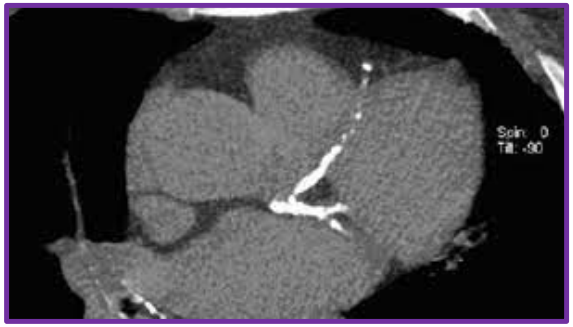
Key Points and Clinical Pearls

- Typical exam findings can provide insight into CV risk
- In females, do a breast and rectal exam, in addition to following guideline recommendations re: mammography and gyn exams, especially if you are considering hormone therapy
- In males, do a breast exam, examine and measure the testes, do a rectal exam and consider testicular ultrasound, if appropriate
- Use the history and physical exam to drive targeted testing
- Test, don’t guess

Laboratory Testing







ausrad.com

Laboratory Testing

- General
  - CBC, CMP with GGT, complete TFTs with thyroid antibodies, fasting insulin, Hb A1c, leptin, RBC Mg and Zn, vitamin D, ferritin, DHEA-S
- Cardiovascular
  - Screening lipid panel, TMAO, hs-CRP, homocysteine
  - Advanced lipid panel: LDL-P, HDL-P, APO B, fibrinogen, Lp(a), Lp-PLA2, myeloperoxidase, ox-LDL, ADMA
  - Genetics: MTHFR, APO E
  - Consider: CIMT, CaC scan, and functional testing

Laboratory Testing

- Female hormone testing
  - Pre and perimenopause
    - DUTCH cycle map + DUTCH complete or DUTCH Plus
    - Serum: FSH, LH, SHBG, prolactin, E2, T (must use LC-MS/MS), Pg, pregnenolone
  - Peri and postmenopause
    - DUTCH complete or DUTCH Plus +/- cycle map
    - Serum: FSH, LH, SHBG, prolactin, E2, T, and P (LC-MS/MS), pregnenolone
- Female additional testing
  - Mammography or alternative, guideline driven
  - Pap, pelvic exam, and rectal exam
  - BMD as indicated

Laboratory Testing

- Males hormone testing
  - DUTCH complete or DUTCH plus
  - Serum: FSH, LH, prolactin, TT (if < 200ng/dL consider LC-MS/MS), Free T (equilibrium dialysis or calculate), E2 (LC-MS/MS), SHBG, PSA, pregnenolone
- Male additional testing
  - Testicular ultrasound
  - BMD as indicated

Treatments

Arterosil

- Strengthens glycocalyx and ameliorates vascular dysfunction
- Rhamnan Sulfate (RS): A sulfated polysaccharide that is the main component of the fiber extracted from the green algae, such as *Monostroma nitidum*
  - Known functions:
    - Antiviral, anticoagulant, and antitumor activities
    - Inhibits hyaluronidase activity and has anti-hypercholesterolemic effects
    - It decreases blood sugar and helps with weight control
  - RS inhibits endothelial cell inflammation
    - Rhamnan sulfate is a powerful glycocalyx regenerating compound
    - Tissue factor (TF) and von Willebrand factor (VWF) are both secreted in response to inflammation
      - TF expression contributes to thrombus formation and VWF increases platelet aggregation
    - RS, in the setting of LPS-induced endothelial cell inflammation, decreases TF and VWF
- **Arterosil has recently been patented for vulnerable plaque stabilization and regression**

Okamoto T, et al. J Nat Med. 2019; 73(3): 614-619
Suzuki K, Terasawa M. Mar Drugs. 2020; 18(4): 228.

Arterosil Restores EGCX Integrity

MRI Carotid Plaque Regression Studies using Arterosil; lipid rich necrotic core (LRNC) reduction 47% (males) and 64% (females)

- **Objective:** Human proof-of-concept pilot study to determine Arterosil's effect on carotid plaque composition
- **Study:** Pre- and post RS nutraceutical treatment (1 BID), MRI PlaqueView was performed
- **Results:** There was a 47% (male) and 64% (female) reduction in carotid plaque LRNC in 60 days
- **Conclusion: Short-term, there was SS carotid plaque regression, 47% in men and 64% in women; warrants a larger study**

Unpublished data: Beijing Hospitals.

Arterosil Restores EGCX Integrity

MRI Carotid Plaque Regression Studies in Patients with Documented CVD using Statins: No reduction in % stenosis found in either study; LRNC reduction 25% (males) and 38% (females)

- **Objective:** Determine rosuvastatin's effect on carotid artery plaque volume
- **Study:** 33 patients with hyperlipidemia and carotid plaque were treated with low or high dose rosuvastatin for 24 month; MRI pre and after 24-months using an FDA-approved technology for advanced plaque characterization and quantification
- **Results:** The average carotid plaque LRNC reduction was 25%
- **Conclusion: In addition to decreasing LDL cholesterol, statins decrease LRNC by an average of 25% using MRI PlaqueView technology**

- **Objective:** Determine the time course of change in carotid plaque morphology and composition with statins
- Study: 33 individuals with either coronary or carotid disease and hyperlipidemia, treated with atorvastatin x 3 years; MRI pre treatment and yearly for 3 years
- Results: The average carotid plaque LRNC reduction was 38%
- **Conclusion: In addition to decreasing LDL cholesterol, statins decrease LRNC by an average of 38% using MRI PlaqueView technology**

Arterosil Restores EGCX Integrity

MRI Carotid Plaque Regression Studies in Patients with Documented CVD using Statins: No reduction in % stenosis found in either study; LRNC reduction 25% (males) and 38% (females)

- **Objective:** Determine rosuvastatin's effect on quantification
- **Results:** The average carotid plaque LRNC reduction was 25%
- **Conclusion: In addition to decreasing LDL cholesterol, statins decrease LRNC by an average of 25% using MRI PlaqueView technology**

- **Objective:** Determine the time course of change in
- **Conclusion: In addition to decreasing LDL cholesterol, statins decrease LRNC by an average of 38% using MRI PlaqueView technology**

Bottom Line: Arterosil, in the short-term, led to a greater % reduction in LRNC than statins, thus better stabilizing vulnerable plaque

Magnesium

- Magnesium plays a key role in regulating a number of ion transporters, including potassium and calcium channels
  - Modulates neuronal excitation
  - Intracardiac conduction
  - Myocardial contraction
- Role in regulating vascular tone
- Atherogenesis, thrombosis, and vascular calcification
- Endothelial and vascular smooth muscle cell proliferation and differentiation
- Mg deficiency linked to CVDs and increased MI
- Manage 2-6 caps (300-900mg) daily as bisglycinate chelate

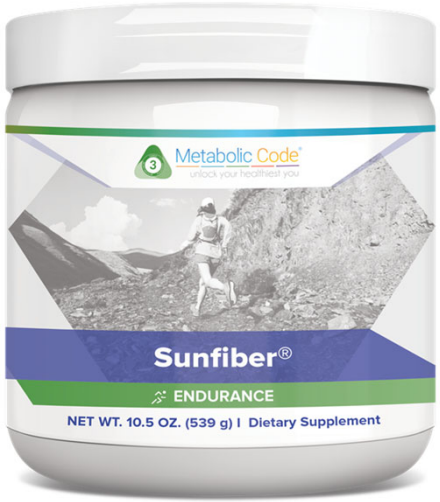
Huerta MG, et al. Diabetes Care. 2005; 28(5): 1175-1181.

Aged Garlic Extract

- Proprietary aged garlic extract supports cardiovascular health
- Over 750 clinical studies supporting uses
- Clinically lowers blood pressure: 16%
- **Leads to plaque regression**
- Supports blood vessel integrity
- Antiglycation, diabetes support
- Improves microbiome
- Immune support
- 1-2 caps 2 times daily (600-1200mg BID)

Reid K, Frank OR, Stocks NP. Maturitas. 2010; 67(2): 144-150.

Sunfiber



- Soluble dietary fiber – partially hydrolyzed guar gum
- Reported beneficial in decreasing cardiovascular risks, reduces cholesterol levels
- Prebiotic – produces SCFAs in the GUT – supports microbiome
- Supports: Gut, immune, cardiovascular, and estrogen metabolism
- 2017 review of 31 meta-analyses reported dietary fiber intake:
  - Significantly reduces CVD and CVD mortality
  - Reduces incidence coronary artery disease and stroke
  - Reported to reduce total serum cholesterol and LDL cholesterol levels
- 1 scoopful daily = 14gm

Yoon SJ, et al. J Clin Biochem Nutr. 2006; 39: 134-144.

HPA-Axis Dysfunction

- **QuiCalm**
  - Contains: Relora, Holy Basil, L-theanine
  - Stress, anxiety, promotes relaxation
  - Supports stressful eating
  - Balances cortisol levels
  - Improves neurochemical balance for stress-related food cravings
  - Dose: 1 cap 3x day
- **AdaptCNS**
  - Contains: Rhodiola, Cordyceps, Thai Ginseng (PDE5-I), Schisandra
  - Helps body adapt to stresses, including physical/emotional/mental
  - Improves cortisol levels and adrenal support
  - HPA axis support
  - Helps improve energy and stamina
  - Used in stress and cortisol imbalances with or without anxiety
  - Dose: 2 caps in the am and 1 cap in the afternoon

Libido and Erectile Dysfunction

- T-Time
  - Contains: Thai Ginseng, Tribulus, Testofen, Eurcoyma, PS, Zinc
  - Supports testosterone levels in men and women
  - Helps improve testosterone/cortisol ratio
  - Helps maintain muscle mass and strength
  - Helps improve libido and ED
  - Antioxidant
  - Dose: 2 caps daily
- Yohimbe: 36mg daily
- Citrulline: 1.5 grams/day

Khera M, Goldstein I. BMJ Clin Evid. 2011; 2011: 1803.
Cormio L. et al. Urology 2011; 77(1):: 119-122.
Promthep K, et al. Med Sci Monit Basic Res. 2015; 21:100-108.
Wankhede S, et al. J Sport Health Sci. 2016; 5(2): 176-182.
Steels E, et al. Phytother Res. 2017; 31(9): 1316-1322.

Estrogen: Progesterone Balance

- Contains: wild yam extract, black cohosh
- Actions:
  - Similar to E2, but does not bind to ER
  - Studies support use for menopausal SS
  - May help support BMD
  - Breast protective
  - Dose: 1 pump to forearms 2x weeks
- Monitor hormones regularly

- Effects are dose dependent
- Raises Pg and lowers E2 by blocking FSH and increasing LH
- Increases CNS dopamine, which blocks prolactin release
- May improve: PMS, breast tenderness
- Do not use if: hormone driven cancers, pregnancy, breast feeding (lowers prolactin), Parkinson's disease (might limit Parkinson's drug effectives)

Van Die MD, et al. Planta Med. 2013; 79(7):: 562-575.

Case Studies

essay-lib.com

Peter: A 50 Year Old Male

- Peter is a 50-year old lawyer who has been working form home since the pandemic. He states that he cannot concentrate, his work performance has decreased, and he has a foggy brain all the time. He is here because his spouse insisted. He has had 6-9 months of decreased libido, erectile dysfunction (ED), reduced spontaneous and sex-related erections, and decreased orgasmic function. Prior to 9 months ago, he did have decreased morning erections, which he thought was normal for his age, but was w/o any other sexual symptoms.
- He sleeps 6-7 hours each night such that he can wake up at 0400 to exercise for 2-hours/d (ironman), everyday, with no off days. He survives on coffee all day, otherwise he could not keep up. His diet is on and off; lately, mostly off. When on, he eats a Mediterranean style diet that is gluten and dairy free. His diet lately, consists of 1-2 meals a day, processed foods, lots of carbs, few vegetables, and a lot of animal protein
- CVD risk factors include: Borderline HTN, hyperlipidemia, IR, ED, and (+) FH

Peter: A 50 Year Old Male

- Meds: None
- Allergies: none
- PMHx: Vasectomy at 45 years old
- Family History: Dad had 1st MI at 45 and is APO E 3/4, his older brother had his 1st MI at 50 and is also APO E 3/4
- Social History: happily married for 25-years, 3 grown healthy children; he drinks red wine with dinner on weekends, he never smoked
- ROS: remarkable for irritable bowel and testicular shrinkage over past 6 months
- PE: BP: 150/90 (similar to what he gets at home), HR: 90, 6'0 tall , 190 pounds, BMI: 25.8 (barely overweight), waist to hip ratio = 1.3: 1. JVP: normal, CV exam: (+) S4, Pulses: symmetrical and equal, testicular and rectal exams: normal. Scored an 8 on the ADAM (moderate ED)

Peter: History Summary

- 50 year old, asymptomatic male with CVD risk factors and sexual SS
  - Symptoms: decreased libido
  - Signs: ED, HTN, elevated HR, increased BMI and W:H ratio, HLD, and IR
  - CV risk factors: ED, HTN, HLD, IR, (+) FH premature CAD, abdominal obesity
- Peter probably has HPA axis dysfunction
  - Symptoms: he cannot concentrate, work performance has decreased, and he has a foggy brain all the time
  - Signs: poor sleep, needs coffee to keep going, over exercises
- Peter probably has TD
  - ED, decreased libido, testicular shrinkage brain fog, MetS
- Peter has dysbiosis with metabolic endotoxemia

Peter: Laboratory Testing

- General
  - CBC, CMP with GGT, complete TFTs with thyroid antibodies, fasting insulin, Hb A1c, RBC Mg and Zn, vitamin D, ferritin
- Cardiovascular
  - Screening lipid panel, TMAO, hs-CRP, homocysteine
  - Advanced lipid panel: LDL-P, HDL-P, APO B, fibrinogen, Lp(a), Lp-PLA2, myeloperoxidase, ox-LDL, ADMA
  - Genetics: MTHFR, APO E
  - Consider: CIMT and CaC scan

Laboratory Testing

- Males
  - DUTCH plus
  - Serum: FSH, LH, prolactin, TT (if < 200ng/dL consider LC-MS/MS), Free T (equilibrium dialysis or calculate), E2 (LC-MS/MS), SHBG, PSA
- Male additional testing
  - Testicular ultrasound

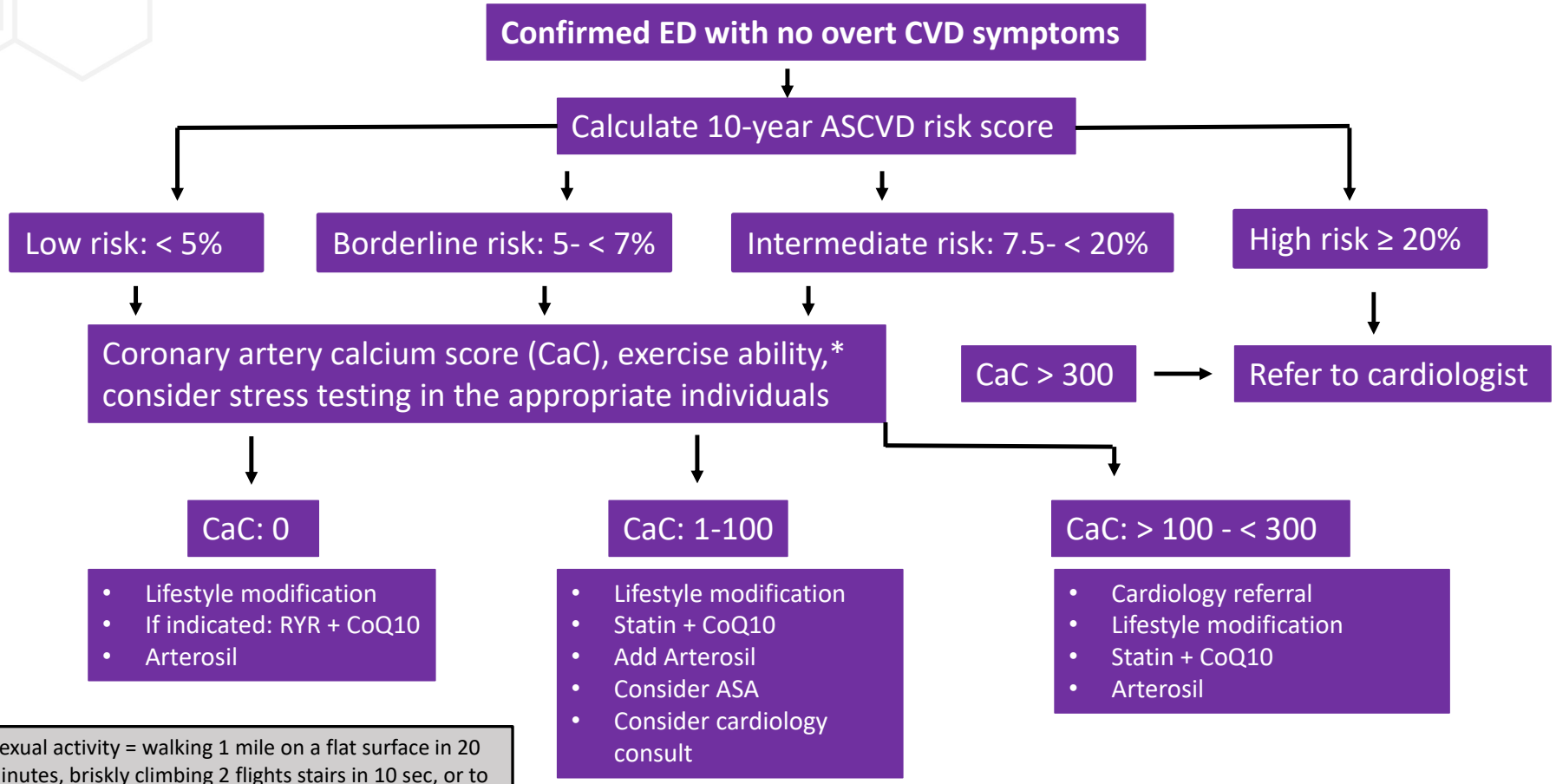
Laboratory Results

- General:
  - Glycemic parameters: FBS: 100, FI: 10, HbA1c: 5.9
  - Hormones: vitamin D: 30
  - Thyroid: TSH 1.0, T4: 1.5, T3: 3.2, RT3: 12, TPO: 65
- Cardiovascular:
  - Risk markers: Hs-CRP: 2.5 (goal < 1), homocysteine: 10 (goal 5-8), TMAO: 8.0 (≤ 6.2), ADMA: 125 (high risk, goal < 100)
  - Advanced lipid profile: TG: 180, LDL-P: 1300 (mod risk, < 1138 optimal), HDL-P: 5000 (high risk), APO B: 110 (mod risk)
  - Genetics: APO E 3/3
  - CIMT: 0.7 (goal < 0.5)
- Hormone:
  - TT: 225ng/dL, Free T: 55pg/mL, E2: 18pg/mL (LC-MS/MS), SHBG: 13; LH: 5.0
  - Ultrasound: 8 (range 12.0-19mL^2)

Question?

Do we need additional CV testing?

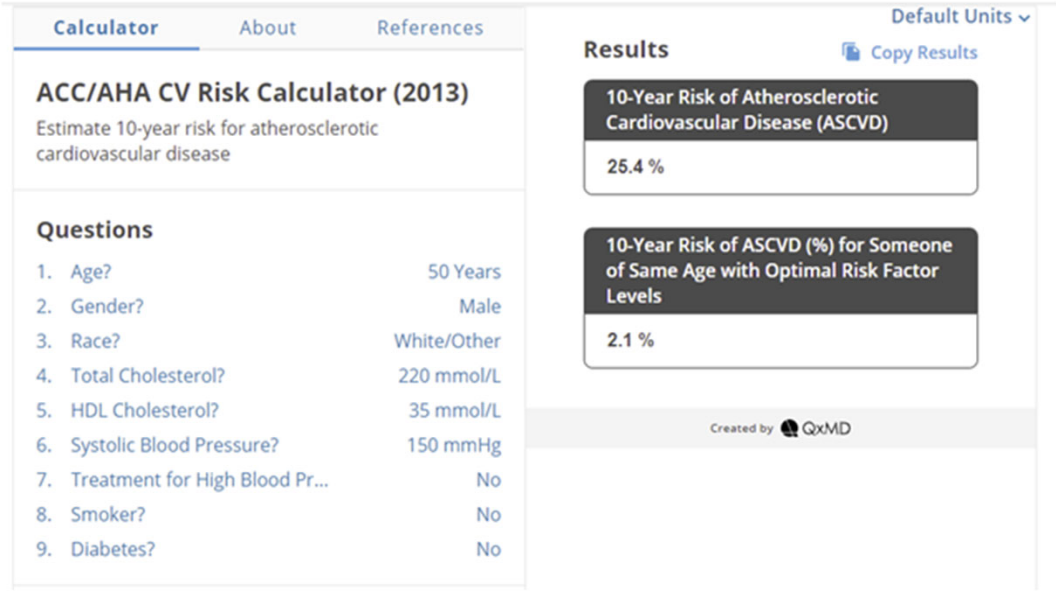
Decision Tree



- Sexual activity = walking 1 mile on a flat surface in 20 minutes, briskly climbing 2 flights stairs in 10 sec, or to 4 min of the Bruce treadmill protocol.

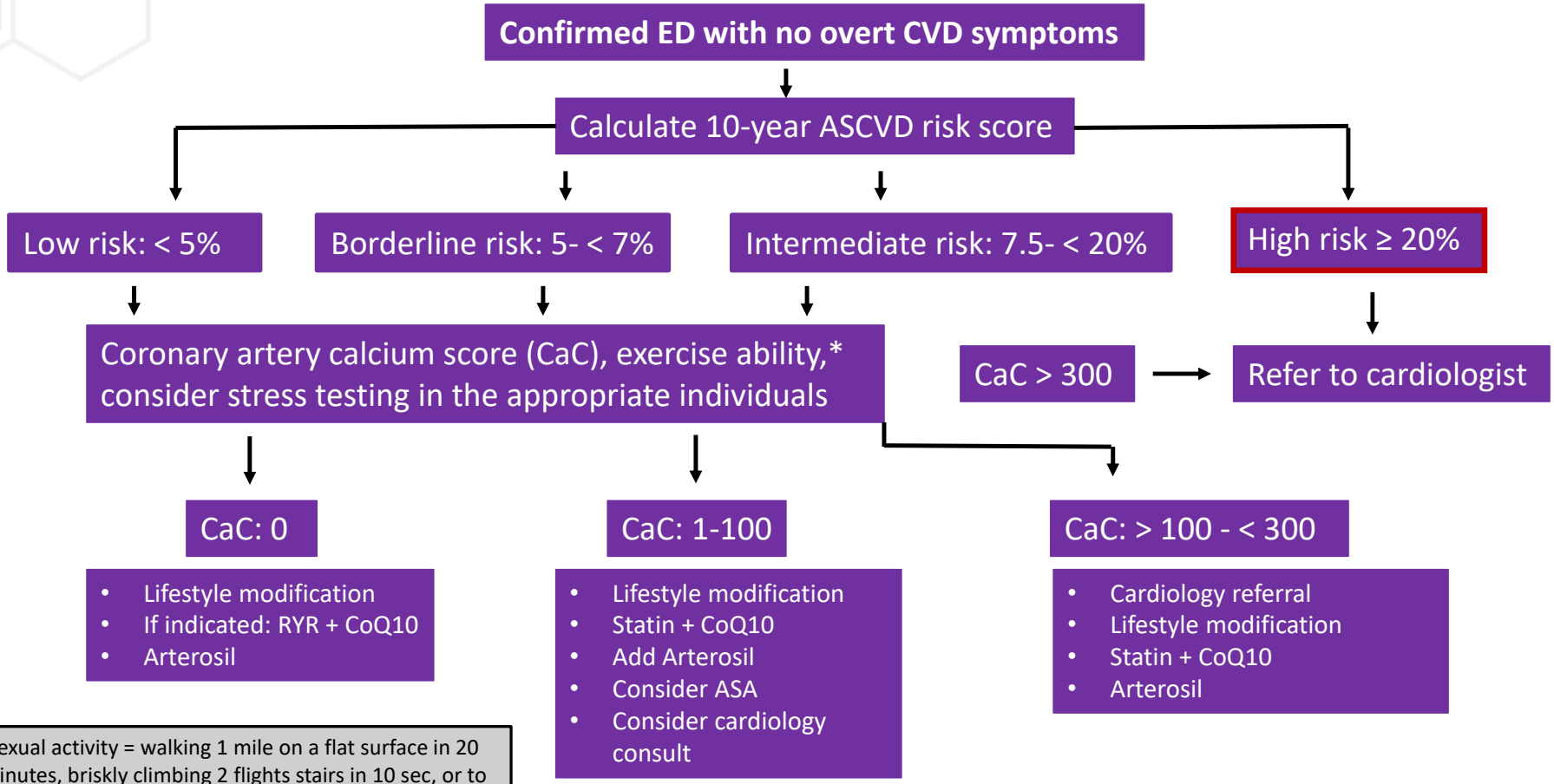
Adapted from: Miner M, et al. Sex Med Rev. 2019 7(3): 455-463.
Gandaglia G, et al. Eur Urol. 2014; 65(5): 968-978.

Peter: ACC/AHA CVD Risk Calculator



Lloyd-Jones DM, et al. Circulation. 2019; 139(25): e1162-e1177.

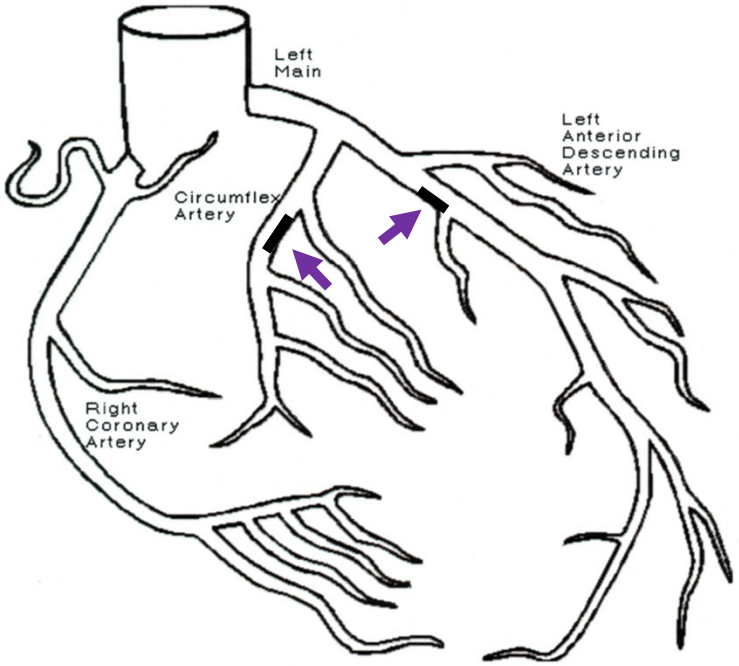
Decision Tree



- Sexual activity = walking 1 mile on a flat surface in 20 minutes, briskly climbing 2 flights stairs in 10 sec, or to 4 min of the Bruce treadmill protocol.

Adapted from: Miner M, et al. Sex Med Rev. 2019 7(3): 455-463.
Gandaglia G, et al. Eur Urol. 2014; 65(5): 968-978.

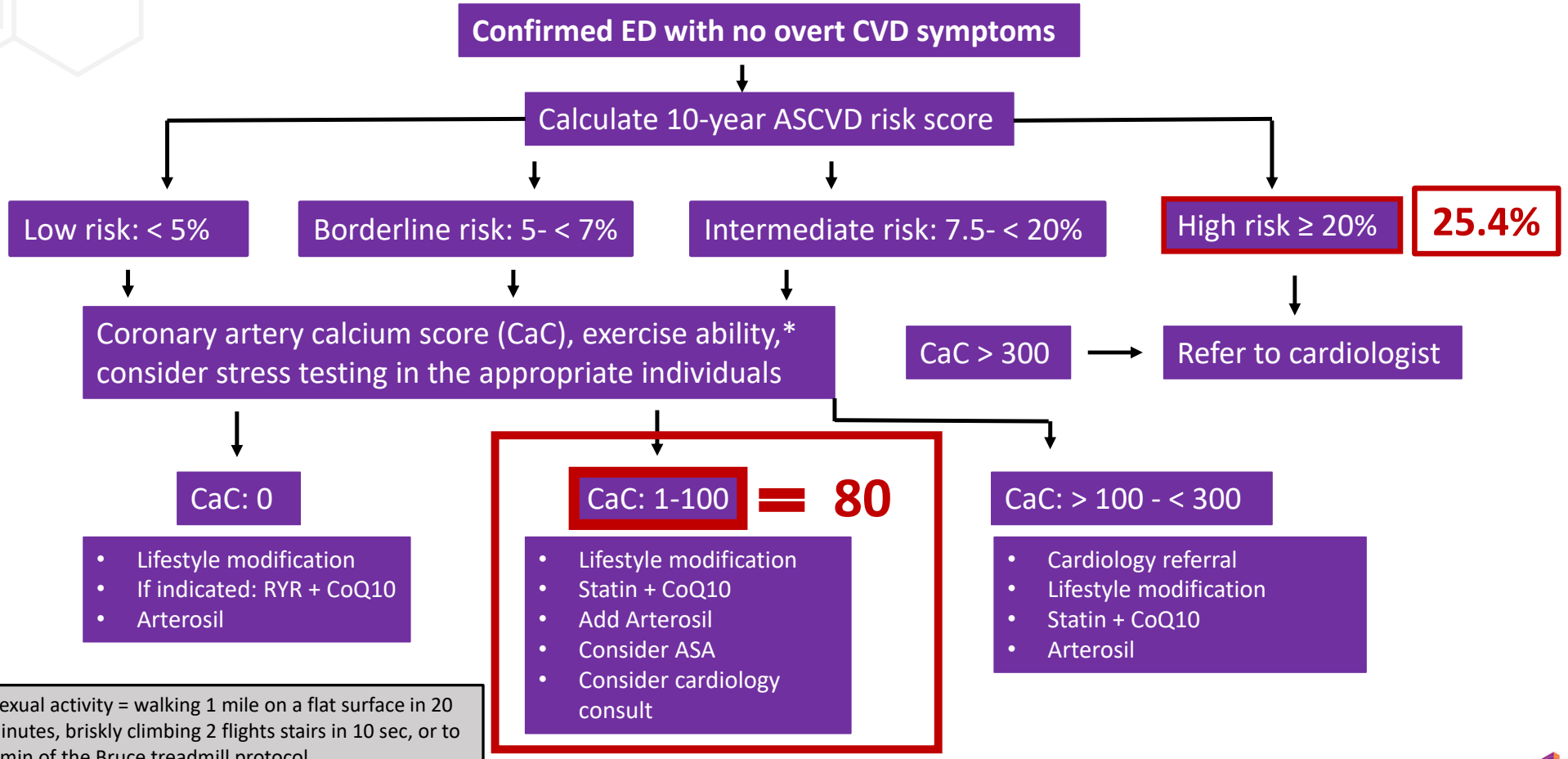
Peter CaC Scan and GXT



This diagram demonstrates the **LOCATION** of coronary artery calcifications only, but **DOES NOT NECESSARILY INDICATE THE PRESENCE, ABSENCE OR LOCATION OF A STENOTIC LESION.**

- Bruce-protocol GXT: 12 minutes, achieved 100% max HR, no ECG changes
- Resting HR: 50 beats/min
- HRRT: 125 at 1 minute (160-12 = 148)
- HRV: 75

Decision Tree



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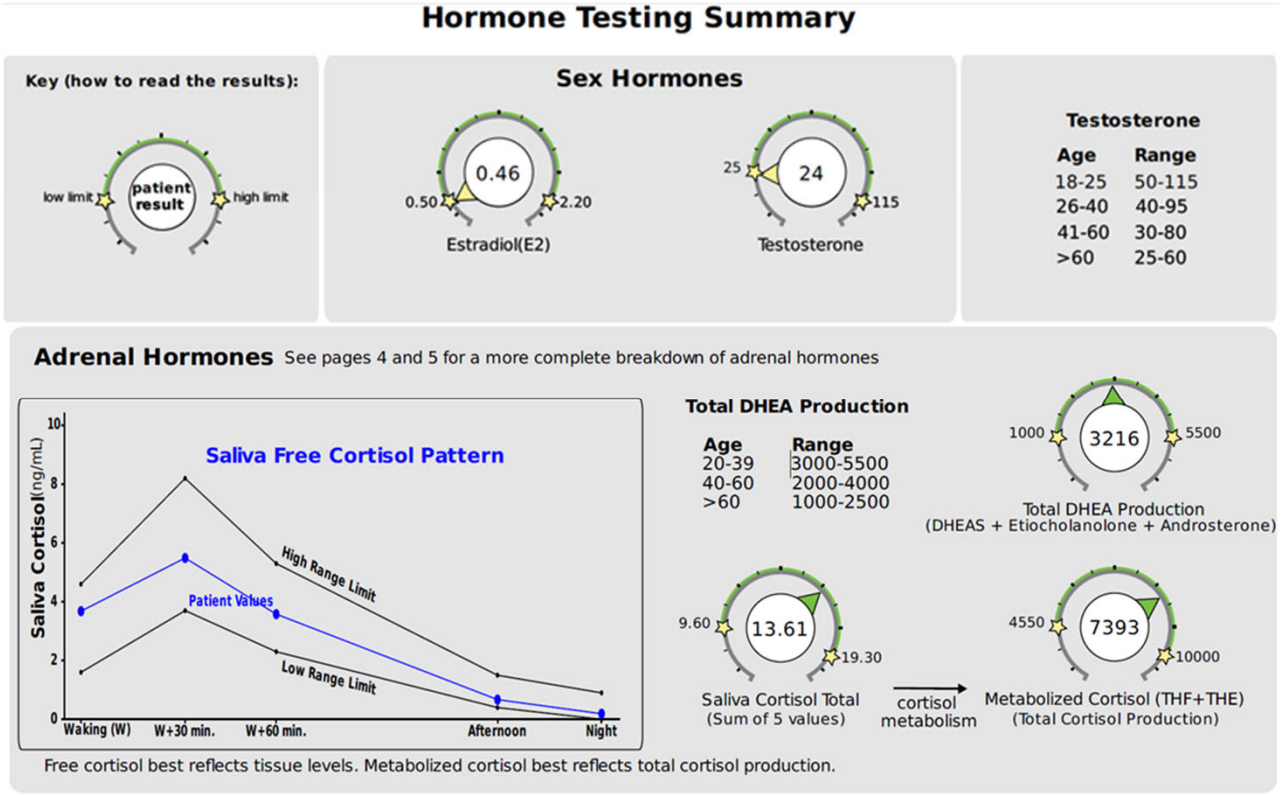
Adapted from: Miner M, et al. Sex Med Rev. 2019 7(3): 455-463.
Gandaglia G, et al. Eur Urol. 2014; 65(5): 968-978.

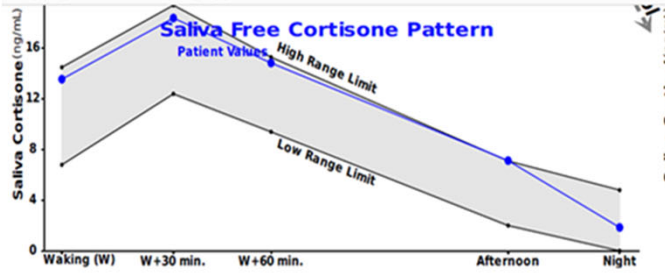
Peter’s DUTCH Plus

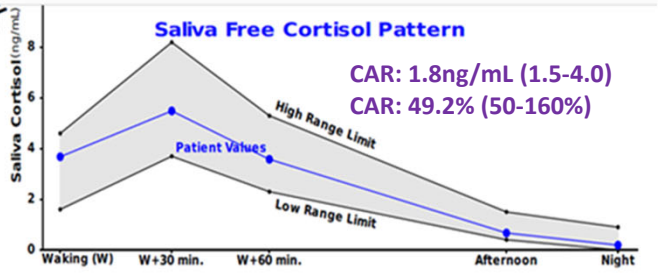


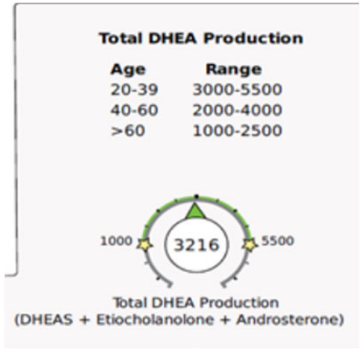
- The patient reports using a glucocorticoid. This may suppress adrenal function. See provider comments for more details.

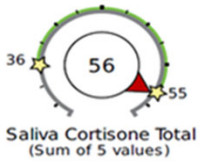
The Cortisol Awakening Response (CAR) was 1.81ng/mL (expected range 1.5-4.0) or 49.2% (range 50-160%). See page 5 for more details.

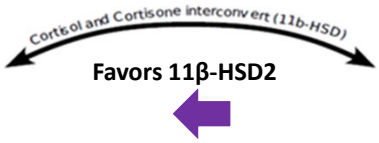
Peter's HPA Axis Assessment

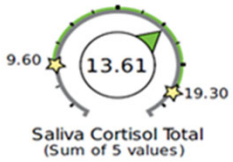




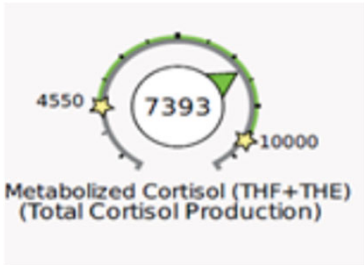


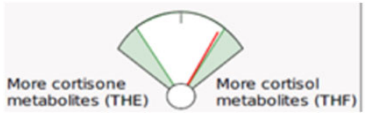






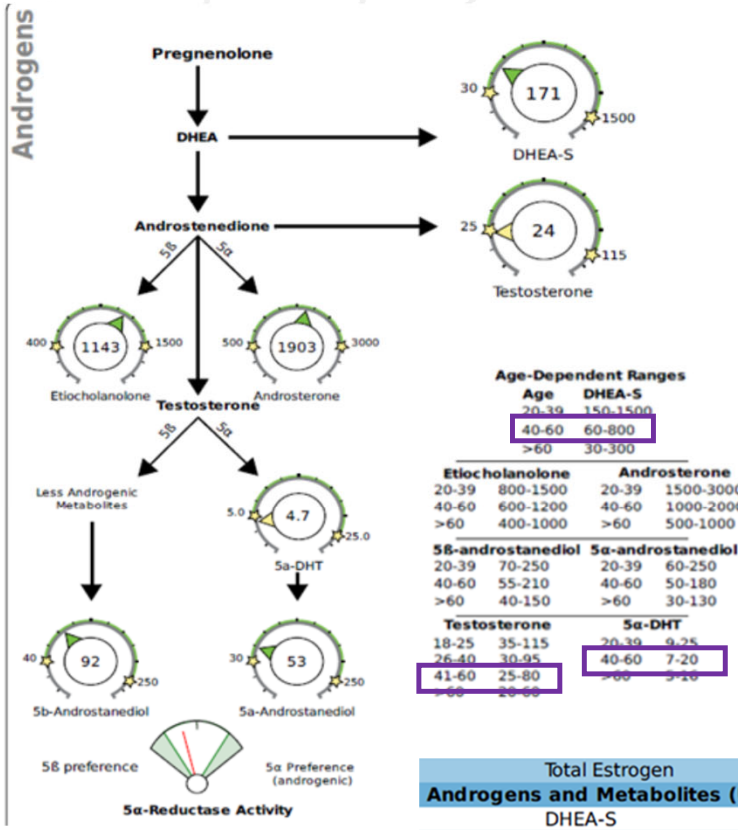
- See this pattern with:
  - Inflammation
  - IR/DM
  - Chronic stress





Glutathione Marker (may be deficient if low or high) - (Urine)				
Pyroglutamate	Low end of range	41.8	ug/mg	38 - 83
Melatonin* (Waking)	Low end of range	17.1	ng/mg	10 - 85
Oxidative Stress / DNA Damage, measured as 8-Hydroxy-2-deoxyguanosine (8-OHdG) - (Urine)				
8-OHdG (Waking)	Above range	13.0	ng/mg	0 - 8.8

Peter's Androgens



Age-Dependent Ranges

Age	DHEA-S
20-39	150-1500
40-60	60-800
>60	30-300

Etiocholanolone		Androsterone	
20-39	800-1500	20-39	1500-3000
40-60	600-1200	40-60	1000-2000
>60	400-1000	>60	500-1000

5ß-androstanediol		5α-androstanediol	
20-39	70-250	20-39	60-250
40-60	55-210	40-60	50-180
>60	40-150	>60	30-130

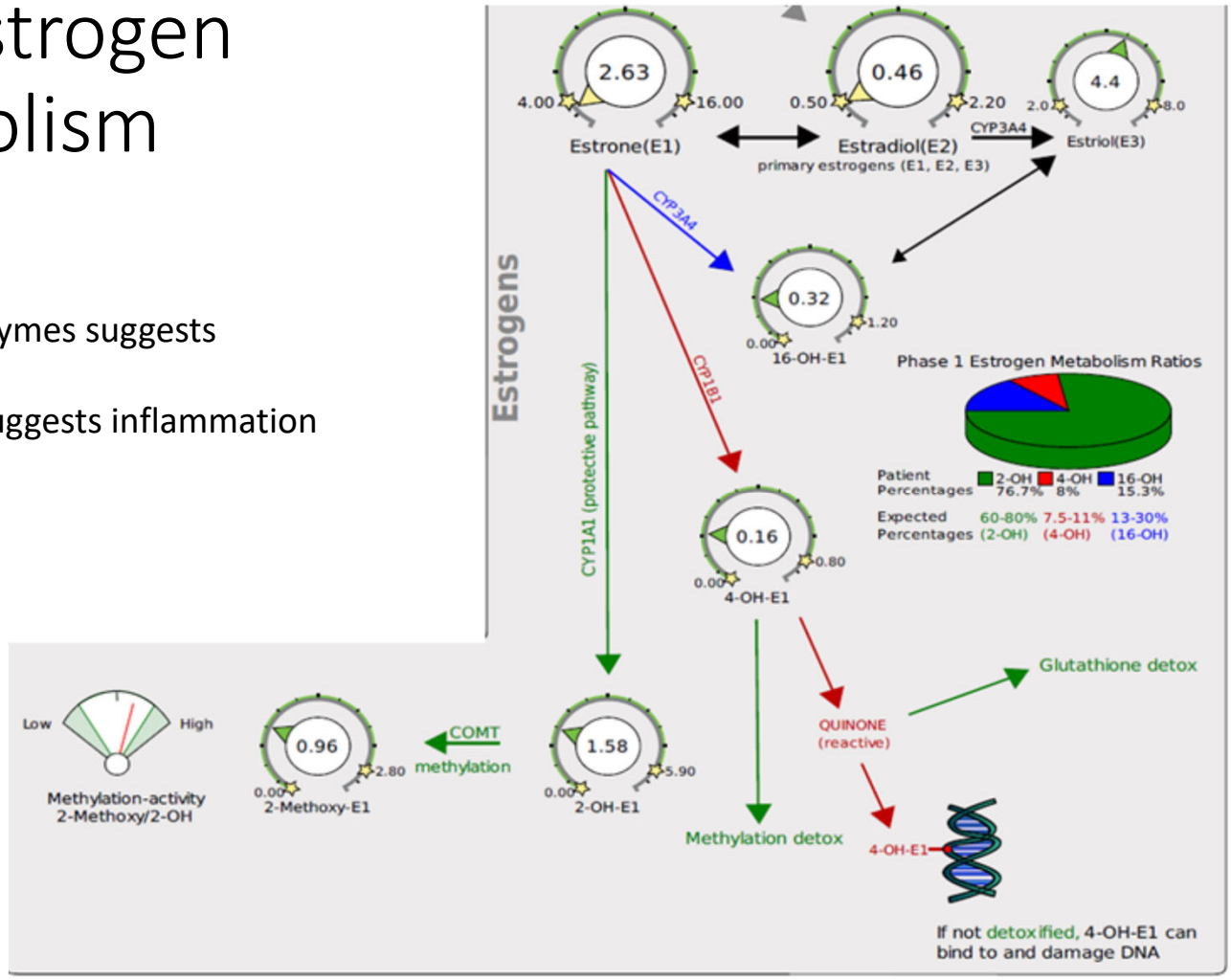
Testosterone		5α-DHT	
18-25	35-115	20-39	9-25
26-40	30-95	40-60	7-20
41-60	25-80	>60	5-16
>60	20-60		

- DHEA-S: adrenal cortex origin, not optimal or where would expect for 50 year old
- Etiocholanolone and Androsterone are both DHEA and T metabolites, normal range
- T, DHT, and 5α and 5β metabolites are low, no UGT SNP

	Total Estrogen	Low end of range	10.8	ng/mg	10 - 34
Androgens and Metabolites (Urine)					
	DHEA-S	Low end of range	170.6	ng/mg	30 - 1500
	Androsterone	Within range	1902.5	ng/mg	500 - 3000
	Etiocholanolone	Within range	1143.3	ng/mg	400 - 1500
	Testosterone	Below range	24.01	ng/mg	25 - 115
	5a-DHT	Below range	4.7	ng/mg	5 - 25
	5a-Androstanediol	Low end of range	52.6	ng/mg	30 - 250
	5b-Androstanediol	Within range	92.3	ng/mg	40 - 250
	Epi-Testosterone	Below range	24.8	ng/mg	25 - 115

Peter's Estrogen Metabolism

- Upregulation of all CYP enzymes suggests inflammation
- Aromatase upregulation, suggests inflammation



Treatment: Adaptogens

High Cortisol

- Ashwagandha
- L-theanine (mind racing)
- Relora (food cravings)
- Rhodiola (anxiety, performance, decreases CAR)
- Holy Basil (immune modulator, supports BS)
- Phosphatidyl Serine (PS)
- RG3 (CNS immune modulator)
- Melatonin

Mixed Cortisol

- Ashwagandha
- Rhodiola
- Cordyceps: decreases oxidative stress
- PS: decreases cortisol, 300-800mg at HS
- RG3 (CNS immune modulator)
- Melatonin

Low Cortisol

- Licorice: inhibits 11β-HSD2 activity (cortisol to cortisone)
- Glandulars: support

Start low and go slow!

Age, LH, Prolactin

- Primary Hypogonadism
  - T Replacement
- Secondary Hypogonadism

LH RR (1.5-9.3mIU/mL) **LH**

> Upper limits of RR

Could be at the lower end of RR or within the RR

Low Total Testosterone

3 - 18

Prolactin

> 18

Normal

High

- Work-up
  - MRI Brain to rule out prolactinoma
    - Cabergoline (dopamine agonist)
  - Chronic renal?
  - Hypothyroid?
  - Cortisol?

Lifestyle →
- 8-hours restful sleep, movement
- Higher protein, Mediterranean eating

Nutraceuticals →
- Eurycoma, Tribulus, Testofen, Thai Ginseng, Zinc

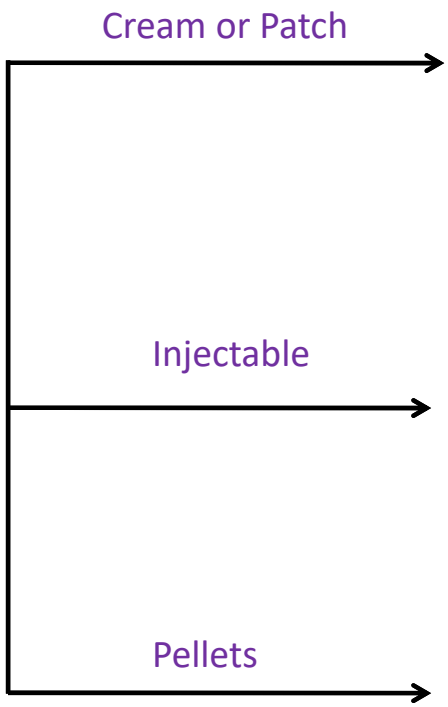
Age < 50-55 →
- Clomid: 5-15mg 3x week, most common
- HCG: 1000 IU 2x week x 6-8 weeks
  - 250 IU 6 d/w x 6-8 weeks
  - 500 IU 3 d/w x 3 weeks, then 500 IU 2d/w x 3 weeks
- Kisspeptin: 10mg at HS 5 d/w x 6 months

Age > 50-55 →
- Testosterone therapy (TTh)

** In men with secondary TD, especially younger men, don't forget to check for heavy metals, biotoxin illness, etc.

** Avoid glandulars with (+) TPO antibodies

Testosterone Options



- Testosterone patch
  - 2.5 and 5mg patches, starting dose is 5mg/day
- Topical Testosterone
  - AndroGel: 50mg/d; if using compounded cream you may need higher dose
- Keep it above the belt and rotate sites: chest/abd/flank/shoulders
- Labs in 1-month, 4-months, 8-months, 12-year, then 2x year is typical

- IM or Sub-Q (more comfortable for patient and as effective)
- Propionate (shortest acting) 10-25mg 2-3x week
  - Can use to dose pellets: for every 25mg place two 75mg pellets
- Enanthate: (for older men, less fluid retention) 25-50mg biweekly
- Cypionate (most common) 25-50mg biweekly

- Pellets - viable option
  - Consider cost
  - Dosing adjustments: patients do not need as much as you think!

**Check PSA before and after initiation
**PSA increase > 0.75ng/mL worrisome PC

Peter's Treatment Plan

System	Treatment
HPA Axis	• AdaptCNS: 2 caps in the AM and 1 cap in the afternoon • chelated Mg: 400mg TID • IV therapy with 2 grams Glutathione QOW • Melatonin troche 10mg, start 2.5mg QHS
CV System	• Gluten and dairy-free Mediterranean diet • Crestor 5mg QHS, CoQ10 300mg QPM • Arterosil 1 cap BID, Aged Garlic 1200mg BID, CoQ10: 300mg at HS • Baby ASA • Sun fiber • Omega 3 FA up to 4-grams/d, Curcumin 1-3grams/d
Hormones	• Testosterone gel 50mg QD • DIM • Vitamin D 5,000 IU/d
Thyroid	• Naltrexone 1.5mg/d, with slow up titration to 4.5mg/d • Moducare: Immune modulator • SPM active: 2 soft gels daily
GUT	• Probiotics • Mediterranean diet

Maggie: A 48 Year Old Perimenopausal Female

- Maggie is a 48 year old PMP female who seeks advice on MHT. Her last cycle was ~ 8 months ago and she is miserable. She has had brain fog, hot flashes, night sweats, and vaginal dryness for ~ 9-10 months. She has no energy, but feels anxious all the time, and her mind cannot stop racing. She has trouble sleeping, waking multiple times. In addition, she feels her heart racing all the time.
- She is happily married and has grown children. She is a physician and has a very busy practice. She has a normal body weight and BMI. She exercises regularly, she primarily runs (4-6 miles/d) with some minimal strength training 7d/week, 2x a day. She takes vitamin D 5000 IU/d, and a multivitamin after a recent BMD documented osteopenia.
- She eats a paleo diet, with organic, grass-fed beef, wild-caught fish, organic, free-range chicken. She drinks no alcohol, doesn't smoke

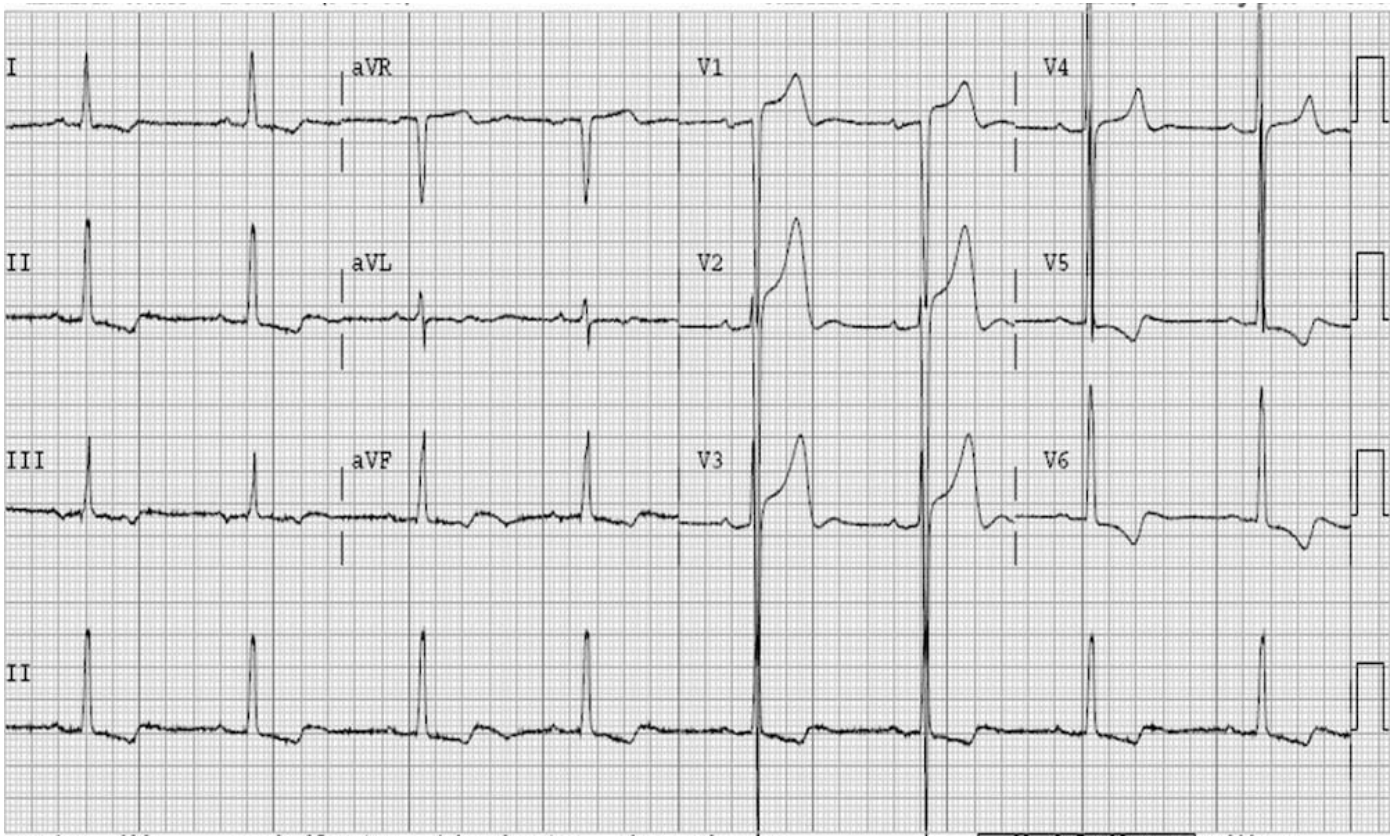
Maggie: A 48 Year Old Perimenopausal Female

- Meds: Lisinopril 5mg/d, multivitamin, vitamin D 5,000 IU/d, methylated B vitamins, IV therapy monthly with 2 grams glutathione
- PMHX: HTN, IR, borderline hyperlipidemia, osteoporosis, recent mammography and gyn exam including pap smear were normal, she had gestational diabetes and preeclampsia with both children
- FH: (+) FH premature CAD in both her mom (MI at age 45), dad (MI age 40), and her brother had an MI 44. Her mom is APO E 3/4, Her dad is APO E 3/4, bother is APO E 4/4. Mom and sister are breast cancer survivors.
- ROS: Night sweats occur multiple times a day, every day; irritable bowel with constipation
- PE: BP: 138/85, HR 95 regular, height is 5’6”, weight 120, BMI: 19.4, waist: hip ratio: 0.7 (normal). JVP: normal, CV exam: (+) S4, Pulses: symmetrical and equal.
- Testing: ECG: prominent voltage, exercise echocardiogram, which was normal, MTHFR (+)(-) C677T, APO E 3/4, BRCA negative

Maggie: History Summary

- 50 year old, symptomatic perimenopausal female with CVD risk factors
  - Symptoms: Hot flashes, night sweats, and vaginal dryness
  - Signs: VMS, HTN, elevated HR, HLD, IR, and osteopenia
  - CV risk factors: ED, HTN, HLD, IR, (+) FH premature CAD, osteopenia
- Maggie probably has HPA axis and autonomic dysfunction
  - Symptoms: No energy, but feels anxious all the time, and her mind cannot stop racing
  - Signs: poor sleep, over exercises, heart racing
- Maggie is perimenopausal (late)
  - VMS, VVA, no cycle for 9-months
- Maggie has dysbiosis with metabolic endotoxemia

Maggie's ECG



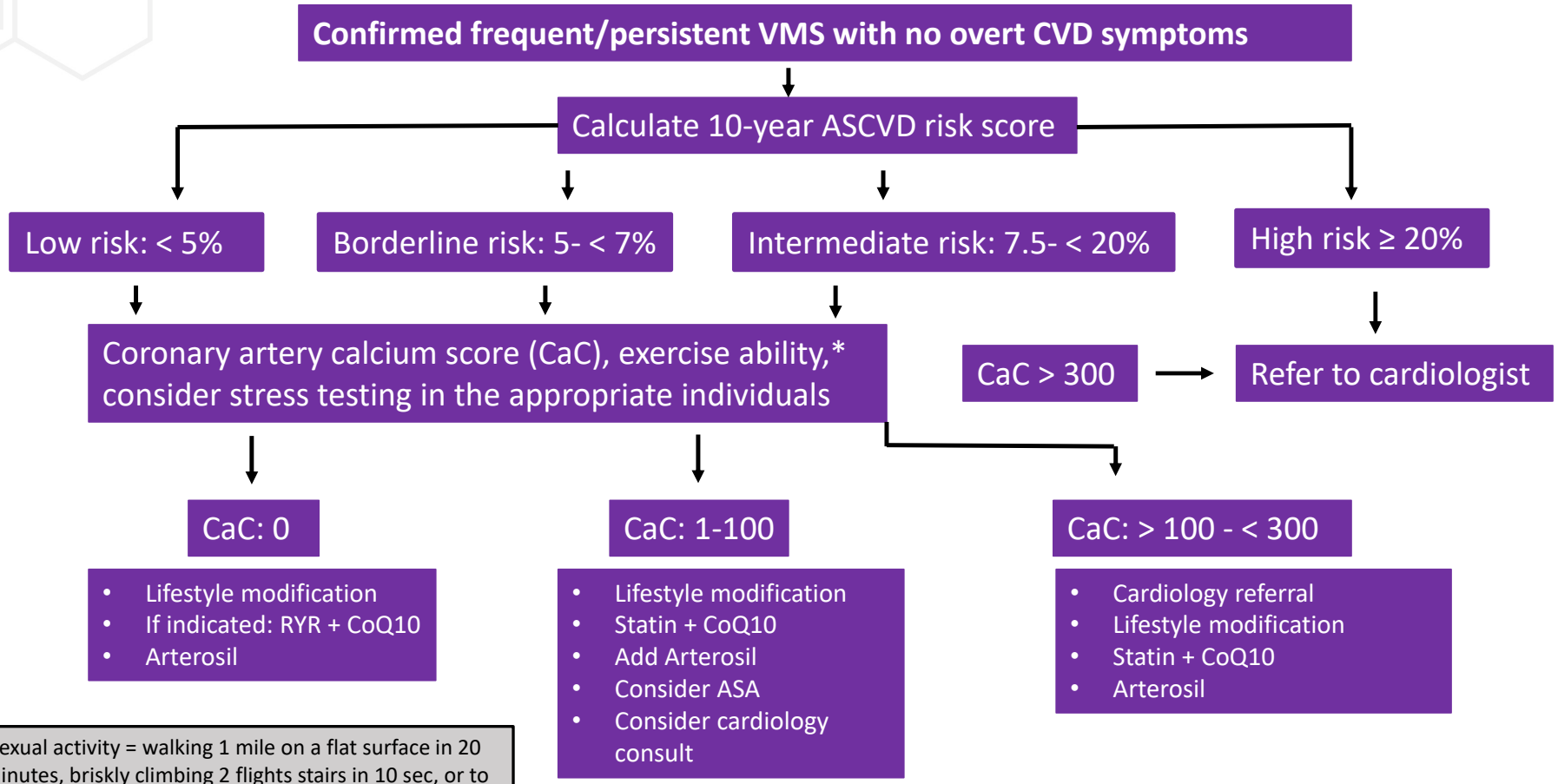
Maggie: Laboratory Results

- General:
  - Glycemic parameters: FBS: 90, FI: 10, HbA1c: 5.7
  - Hormones: vitamin D: 70
  - Thyroid: TSH 0.9, T4: 0.9, T3: 2.7, RT3: 18, TPO: 100
- Cardiovascular:
  - Risk markers: Hs-CRP: 2.3 (goal < 1), homocysteine: 12 (goal 5-8), TMAO: 10.0 (≤ 6.2), ADMA: 125 (high risk, goal < 100)
  - Advanced lipid profile: TG: 100, LDL-P: 1800 (mod risk, < 1138 optimal), HDL-P: 7858 (optimal), APO B: 125 (high risk)
  - Genetics: APO E 3/3
  - CIMT: 0.4 (goal < 0.5)

Question?

Do we need additional CV testing?

Decision Tree



- Sexual activity = walking 1 mile on a flat surface in 20 minutes, briskly climbing 2 flights stairs in 10 sec, or to 4 min of the Bruce treadmill protocol.

Adapted from: Miner M, et al. Sex Med Rev. 2019 7(3): 455-463.
Gandaglia G, et al. Eur Urol. 2014; 65(5): 968-978.

Maggie's ACC/AHA CVD Risk

Calculator | About | References

ACC/AHA CV Risk Calculator (2013)

Estimate 10-year risk for atherosclerotic cardiovascular disease

Questions

1.	Age?	50 Years
2.	Gender?	Female
3.	Race?	White/Other
4.	Total Cholesterol?	250 mg/dL
5.	HDL Cholesterol?	50 mg/dL
6.	Systolic Blood Pressure?	138 mmHg
7.	Treatment for High Blood Pr...	Yes
8.	Smoker?	No
9.	Diabetes?	No

Default Units

Results

Copy Results

10-Year Risk of Atherosclerotic Cardiovascular Disease (ASCVD)

2.9 %

10-Year Risk of ASCVD (%) for Someone of Same Age with Optimal Risk Factor Levels

0.8 %

Created by QxMD

Table 2. Risk-Enhancing Factors for Clinician–Patient Risk Discussion[10]

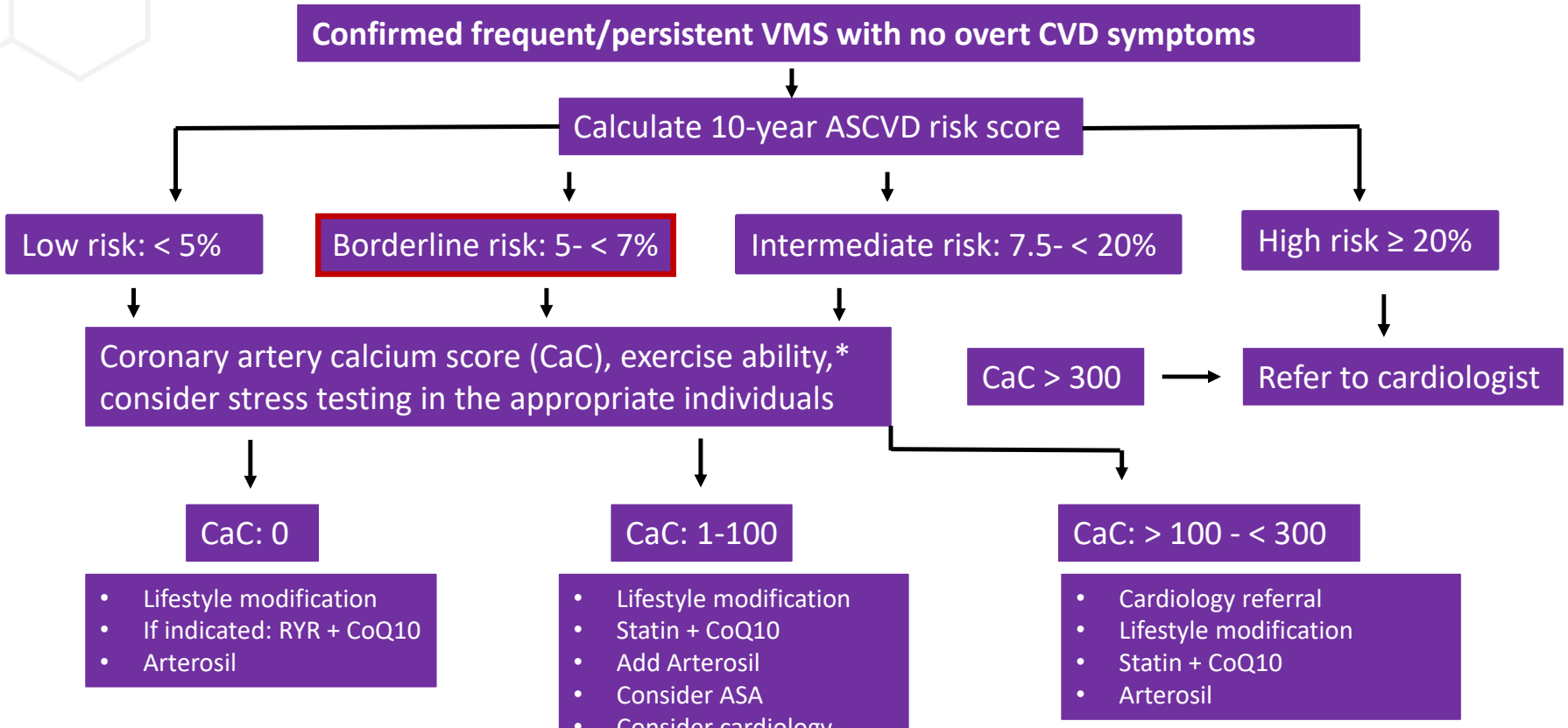
Risk-Enhancing Factors
Family history of premature ASCVD (males, age <55 y; females, age <65 y)
Primary hypercholesterolemia (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*
Metabolic syndrome (increased waist circumference, elevated triglycerides [>150 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)
Chronic kidney disease (eGFR 15–59 mL/min/1.73 m² with or without albuminuria; not treated with dialysis or kidney transplantation)
Chronic inflammatory conditions such as psoriasis, RA, or HIV/AIDS
History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia
High-risk race/ethnicities (eg, South Asian ancestry)
Lipid/biomarkers: Associated with increased ASCVD risk
Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);
If measured:
Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)
Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).
Elevated apoB ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C ≥160 mg/dL and constitutes a risk-enhancing factor.
ABI <0.9

*Optimally, 3 determinations. Reprinted with permission from Grundy SM, et al.[10]

AIDS indicates acquired immunodeficiency syndrome; ABI, ankle-brachial

Lloyd-Jones DM, et al. Circulation. 2019; 139(25): e1162-e1177.

Decision Tree



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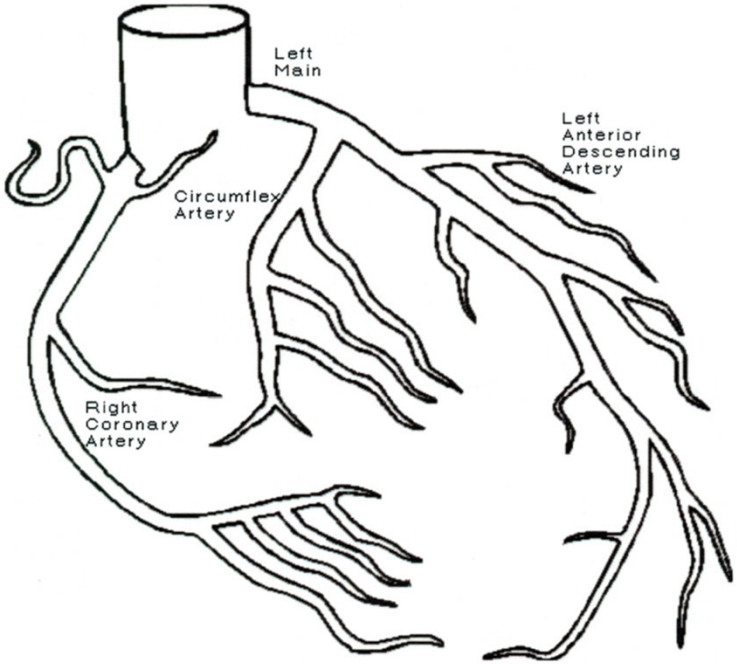
Gandaglia G, et al. Eur Urol. 2014; 65(5): 968-978.

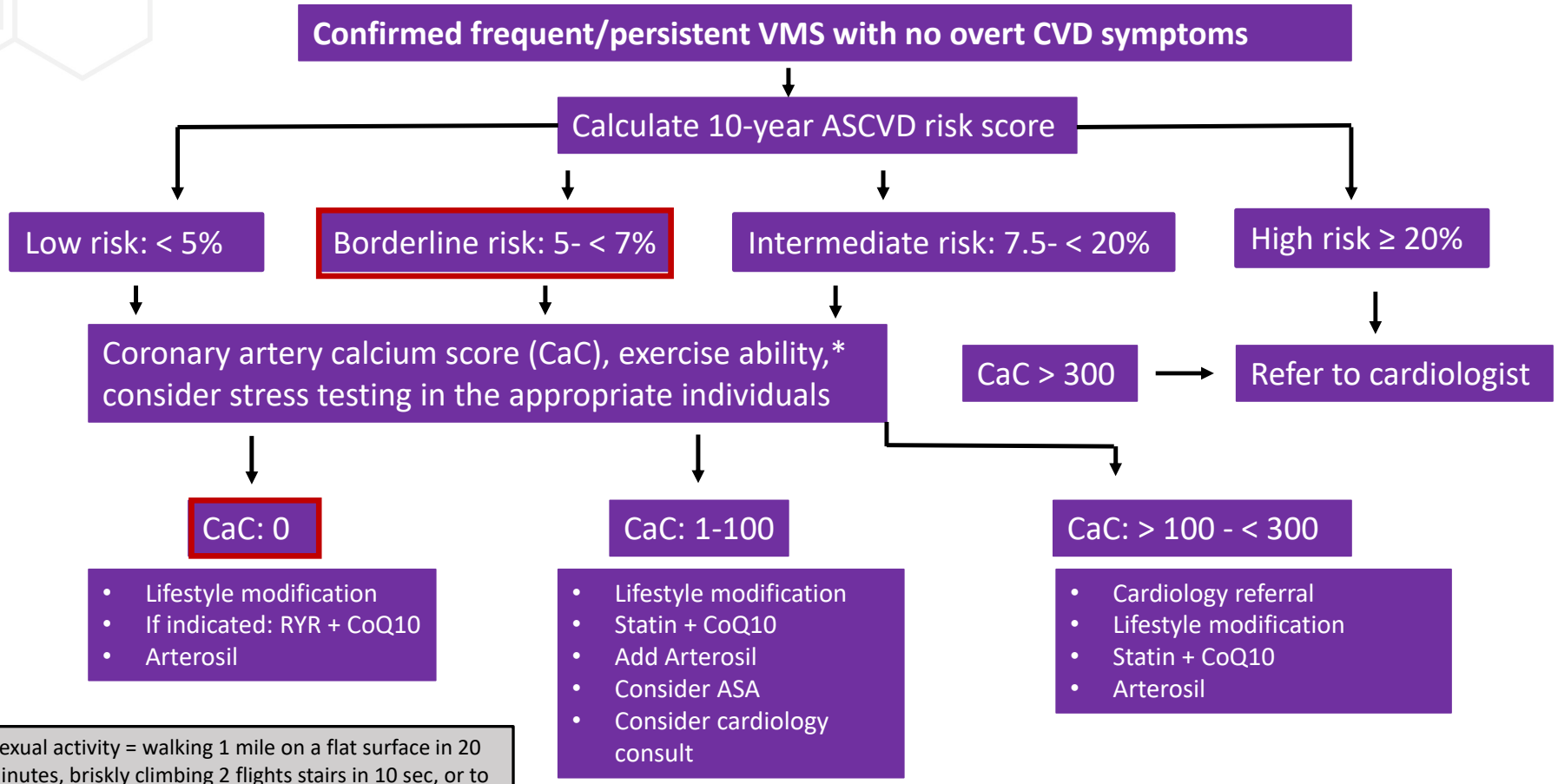
Maggie's CaC and Stress Test



This diagram demonstrates the **LOCATION** of coronary artery calcifications only, but **DOES NOT NECESSARILY INDICATE THE PRESENCE, ABSENCE OR LOCATION OF A STENOTIC LESION.**

- CaC: 0
- Exercise Echo: exercised 10 minutes Bruce protocol, achieved > 100% max HR (170 beats/min), normal echo
- HRRT: 110 beats/min (175-12 = 163)
- HRV: 25 (on lower side)

Decision Tree



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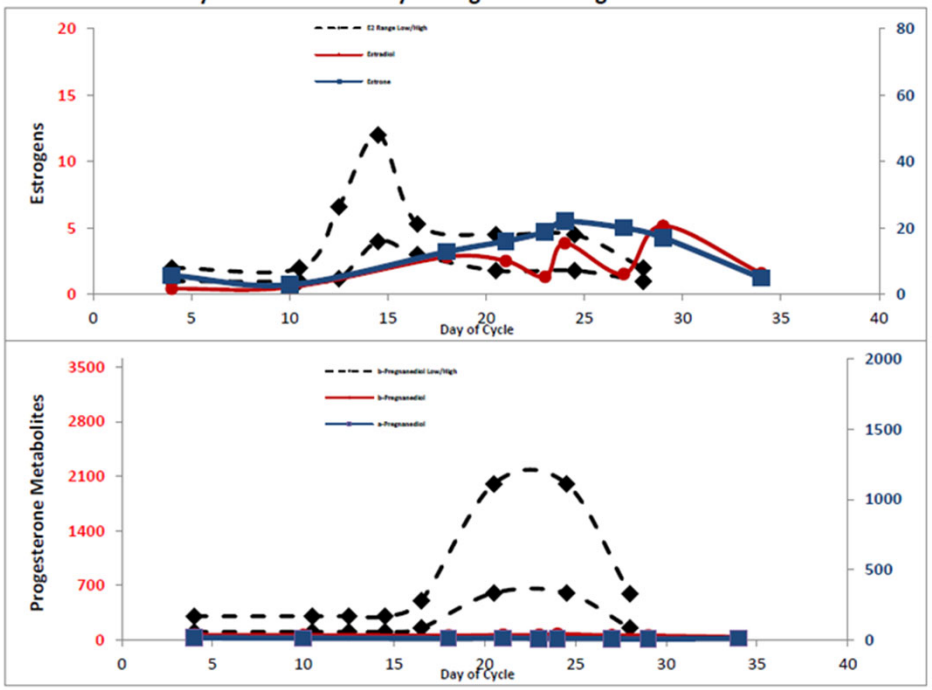
Gandaglia G, et al. Eur Urol. 2014; 65(5): 968-978.

Maggie's Cycle-Map

- Serum hormone labs
  - SHBG: 15nmol/L (17-124)
  - FSH: 75mIU/L
  - LH: 25mIU/L
  - E2: 12pg/mL (< 15, LC-MS/MS)
  - TT: 12ng/dL (2-45, LC-MS/MS)
  - Pg: 0.1ng/mL (≤ 0.2, LC-MS/MS)

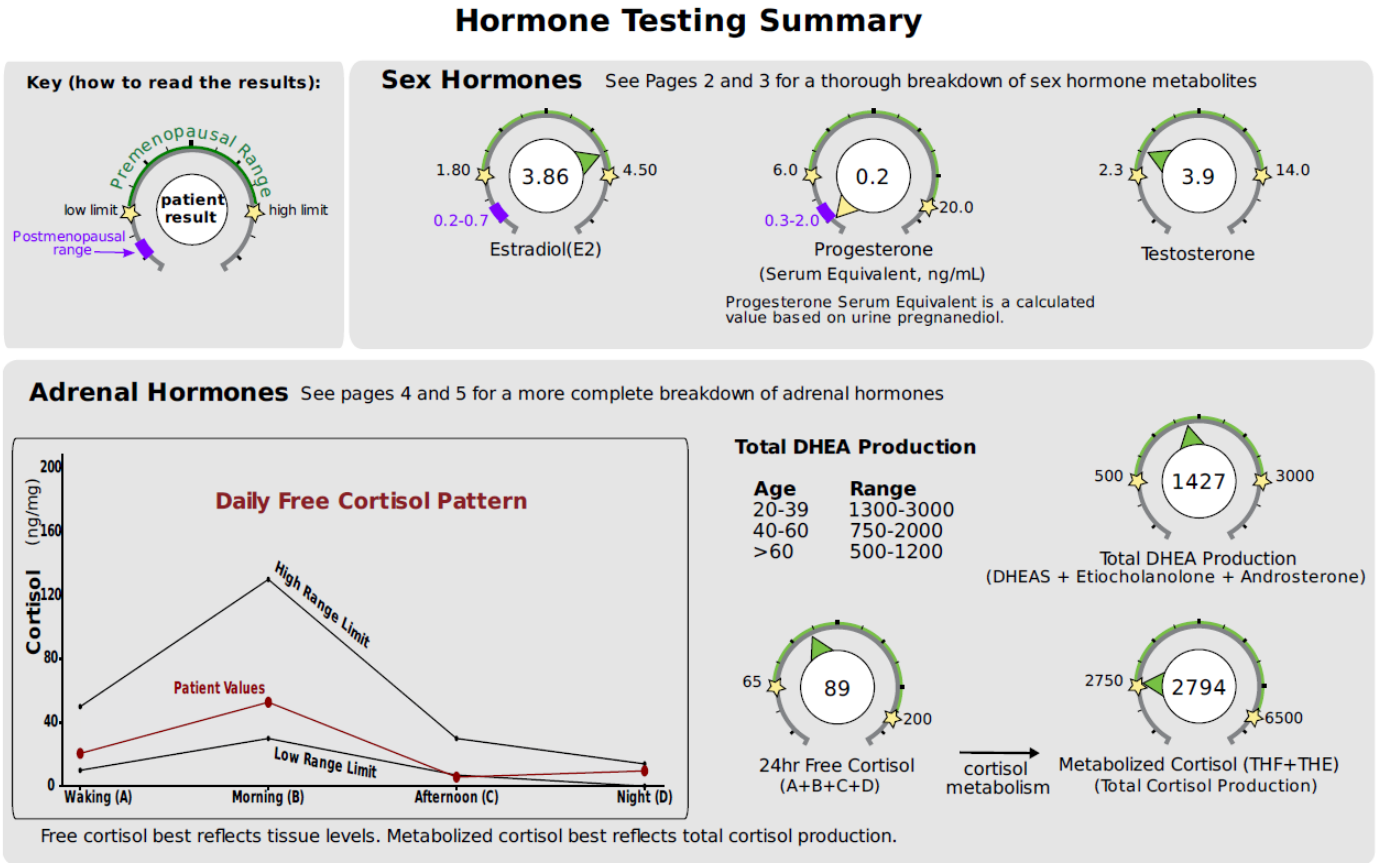


All values given in ng/mg creatinine

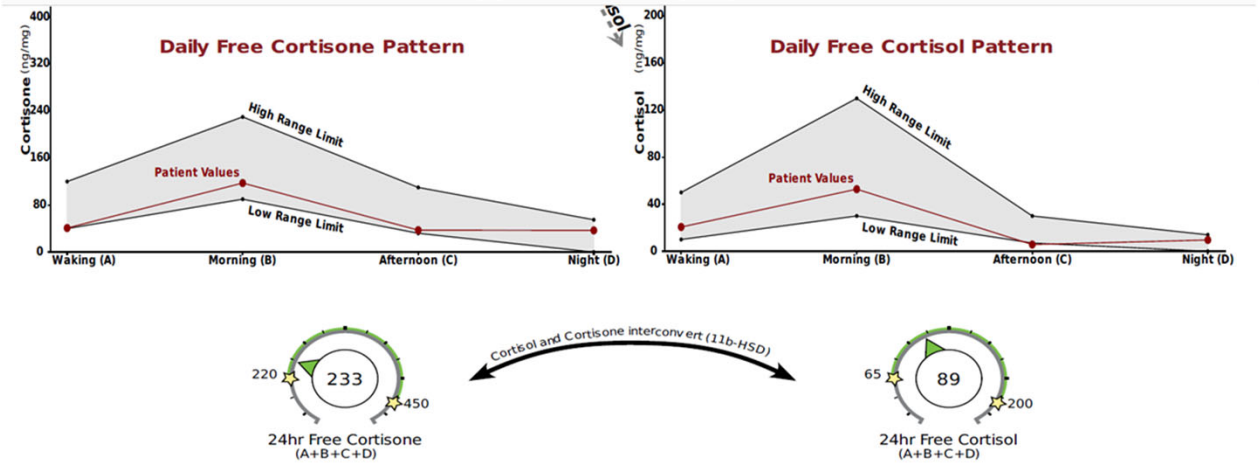
Measurement	1	2	3	4	5	6	7	8	9
Day of Cycle	4	10	18	21	23	24	27	29	34
Estradiol (E2)	0.4	0.5	2.8	2.5	1.3	3.9	1.6	5.2	1.6
Estrone (E1)	5.8	2.9	12.9	16.0	18.9	22.0	20.1	17.1	5.0
a-Pregnanediol	14	11	8	11	8	8	7	5	9
b-Pregnanediol	50	49	43	52	51	63	47	44	27
b-Pg / E2 Ratio	111	89	15	21	38	16	30	9	17

Normal Ranges	Follicular	Ovulatory	Luteal	Postmenopausal
Estradiol	1-2ng/mg	4-12ng/mg	1.8-4.5ng/mg	0.2-0.7ng/mg
Estrone	4-12ng/mg	22-68ng/mg	12-26ng/mg	3.0-7.0ng/mg
a-Pregnanediol	25-100ng/mg	25-100ng/mg	200-740ng/mg	15-50ng/mg
b-Pregnanediol	100-300ng/mg	100-300ng/mg	600-2000ng/mg	60-200ng/mg

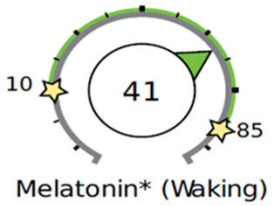
Maggie’s DUTCH Complete

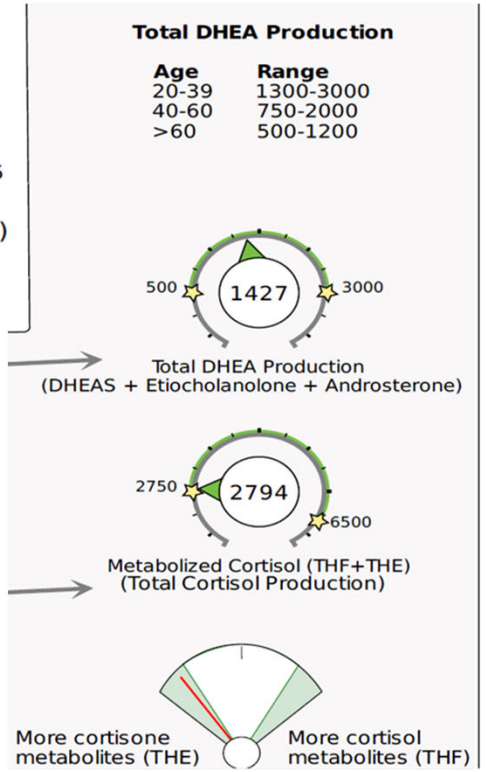


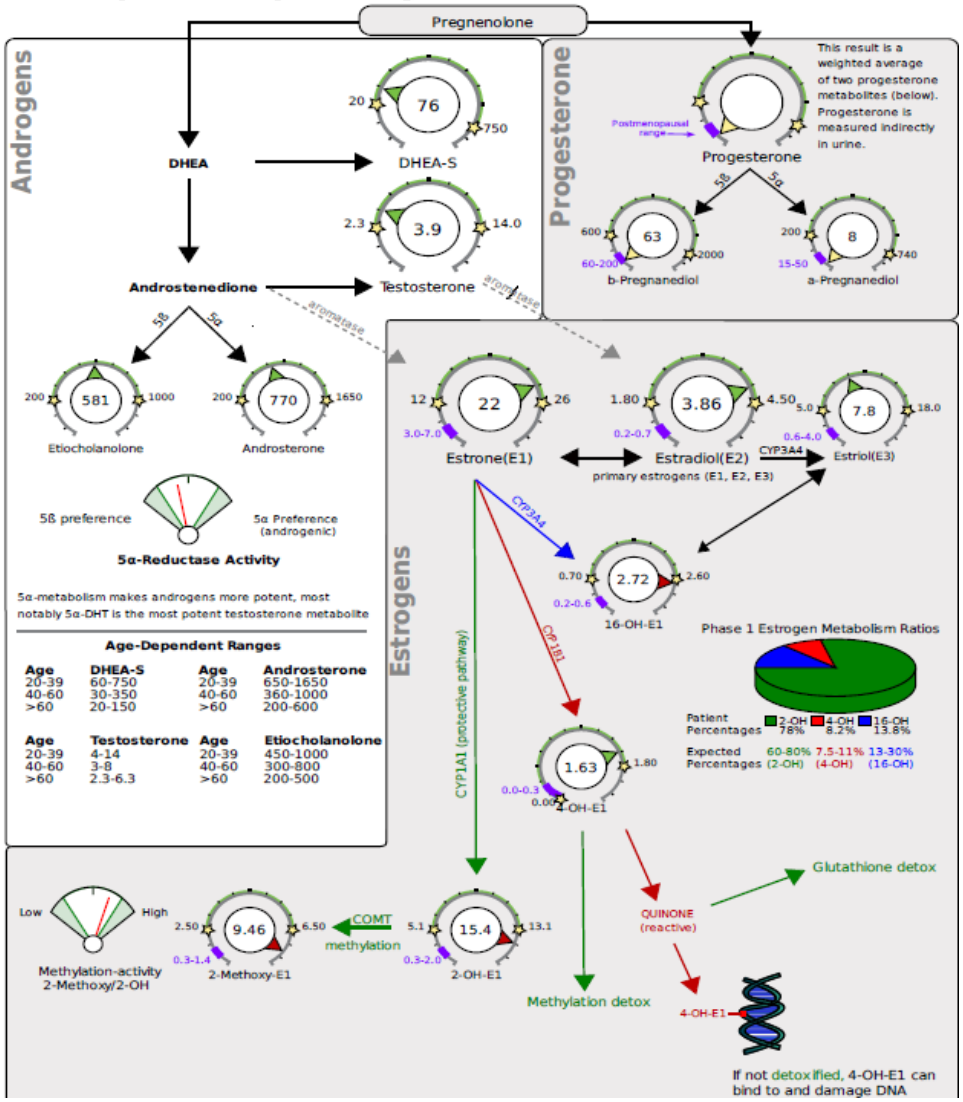
Maggie's HPA Axis Assessment



Pyroglutamate	Low end of range	30.0	ug/mg	28 - 58







Maggie's Metabolites

Test		Result	Units	Luteal* Range	Postmenopausal Range
Progesterone Metabolites (Urine)					
b-Pregnanediol	Below luteal range	62.8	ng/mg	600 - 2000	60-200
a-Pregnanediol	Below luteal range	7.7	ng/mg	200 - 740	15-50
Estrogens and Metabolites (Urine)					
Estrone(E1)	Within luteal range	22.0	ng/mg	12 - 26	3.0-7.0
Estradiol(E2)	Within luteal range	3.86	ng/mg	1.8 - 4.5	0.2-0.7
Estriol(E3)	Within luteal range	7.8	ng/mg	5 - 18	0.6-4.0
2-OH-E1	Above luteal range	15.4	ng/mg	5.1 - 13.1	0.3-2.0
4-OH-E1	High end of luteal range	1.63	ng/mg	0 - 1.8	0-0.3
16-OH-E1	Above luteal range	2.72	ng/mg	0.7 - 2.6	0.2-0.6
2-Methoxy-E1	Above luteal range	9.46	ng/mg	2.5 - 6.5	0.3-1.4
2-OH-E2	High end of luteal range	1.01	ng/mg	0 - 1.2	0-0.3
Total Estrogen	High end of range	63.9	ng/mg	35 - 70	4.0-15
Androgens and Metabolites (Urine)					
DHEA-S	Low end of range	76.0	ng/mg	20 - 750	
Androsterone	Within range	770.3	ng/mg	200 - 1650	
Etiocholanolone	Within range	580.7	ng/mg	200 - 1000	
Testosterone	Low end of range	3.9	ng/mg	2.3 - 14	
5a-DHT	Within range	4.3	ng/mg	0 - 6.6	
5a-Androstanediol	Above range	34.5	ng/mg	12 - 30	
5b-Androstanediol	Within range	32.9	ng/mg	20 - 75	
Epi-Testosterone	Below range	1.4	ng/mg	2.3 - 14	

Treatment: Adaptogens

High Cortisol

- Ashwagandha
- L-theanine (mind racing)
- Relora (food cravings)
- Rhodiola (anxiety, performance, decreases CAR)
- Holy Basil (immune modulator, supports BS)
- Phosphatidyl Serine (PS)
- RG3 (CNS immune modulator)
- Melatonin

Mixed Cortisol

- Ashwagandha
- Rhodiola
- Cordyceps: decreases oxidative stress
- PS: decreases cortisol, 300-800mg at HS
- RG3 (CNS immune modulator)
- Melatonin

Low Cortisol

- Licorice: inhibits 11β-HSD2 activity (cortisol to cortisone)
- Glandulars: support

Start low and go slow!

MHT: Common Herbal Derivatives

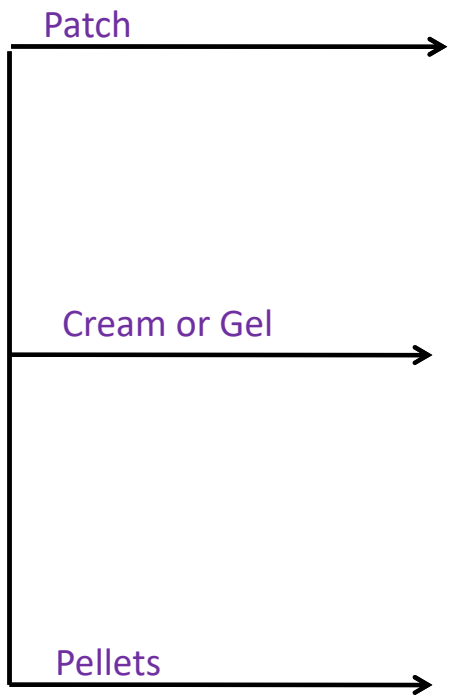
Herbal Derivatives

Scientific Name	Common Name	Effects	Side Effects
Actaea racemosa	Black cohosh	Treatment of menopause symptoms such as hot flash, insomnia, irritability, but also musculoskeletal pain, fever, cough.	Gastrointestinal discomfort.
Evening Primrose Oil	Oenothera biennis oil	Treatment for menopausal and premenstrual symptoms, but also for atopic dermatitis and rheumatoid arthritis.	Gastrointestinal disorders and interaction with antiepilectic drugs.
Foeniculum vulgare	Fennel	Treatment of hot flashes, anxiety, and vaginal atrophy.	No side effects reported.
Ginkgo biloba	Ginkgo	Treatment of attention disorders in postmenopausal women.	Gastrointestinal disorders, allergic reactions, headache, and lowering of seizure threshold.
Glycyrrhiza glabra	Licorice	Treatment of hot flash duration.	Cardiovascular disease, hypercortisolism, hypokalemia, and hypernatremia.
Hypericum perforatum	St. John's Wort	Treatment for the vasomotor symptoms of postmenopausal women.	Gastrointestinal disease, sensitivity to light, fatigue.
Medicago sativa	Alfalfa	Effect on neurovegetative menopausal symptoms.	Possible infection with Salmonella, Escherichia coli, and Listeria.
Melissa officinalis	Lemon balm, bee balm or honey balm	Effect on anxiety.	No side effect reported.
Panax ginseng	Ginseng	Treatment of sleep disorders, depression, and sexual function.	Possible effect on endometrial thickness.
Passiflora incarnata	Passion fruit	Treatment of vasomotor symptoms, insomnia, anxiety and dysmenorrhea.	No side effect reported.
Pimpinella anisum	Anise	Treatment of hot flashes but it also exerts an antiulcer action.	No side effects reported.
Salvia officinalis	Sage herb	Treatment of hot flashes and sweats.	Possible interaction with diabetes and blood pressure.

Scientific Name	Common Name	Effect	Side Effects
Trifolium pretense	Red clover	Treatment of hot flashes and it also exerts a bone preventing loss.	No side effects reported.
Trigonella foenum	Fenugreek	Treatment for hot flashes and osteopenia.	No particularly side effects.
Valerian officinalis	Valerian	Useful for hot flashes, anxiety, sleep disorders and dysmenorrhea.	No side effects reported.
Vitex agnus-castus	Chaste tree, chasteberry or monk's pepper	Treatment for vasomotor symptoms and sleep diseases.	Not reported.

De Fransiscis P, et al. Medicina (Kaunas). 2019; 55(9): 544.

Estradiol Options



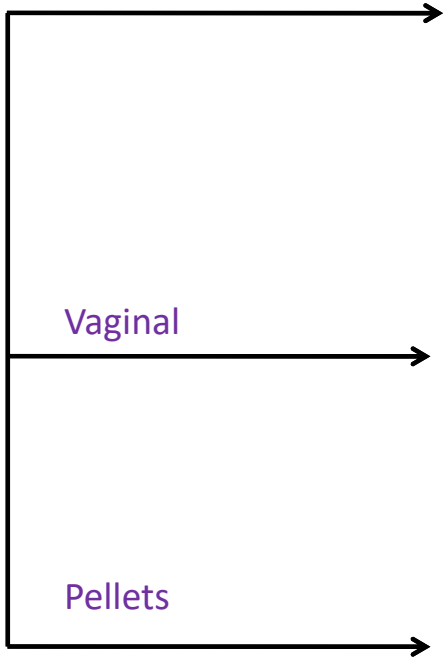
- Estradiol patch: Typical starting dose is 0.025mg/d
  - Doses as low as 0.014 mg/d relieves VMS, VVA symptoms, and prevents osteoporosis
  - Place patch on a fatty area – abdomen or buttocks
  - Buttocks gets increased absorption – FDA studies
- Labs in 12 weeks

- Creams must be compounded, usually E2 and E3
  - Typical ratios 80: 20, 50: 50
  - Common E2 starting dose is 0.25-0.50mg/day
  - No outcome studies regarding creams
- Gel doses are product specific, not FDA approved for osteoporosis prevention

- Would avoid
- Not a good option for E2 delivery

MUST use either:
- **OMP 200mg/d at HS, balance E2's effects or**
- **VMP 100-200mg/d, or 45mg daily**

Testosterone Options



- Typical dose range: 0.5-5.0mg/d
- Perimenopause: 1.0-3.0mg/day starting dose
- Menopause: 1.0-2.0mg/d starting dose
- May start T prior to E2 with Pg
- Monitor labs
  - Serum and urine

- Lower 1/3 vagina/labia
- Dose range: 0.25-2.0mg/d
- Most common: 0.5-1.0mg/d

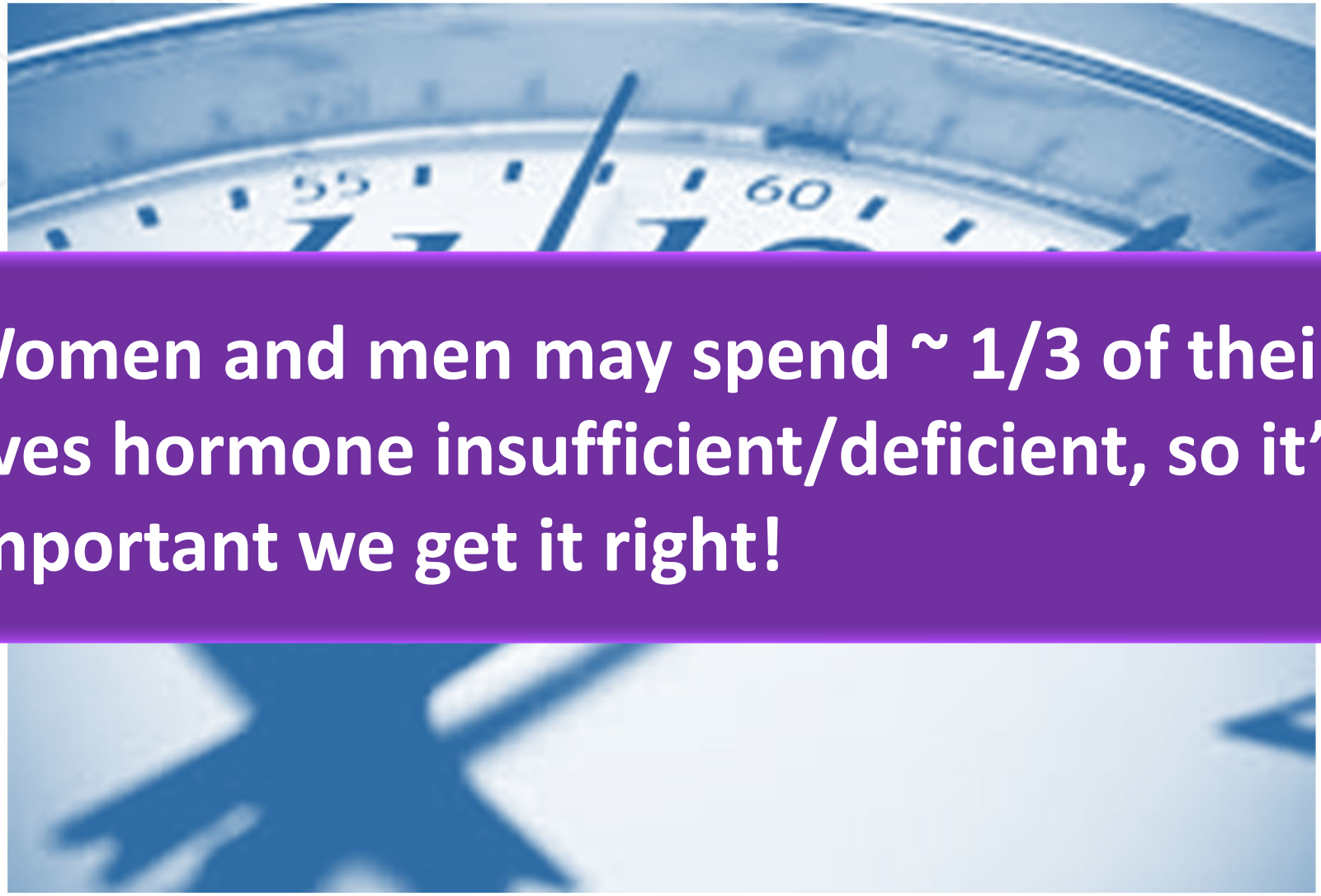
- An excellent option
  - Must understand hormone metabolism and detoxification
  - Dosing range 50-150mg
  - Most common doses: 75-125mg
- Patients require less T than you think!

Maggie's Treatment Plan

System	Treatment
HPA Axis	• AdaptCNS: 2caps in the AM and 1 cap in the afternoon • Chelated Mg: 400mg TID • IV therapy with 3 grams Glutathione QOW • Melatonin troche 10mg, start 2.5mg QHS
CV System	• RYR 4800mg/d • Arterosil 1 cap BID, Aged Garlic 1200mg BID, CoQ10 300mg @ HS • Sun fiber • Omega 3 fish oil 1-4 grams/d, Curcumin 1-3grams/d
Hormones	• Estradiol patch: 0.025mg/d, OMP: 200mg at HS, T cream: 1.0mg/d • DIM: BID • Vitamin D 5,000 IU/d
Thyroid	• Compounded 38/9 mcg T4/T3 or thyrocomplex 2 in AM and 1 in afternoon • Naltrexone: 1.5mg titrated to 4.5mg @ HS • SPM active: 2 soft gels daily • Moducare: Immune modulator
GUT	• Probiotics • Mediterranean, gluten- and dairy-free diet

Final Thoughts

- CVD is a chronic inflammatory disease
- HPA axis dysfunction, autonomic dysregulation, and hormone dysregulation increase CV event rates
- Optimal hormone levels are necessary for CV health
- Learn and understand hormone metabolomics, it is essential for optimal health
- Ask yourself: are your decisions evidence-based?
- Are you questioning the absolutes and asking: where is the evidence?



Women and men may spend ~ 1/3 of their lives hormone insufficient/deficient, so it's important we get it right!

MONITORING (B)HRT WITH LAB TESTING

Tutorials available at www.dutchtest.com/videos/hormone-tutorials

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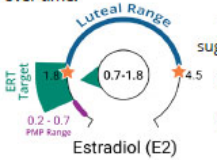
Can serum or DUTCH, as a standalone test, effectively monitor HRT? ✔ Yes ✖ No ? Maybe

Oral Progesterone (OMP)	Estradiol (E2) Patches	E2 Gels & Creams (Skin)	Vaginal E2 & Testosterone (T)	Vaginal Progesterone (Pg)	Transdermal (TD) Testosterone	Testosterone Injections & Pellets
✔ DUTCH	✔ DUTCH	✔ DUTCH	✔ DUTCH	✖ DUTCH	? DUTCH	? DUTCH
The DUTCH Test® provides useful feedback when using OMP in women with PMP sleep disturbances. 5a (more active) and 5b metabolites are measured to individualize OMP dosing. OMP's sleep effects are via its 5a metabolites, predominately allopregnanolone binding to the GABA receptor. No lab test reflects OMP's effect on the endometrium.	Values between the top of the postmenopausal range and the lower limit of the premenopausal range correlate with patient clinical improvement (bone density, hot flash relief, etc.). Doses that push levels to the middle of the premenopausal range and beyond may be excessive. DUTCH is preferred over serum because in addition to metabolites, dried urine averages out the daily up and down E2 patterns. This is particularly helpful with gels and creams that may have serum values that change rapidly over time.  The aggregate clinical data suggests that a serum (LC-MS/MS) E2 level of ~20-40pg/mL improves clinical outcomes (VMS, VVA, BMD). This approximates a DUTCH value of ~ 0.7-1.8ng/mg.		The DUTCH Test® is unique in that it removes potential contamination, and monitoring is helpful with E2 and T. Very low doses may impact local tissue without increasing lab values. For local (not systemic) E2 therapy, keep urine E2 in PMP range.	Pg is measured indirectly in urine by measuring pregnanediols. These metabolites may be underrepresented when Pg is taken vaginally. Serum Pg seems to increase to a higher degree than urine metabolites with vaginal Pg application.	Levels generally parallel changes in serum and clinical outcomes (increased lean body mass, erythrocytosis, etc. in men). Epi-testosterone (Epi-T) values can be used to assess gonadal suppression due to TRT (Epi-T levels in men decrease as TRT increases and are <10ng/mg with complete suppression).	Injections and pellets increase levels, as expected, but the increase may exceed what is seen in serum testing. DUTCH allows for monitoring both the dosing of hormones as well as metabolic patterns.
			Vaginal E2, Pg, and T are systemically absorbed. If placed in the top 1/3 of the vagina, a higher dose will get to the uterus (uterine 1st pass effect), which may be helpful for Pg, but not E2.		Urine testosterone does not correlate as reliably to T serum values, compared to E2 and other tests. Urine testing is best suited as a complimentary test to serum for T and should not be used solely for TRT decisions.	
✖ SERUM	✔ SERUM	? SERUM	✔ SERUM	? SERUM	✔ SERUM	✔ SERUM
Results go up and down quickly. If taken at bedtime, levels return to baseline within a few hours. Results can also be inaccurate due to progesterone metabolites cross-reacting with immunoassay tests.	Serum testing is well suited for use with these types of therapies. Results increase with increased dosing in a fairly linear fashion. Most recommendations are to push serum E2 levels to 20-40pg/mL for clinical impact.	The only published data for E2 creams shows serum results move up and down within a few hours, so serum testing can easily underestimate clinical impact. DUTCH results average out the daily up and down pattern and may be a better option.	Serum results rise quite dramatically with what may seem like modest doses due to the high uptake of hormones across the mucosal membrane. However, values may rise and fall quickly, so be careful with the interpretation of both low and high results.	Serum values increase with dosing and likely represent systemic exposure to Pg. However, the uterine first-pass effect loads the uterus with high levels of Pg (which may be desirable) and serum does not reflect uterine hormone levels.	A great deal of published research shows that serum levels reflect clinical changes in both men and women taking TD T. Be aware of potential up and down patterns throughout the day, but serum is the best tool for monitoring doses of TD T in both men and women.	Serum testing is well suited for use with these types of therapies. Results increase with increased dosing in a fairly linear fashion. Test injections halfway between doses or right before a dose.
✖ SALIVA	The literature does not support salivary testing's use for monitoring TD hormone creams. The saliva data is limited and, in fact, there are no saliva testing outcome studies using TD creams, injections, estradiol patches, oral estradiol, or vaginal hormones. While salivary testing is the gold standard for free cortisol measurement, avoiding its use for monitoring HRT is advised. For situations where saliva testing may parallel the clinical impact, DUTCH or serum testing are better options (see above).					
✖ Oral Estradiol, Estradiol Pellets, or Sublingual Hormones	Though not recommended, if you choose to use either oral estradiol or estradiol pellets, serum testing can monitor both, whereas urine should only be used with pellet therapy. Sublingual hormones may be used in some situations but lab monitoring is not helpful in optimizing doses.					
✖ Transdermal Progesterone	In PMP women, the evidence does not support TD Pg's use to protect the endometrium. When prescribed, laboratory monitoring is not helpful for TD Pg dosing.					

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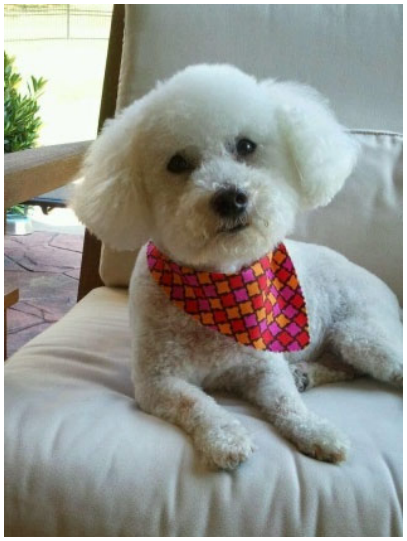

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