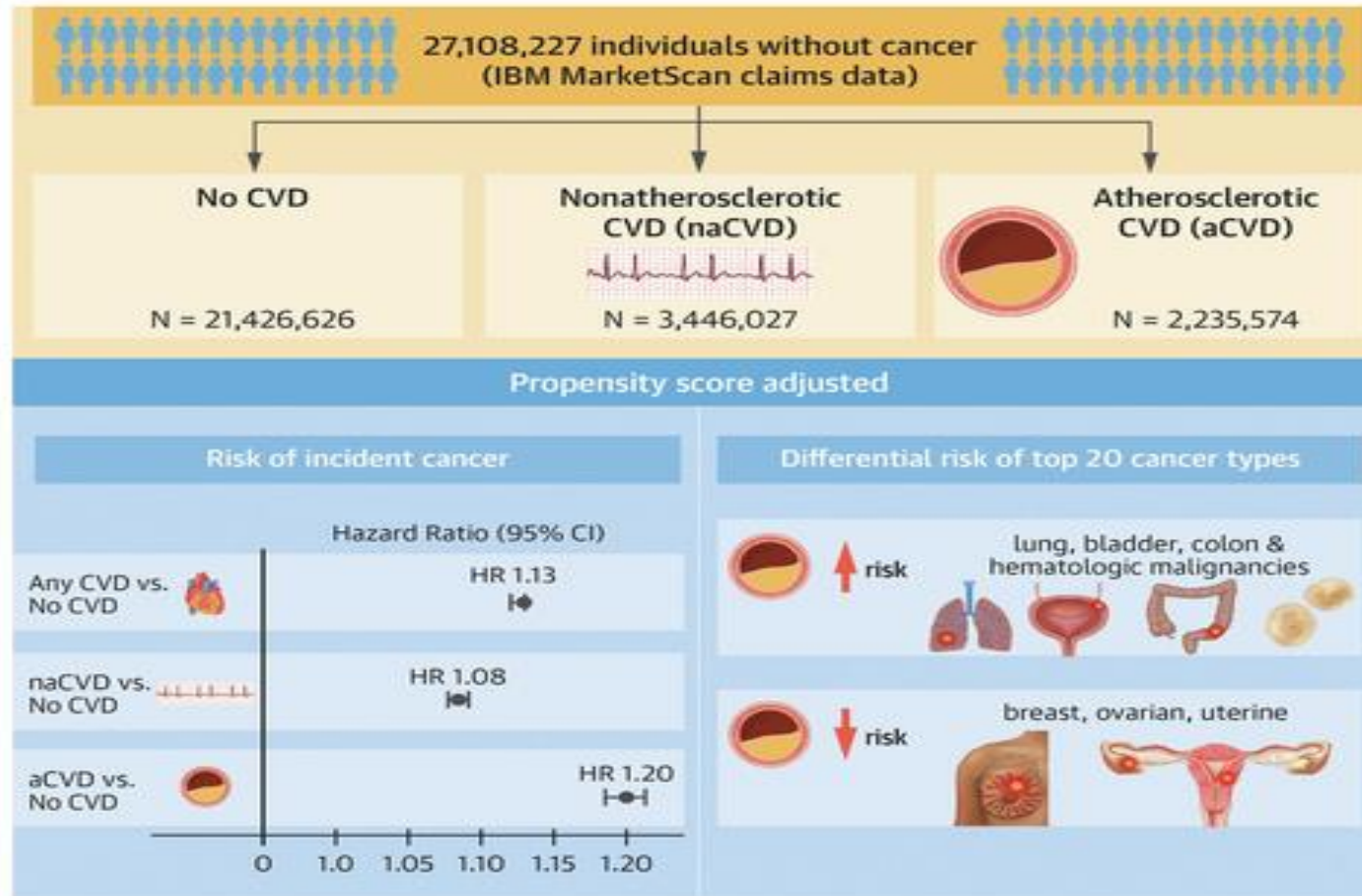


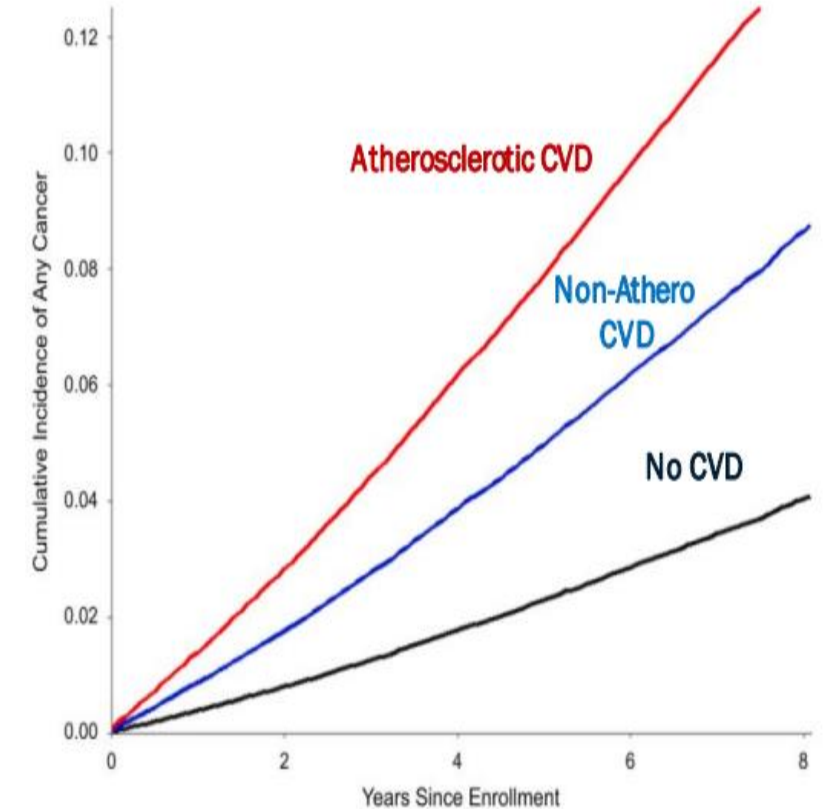
Cardiac risk management and healthy living for men with prostate cancer
October 2024
Dr Jason Kaplan FRACP FACC – Cardiologist St Vincents Clinic, NSW
Cardiology

CENTRAL ILLUSTRATION: Risk of Cancer After Diagnosis of Cardiovascular Disease



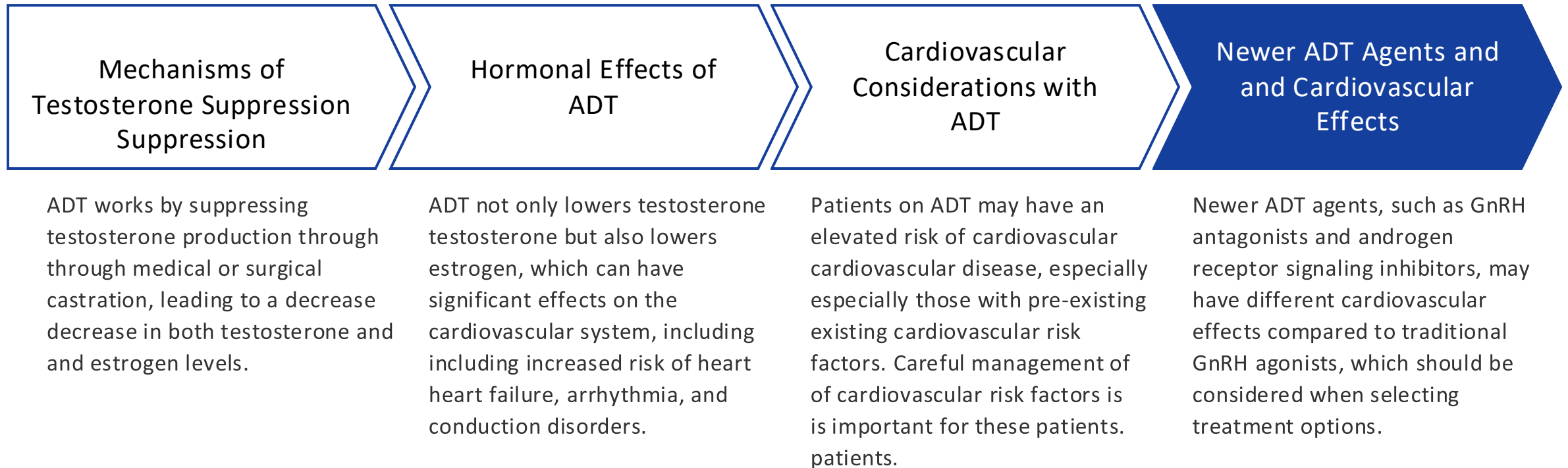
Bell CF, et al. *J Am Coll Cardiol CardioOnc*. 2023;5(4):431-440.

CVD → Cancer

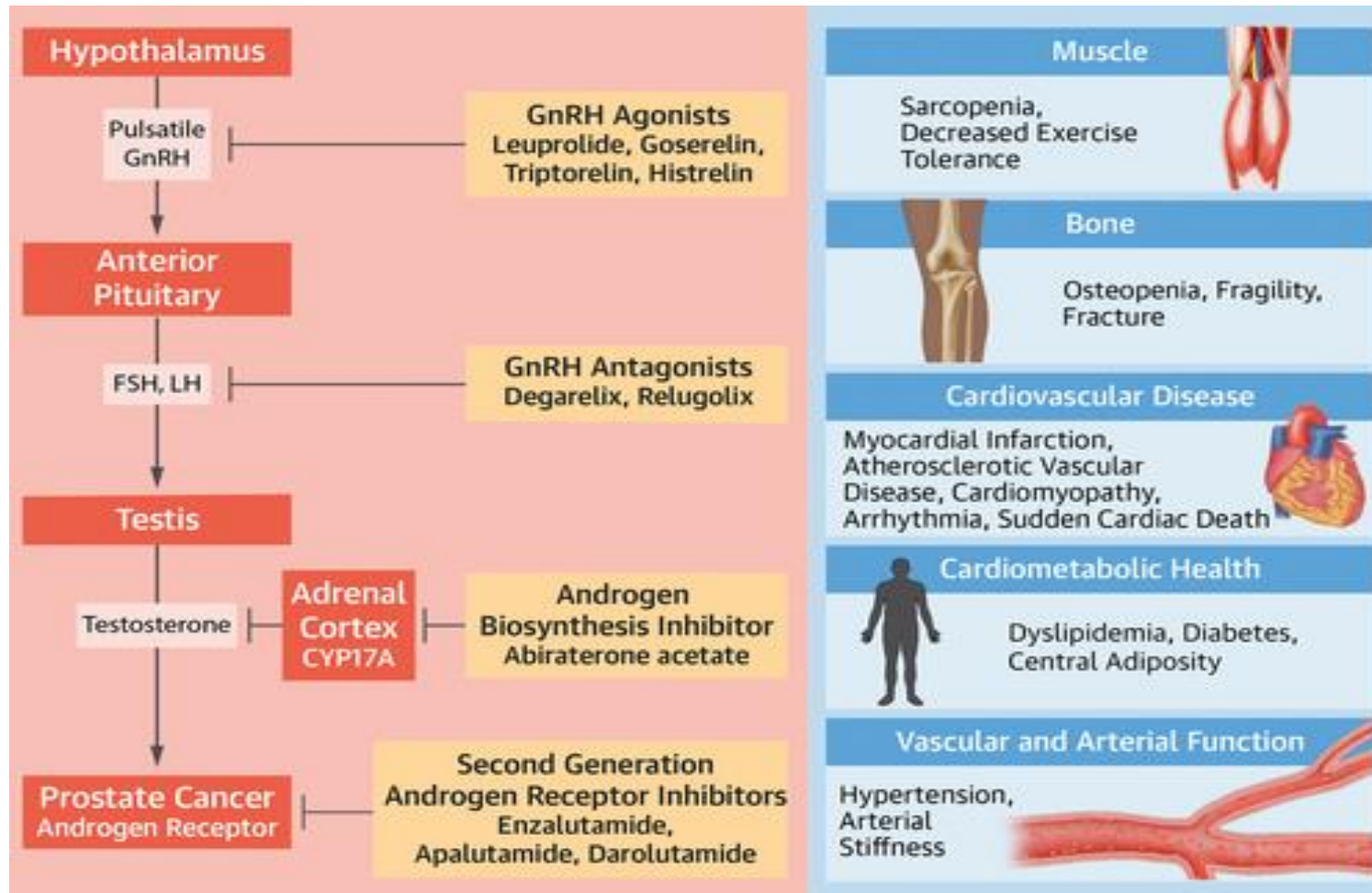


Caitlin F. Bell et al. *J Am Coll Cardiol CardioOnc* 2023; 5:431-440.

ANDROGEN DEPRIVATION THERAPY



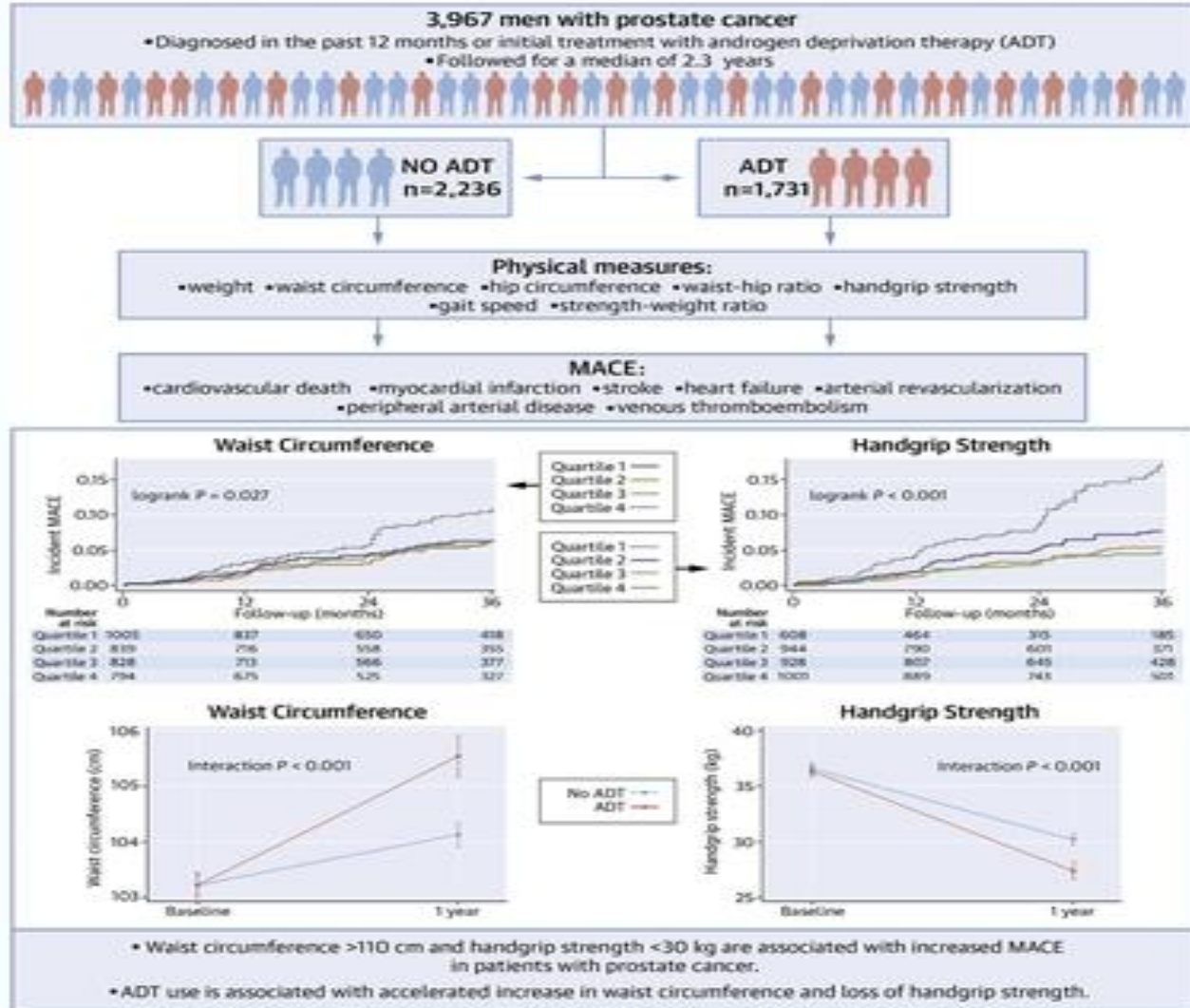
ADT Negatively affects CVS RF



- Androgen deprivation therapy is associated with metabolic derangements due to profound hypogonadism that can increase the risk of CV disease in prostate cancer survivors
- Therapeutic advances have resulted in prolonged patient exposure to androgen deprivation therapy, thereby increasing CV complications for many prostate cancer survivors.
- ADT Negatively affects CVS RF

Vivek Narayan et al. *J Am Coll Cardiol CardioOnc* 2021; 3:737-741.

CENTRAL ILLUSTRATION: Adverse Cardiovascular Events, Adiposity, and Muscle Strength and Their Relationships With ADT



Leong DP, et al. JACC CardioOncol. 2024;6(5):761-771.

Darryl P. Leong et al. J Am Coll Cardiol CardioOnc 2024; 6:761-771.

ADT was associated with increased adiposity and reduced strength over 12-month follow-up. High waist circumference and low baseline strength were associated with future adverse cardiovascular outcomes.

CASE PRESENTATION

- Mr. TF is a 67-year-old man with a history of localized prostate cancer treated with radical
- prostatectomy and adjuvant radiation in 2017
- • Gleason 4+4, Grade group 4 prostate adenocarcinoma, with pre-op PSA 11.37 ng/mL
- • Positive extracapsular extension and positive right apical margin demonstrating higher risk
- • By 1/2019, PSA began increasing slowly, reaching 2.9 ng/mL in January 2020
- • Re-staging scans were negative, but when his PSA reached 5.5 ng/mL in 6/2020, he started on
- androgen deprivation therapy (ADT) due to the high PSA
- • Due to a very busy work schedule, TF is not very active and has:
- – Borderline diabetes- HBA1C 6.1 , Impaired FBSL and elevated fasting insulin
- – Fasting triglycerides of 4.3mmol/L. LDL 3.8mmol
- – Blood pressure between 135-150/80-90
- – And is moderately overweight (BMI of 28, waist circumference of 110 cm). OSA
- - Social, Business Diet and alcohol pattern.

CARDIOVASCULAR RISK IN PROSTATE CANCER PATIENTS

● RACDICAL-PC Study

Prospectively
characterized 2,811
men with prostate
cancer

● 23% had pre-existing CVD

Highlighting the high
prevalence of
cardiovascular disease in
this population

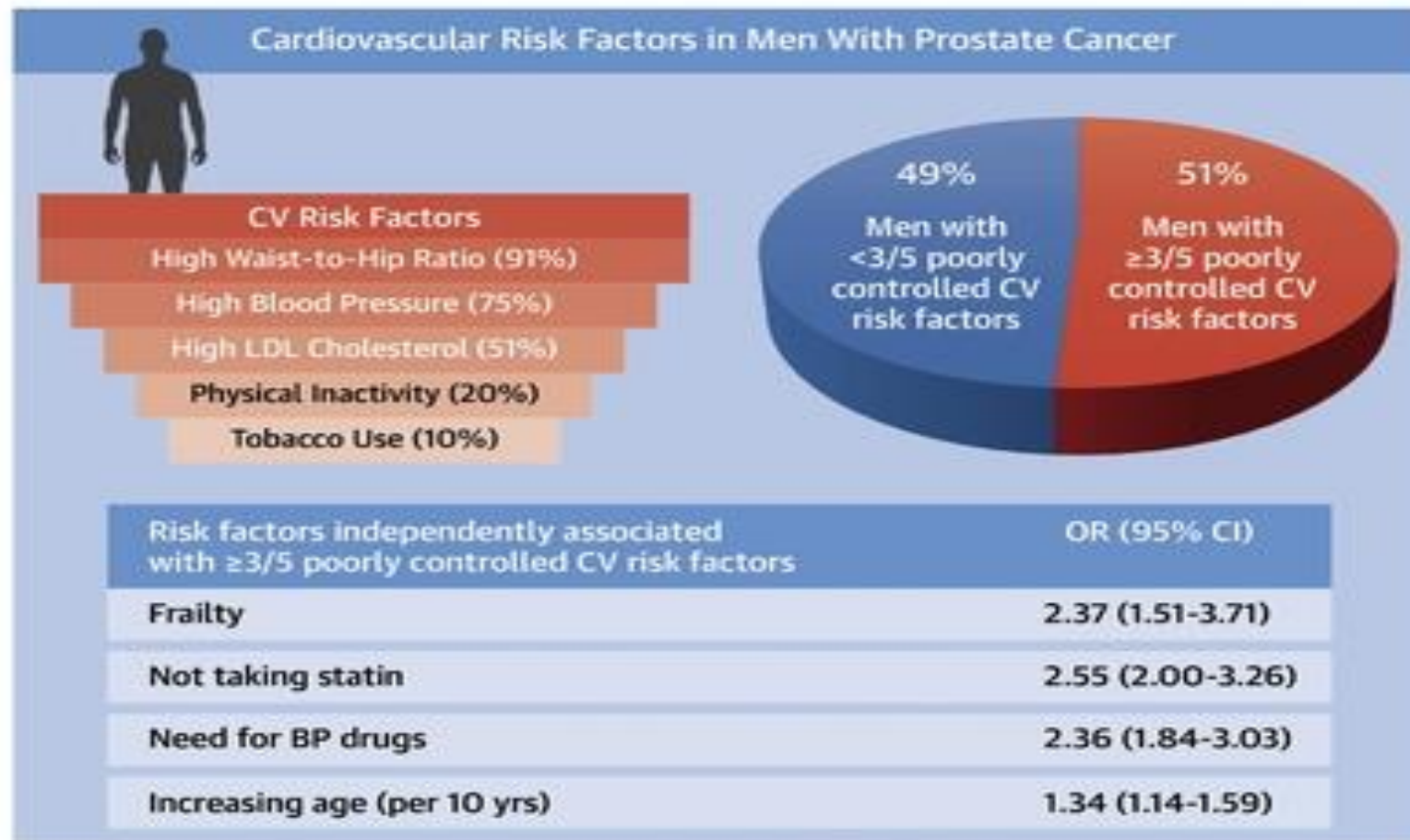
● 51% had poorly controlled CV risk factors

Indicating suboptimal
suboptimal
management of
modifiable risk factors

● CVD is the biggest competing risk of death

Other than prostate
cancer itself, emphasizing
the importance of
cardiovascular care

CENTRAL ILLUSTRATION: Poor Control of Cardiovascular Risk Factors in Men With Prostate Cancer

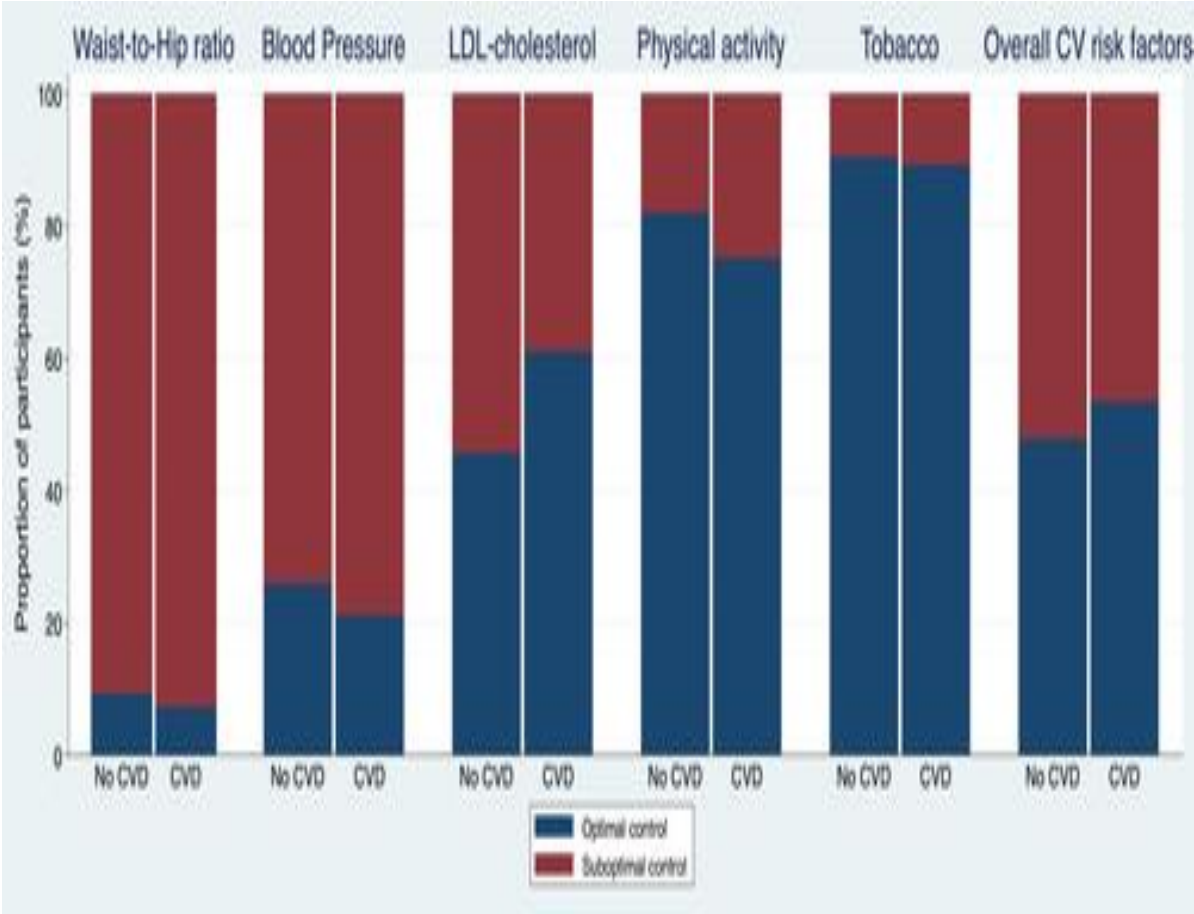


Klimis H, et al. *J Am Coll Cardiol CardioOnc*. 2023;5(1):70-81.

Harry Klimis et al. *J Am Coll Cardiol CardioOnc* 2023; 5:70-81.

DEFINITION OF POORLY CONTROLLED RISK FACTORS

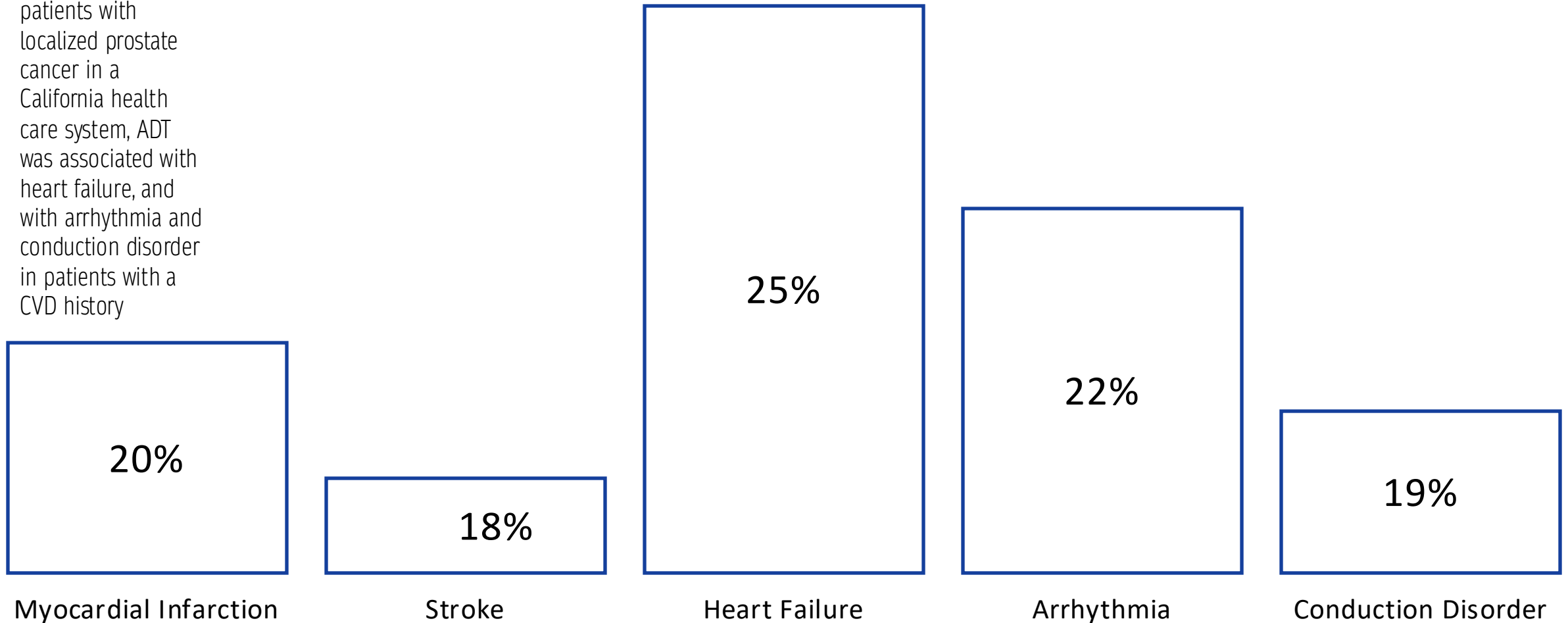
Cardiovascular Risk Factor	Threshold for Poor Control	Participant Population
LDL cholesterol ^a	>2.0 mmol/L	Established CVD or Chronic kidney disease or Baseline Framingham Risk Score ≥ 15 (ie, $\geq 20\%$ 10-y incident CVD risk)
	≥ 3.5 mmol/L	Baseline Framingham Risk Score <15%
Blood pressure ^a	$\geq 140/90$ mm Hg	No target end-organ damage and No cardiovascular risk factors (excluding blood pressure)
	$\geq 130/80$ mm Hg	Diabetes
	Systolic blood pressure ≥ 120 mm Hg	Established CVD or Chronic kidney disease or Baseline Framingham Risk Score $\geq 15\%$ 10-y incident CVD risk or Age ≥ 75 y
Waist:hip ratio	>0.90	All participants
Current smoker	Regularly smoking within previous 12 months	All participants
Physical inactivity	<30 min of moderate physical activity 5 d/wk (<600 MET min/wk) ⁴²	All participants



ADT AND CARDIOVASCULAR EFFECTS

Incidence of adverse cardiovascular events in patients treated with ADT compared to non-ADT groups, reported as percentages

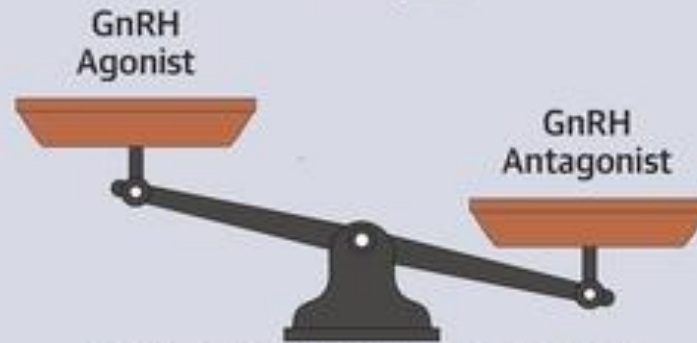
In a cohort of 7637 patients with localized prostate cancer in a California health care system, ADT was associated with heart failure, and with arrhythmia and conduction disorder in patients with a CVD history



CENTRAL ILLUSTRATION: Systematic Review of Randomized Controlled Trials Evaluating Gonadotropin-Releasing Hormone Antagonists vs Agonists

Myocardial Infarction, Stroke, and All-Cause Mortality in Men With Prostate Cancer

Meta-analysis of 11 randomized trials
N = 4,248



MACE—RR 0.57 (95% CrI: 0.37-0.86)

All-cause mortality—RR 0.58 (95% CrI: 0.32-1.06)

GnRH antagonists associated with lower MACE risk and nonsignificantly decreased mortality risk, compared with GnRH agonists

Nelson AJ, et al. *J Am Coll Cardiol CardioOnc*. 2023;5(5):613-624.

Adam J. Nelson et al. *J Am Coll Cardiol CardioOnc* 2023; 5:613-624.

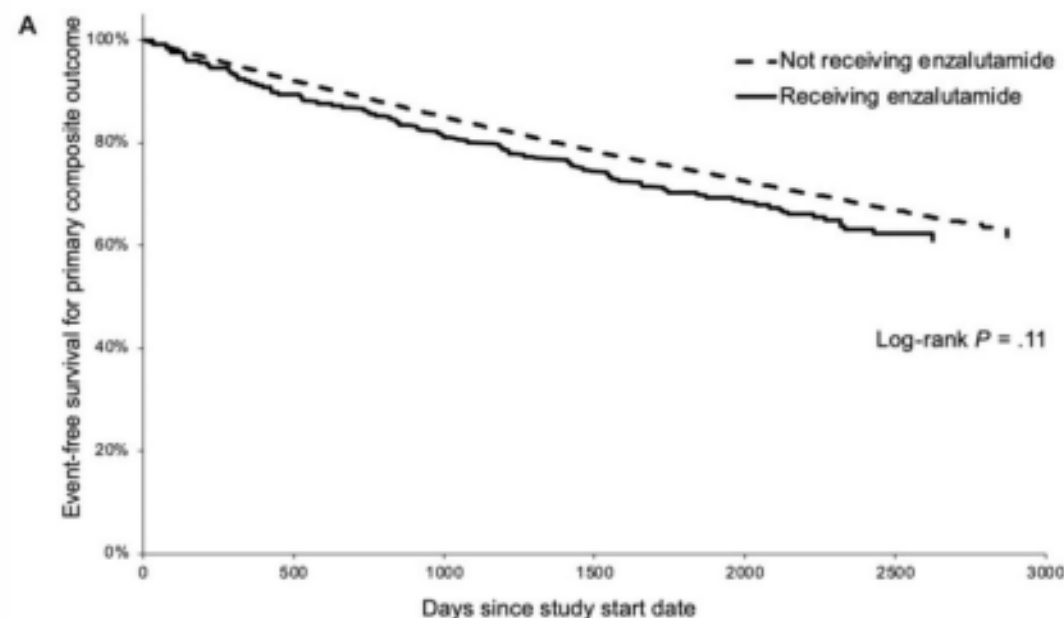
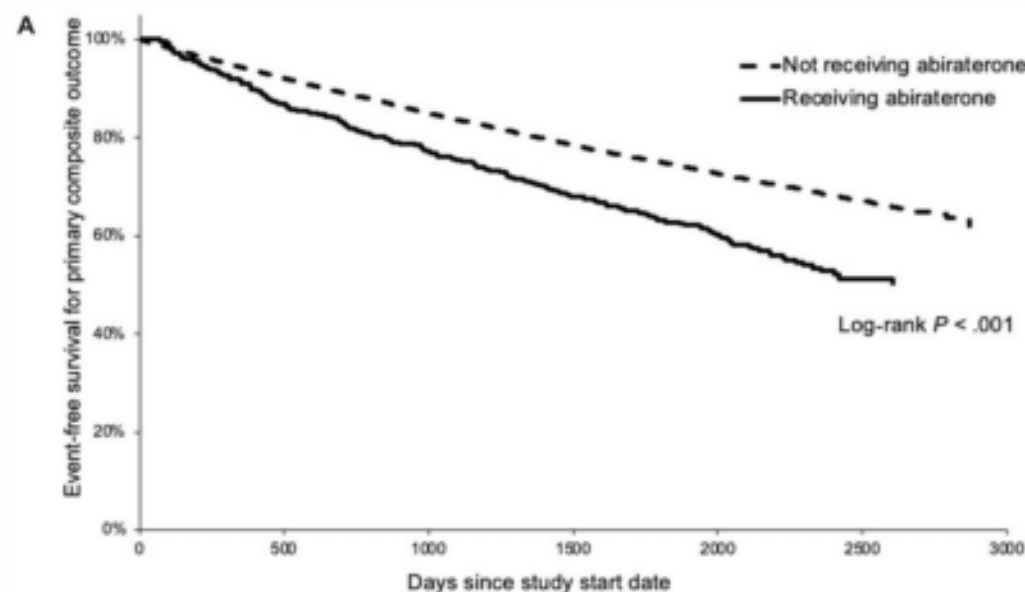
COMBINATION THERAPY

Patients with prostate cancer who are treated with a combination of androgen deprivation therapy (ADT) and androgen receptor signaling inhibitors like abiraterone or enzalutamide have an increased risk of cardiovascular events, particularly in those with pre-existing cardiovascular disease or multiple comorbidities.

CV RISK AND ANDROGEN RECEPTOR SIGNALING INHIBITORS

- Abiraterone is associated with an increased risk of CV events, fluid retention and HTN
- Enzalutamide is associated with an increased risk of HTN
- Apalutamide is associated with HTN and ischemic heart disease

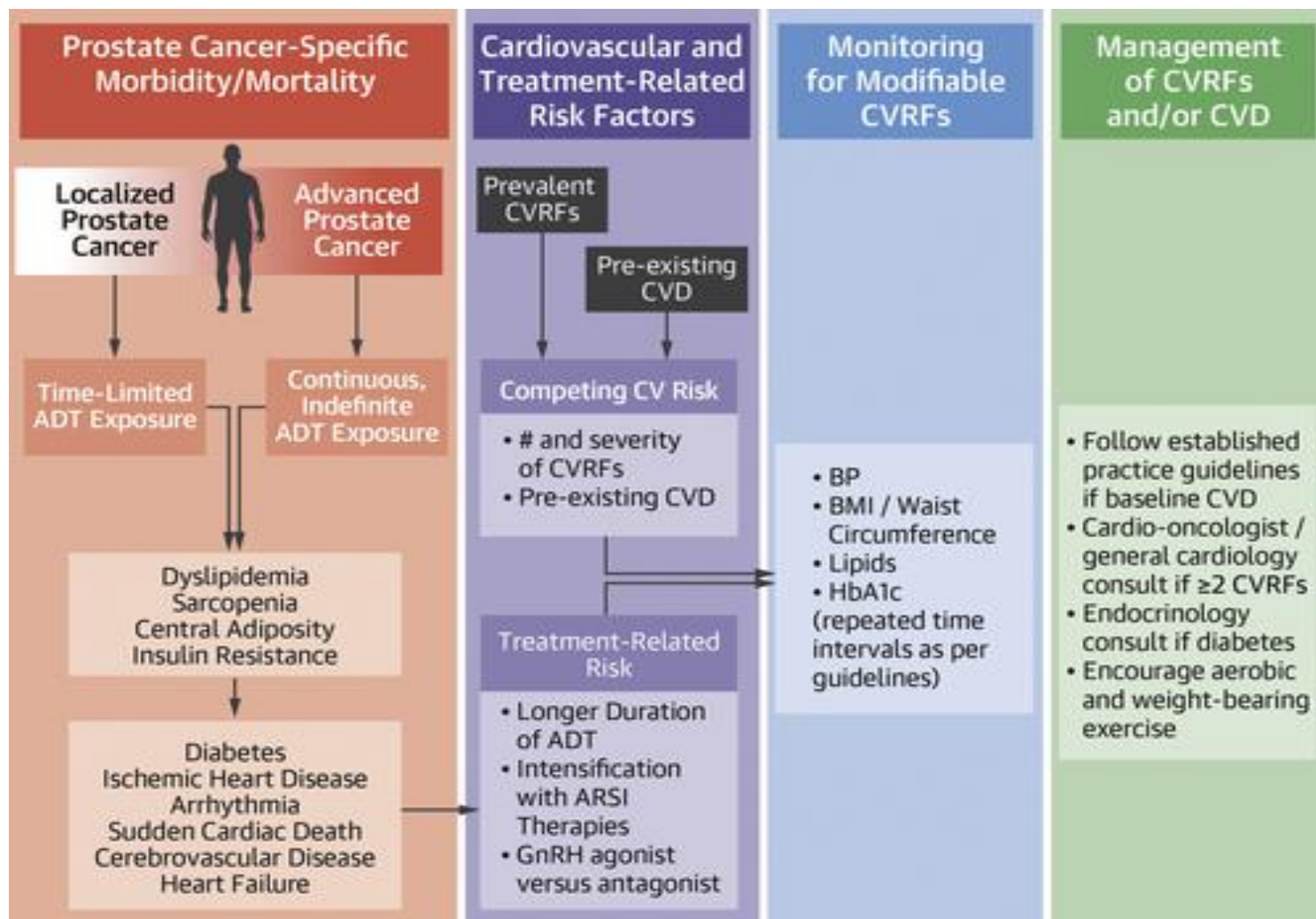
Adverse Cardiovascular Events: Abiraterone and Enzalutamide



Both abiraterone and enzalutamide were associated with increased risk of major metabolic or CV event (hospitalization or ED visit for DM, HTN, or CVD) in SEER-Medicare dataset. Abiraterone also associated with increased risk of outpatient visit for these events.

Lai L, et al. JNCI, 2022.


ADT and CV Risk Factors: Suggested Management Approach



Also Consider testing of atherosclerosis

- Coronary calcium score
- Carotid doppler
- Baseline testing of fitness and functional capacity
- Is there a role for Semaglutide to help with weight loss ?
- If DM as well , are they on SGLT2 inhibitors
- Consider Aspirin use

Vivek Narayan et al. *J Am Coll Cardiol CardioOnc* 2021; 3:737-741.

- 
- Started on statin, Metformin , Exercise physiology, Diet
 - He continued to receive treatment with ADT, but his PSA started to rise in November of 2021
 - Re-staging scans were again negative, and his testosterone was in the castrate range
 - Because he now had non-metastatic castration-resistant prostate cancer, he was started on enzalutamide in combination with ADT
 - What does he need to think about now?

- NOTE STATIN DRUG -DRUG INTERACTION
- ENZALUTAMIDE(CYP3A4 INDUCERS -STRONG) MAY REDUCE LEVEL ATORVASTATIN
- ABIRATERONE ACETATE MAY ENHANCE THE MYOPATHIC (RHABDOMYOLYSIS) EFFECT OF HMG-COA REDUCTASE INHIBITORS (STATINS).

Mediterranean Diet: well established CVD benefits

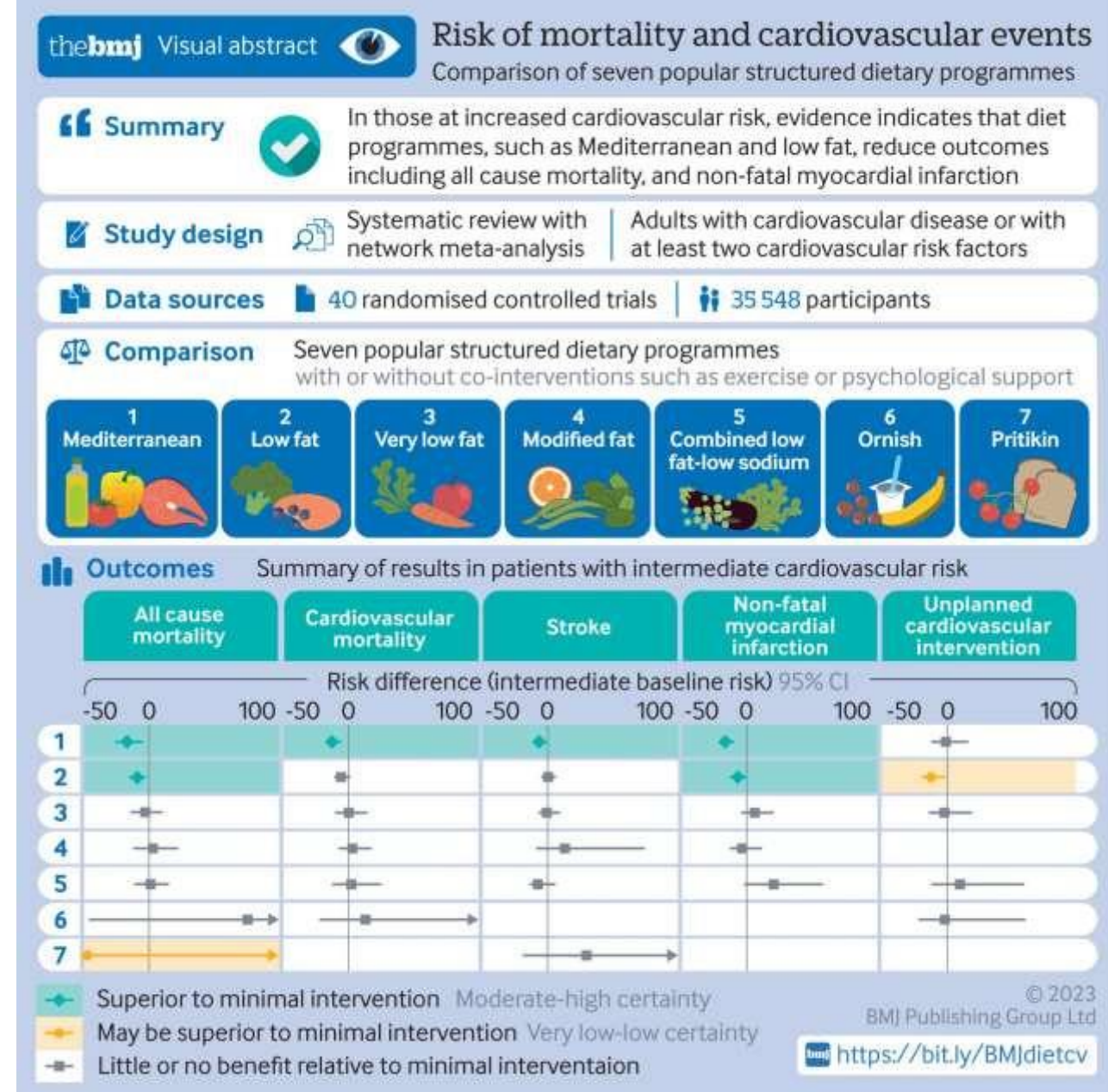
Observational studies RCT evidence including

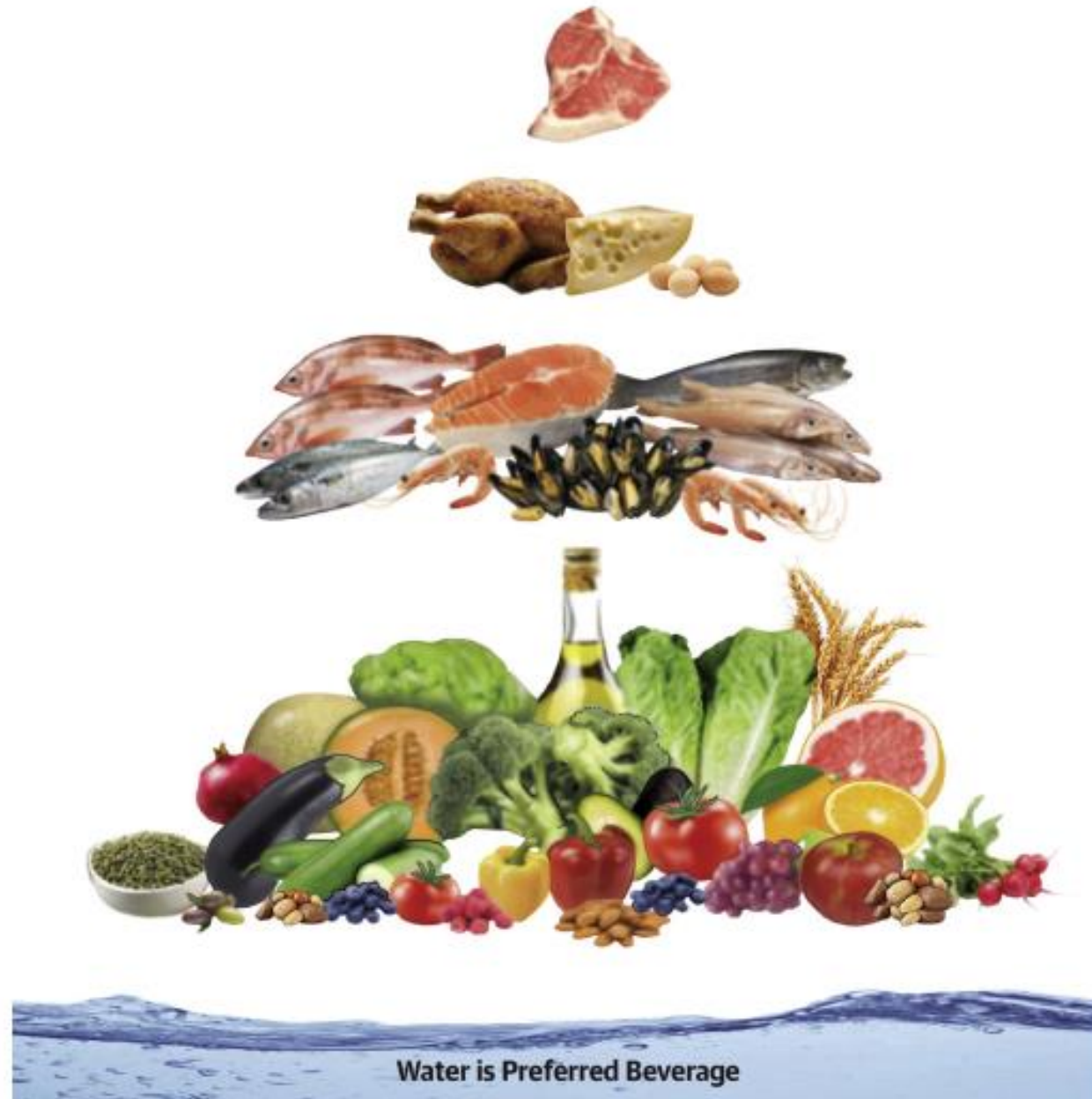
- Lyon Heart (secondary prevention trial)
- PredimedTrial (primary prevention)

➤ Have established the CVD benefit of Mediterranean Diet

Mediterranean diet proved superior to minimal intervention for the prevention of ;

- all cause mortality [OR 0.72(0.56 -0.92)]
- CV mortality [OR 0.55 (0.39 -0.78)]
- stroke[OR 0.65 (0.46 -0.93)]
- non-fatal MI[OR 0.48 (0.36 -0.65)].





[James H. O'Keefe](#)
, [Noel Torres-Acosta](#)
, [Evan L. O'Keefe](#)
, [Ibrahim M. Saeed](#)
, [Carl J. Lavie](#)
, [Sarah E. Smith](#)
, and [Emilio Ros](#)

[JACC](#). 2020 Sep, 76 (12) 1484–1493

TABLE 2 Pesco-Mediterranean Diet

Recommended	Goal	Caution	Goal	Avoid
Fish/seafood	≥ 3 times/week	Lean fresh red meat	≤ 1 time/week	Processed meats (e.g., bacon, sausage, hot dogs, ham, deli meats, cold cuts)
Vegetables	≥ 3 servings/day	White meat	≤ 2 times/week	Sweets
Fresh fruits	≥ 2 servings/day	Eggs	≤ 5 yolks/week	Butter and margarine
Legumes	≥ 3 servings/week	Dry red wine	≤ 6 oz/day ♀	Most refined carbohydrates such as products made with added sugars and/or white flour (e.g., commercial bakery goods, cookies, cakes, pies, candy, mashed potatoes, rolls, tortillas, and chips)
Whole grains	≤ 3 servings/day		≤ 12 oz/day ♂	
Tree nuts	≥ 1 serving/day			
EVOO	≥ 4 tablespoons/day	Soft cheeses		Soda drinks and sweetened fruit juices
Sofrito*	≥ 2 servings/week	Dark chocolate	$> 50\%$ cocoa	Artificially sweetened beverages and foods

*A sauce made with tomato and onion, typically including garlic and aromatic herbs slowly simmered in olive oil.

EVOO = extra-virgin olive oil.

Replace animal with plant protein

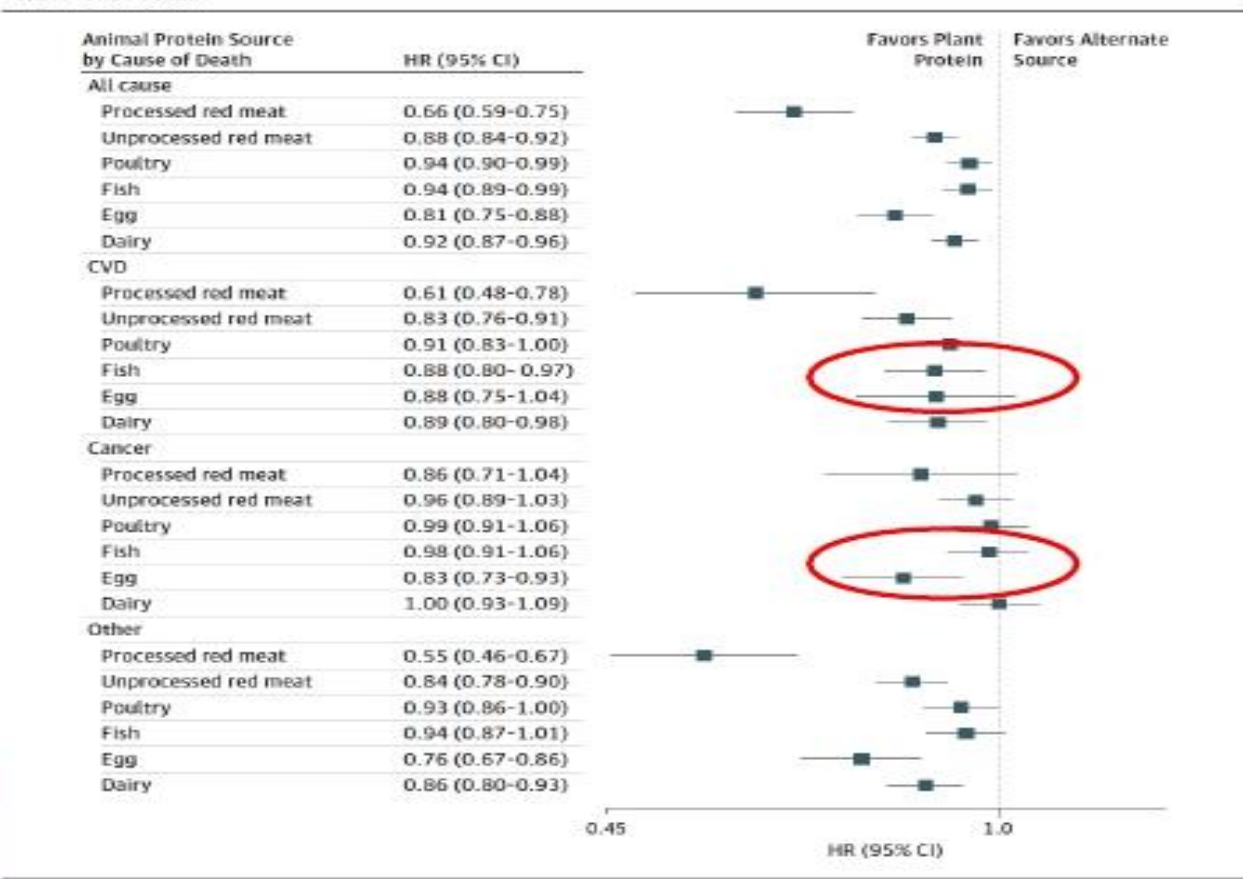
- Diets of 131,342 participants from the Nurses' Health Study and Health Professionals Follow-up Study.
- Animal protein intake was associated with an increased risk for death from diseases, especially cardiovascular disease, and plant protein intake was associated with a lower risk for mortality.
- HRs for all-cause mortality were 0.66 (95% CI, 0.59–0.75) when 3% of energy from plant protein was substituted for an equivalent amount of protein from processed red meat, 0.88 (95%CI, 0.84–0.92) from unprocessed meat, and 0.81 (95%CI, 0.75–0.88) from egg.

This is a 44% reduction, 12% reduction, and 19% reduction in mortality.



Data from the study

Figure. Risk for Mortality Associated With Replacement of 3% Energy From Various Animal Protein Sources With Plant Protein



N=131,342, 64.7%F,
3,540,791 person
years of follow-up

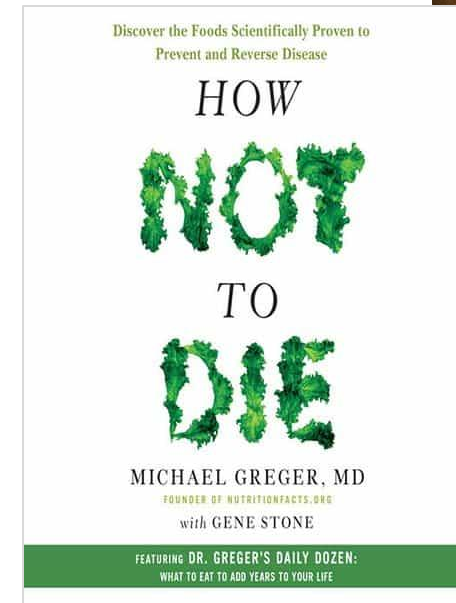
JAMA Intern Med. 2016;176(10):1453-1463.

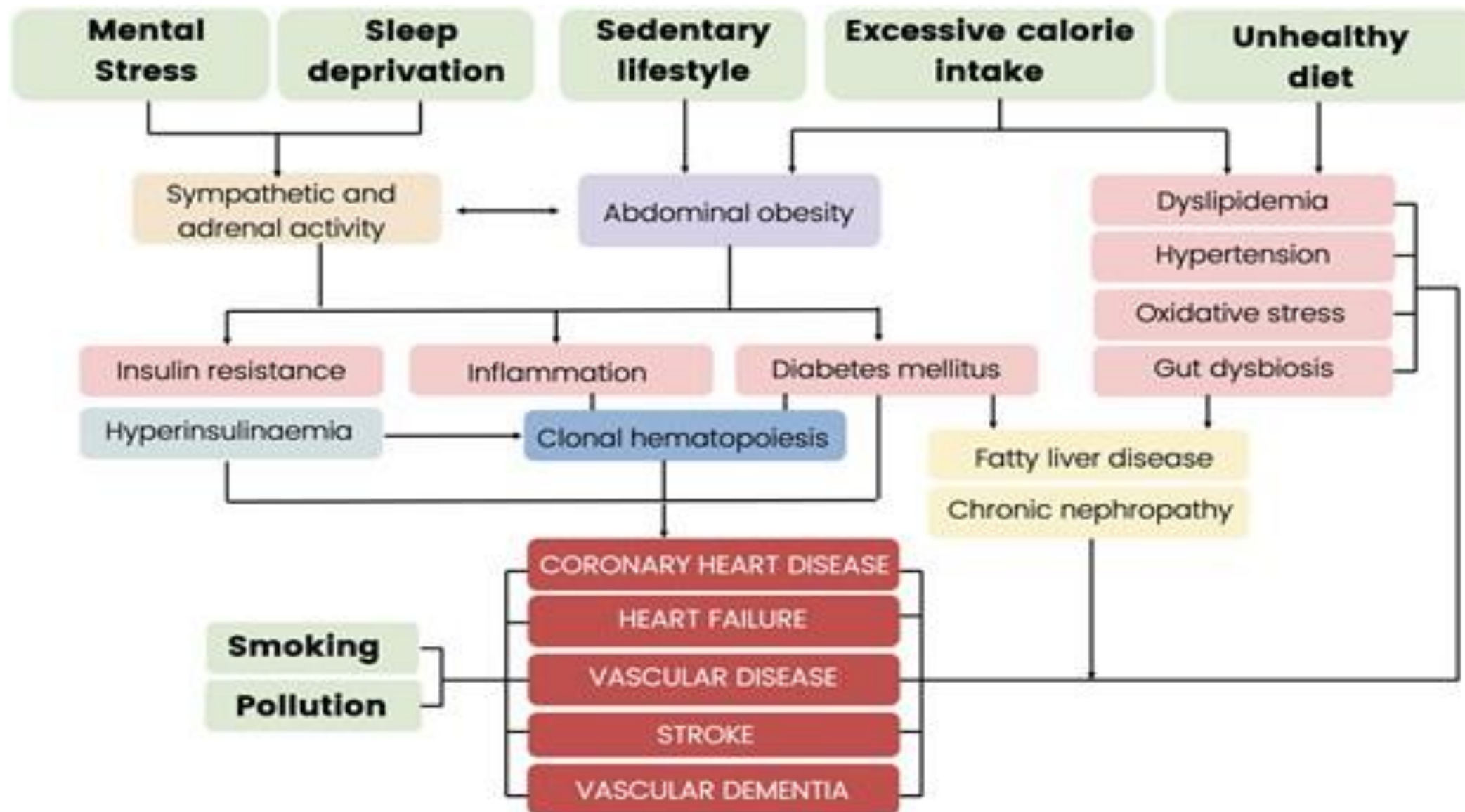


Resources to get started

- Dr Michael Greger “How not to Die”
- Nutritionfacts.org
- Forks Over Knives
- Gamechangers Movie and Website
- Dr Neal Barnard
- WEBSITES

- www.NutritionFacts.org
- www.PCRM.org/Health
- www.TrueHealthInitiative.org
- www.ForksOverKnives.com
- www.cuisinicity.com
- <https://thebigswich.com/>
- www.responsiblefoods.org





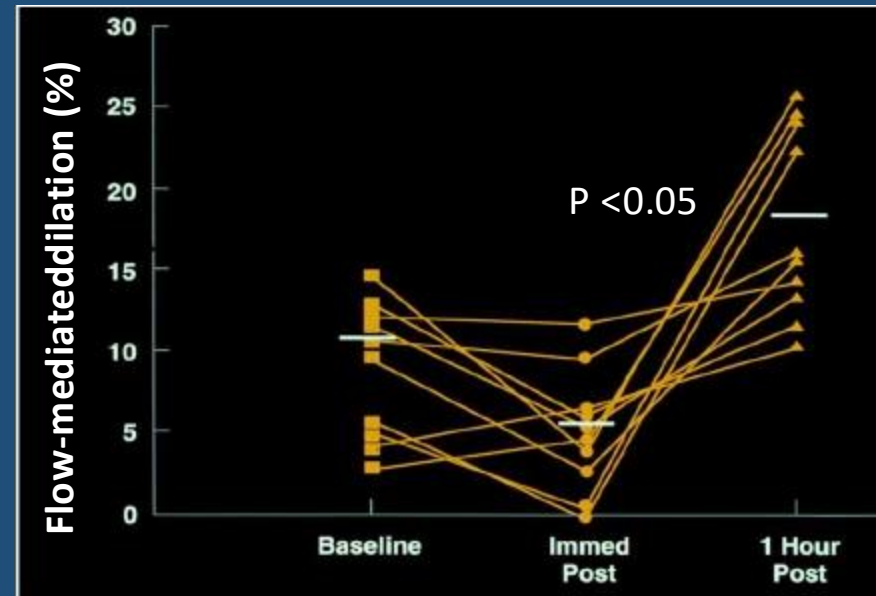
European Heart Journal, ehab633, Fontana et al.

<https://doi.org/10.1093/eurheartj/ehab633>

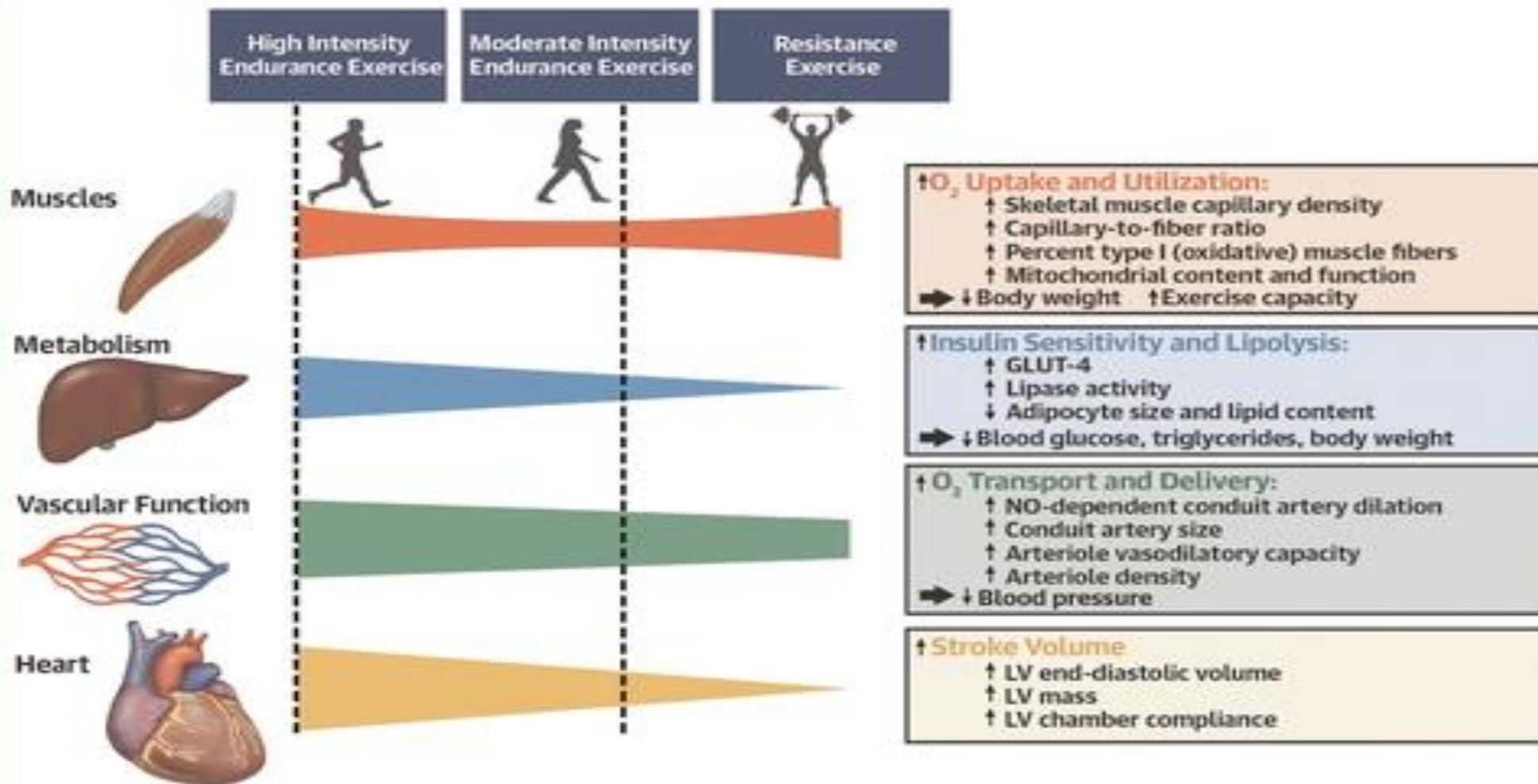
Beneficial CV Effects of Physical Activity/CRF

The Effects Are PLEOTROPIC

- **Decreases all-cause mortality**
- **Decreases CV event rates**
- Decreases depression
- Increases quality of life
- Decreases atherosclerosis progression
- Increases exercise capacity
- Preserves endothelial progenitor cells
- **Improves endothelial function** →
- Decreases inflammation
- Decreases platelet aggregation
- Increases fibrinolysis
- Decreases weight
- Decreases blood pressure
- Improves insulin sensitivity
- Decreases triglycerides
- Increases HDL-C
- Increases coronary reserve
- Increases epicardial coronary artery diameter
- Increases coronary collaterals
- Increases ischemic preconditioning
- Increases ventricular fibrillation threshold
- Increases myocardial capillary density
- Increases RBC deformability



CENTRAL ILLUSTRATION: Differing Forms of Exercise Trigger Differing Physiological Adaptations



Tucker WJ, et al. J Am Coll Cardiol. 2022;80(11):1091-1106.

Exercise in middle-aged sedentary individuals

ORIGINAL RESEARCH ARTICLE

Reversing the Cardiac Effects of Sedentary Aging in Middle Age—A Randomized Controlled Trial

Implications For Heart Failure Prevention



Erin J. Howden, PhD
Satyam Sarma, MD
Justin S. Lawley, PhD
Mildred Opondo, MD
William Cornwell, MD
Douglas Stoller, MD, PhD
Marcus A. Urey, MD
Beverley Adams-Huet, MS
Benjamin D. Levine, MD



Increased fitness



Increased LVEDV



Decreased cardiac stiffness

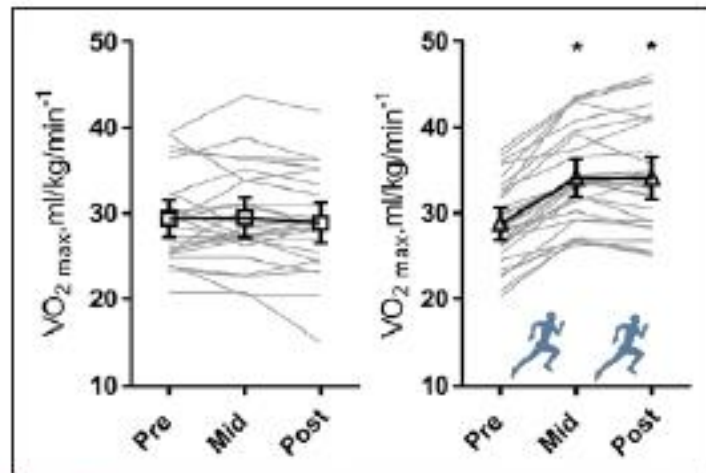


Figure 2. Effect of intervention on maximal exercise capacity.

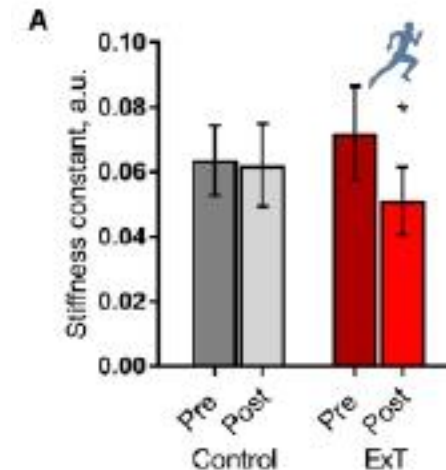
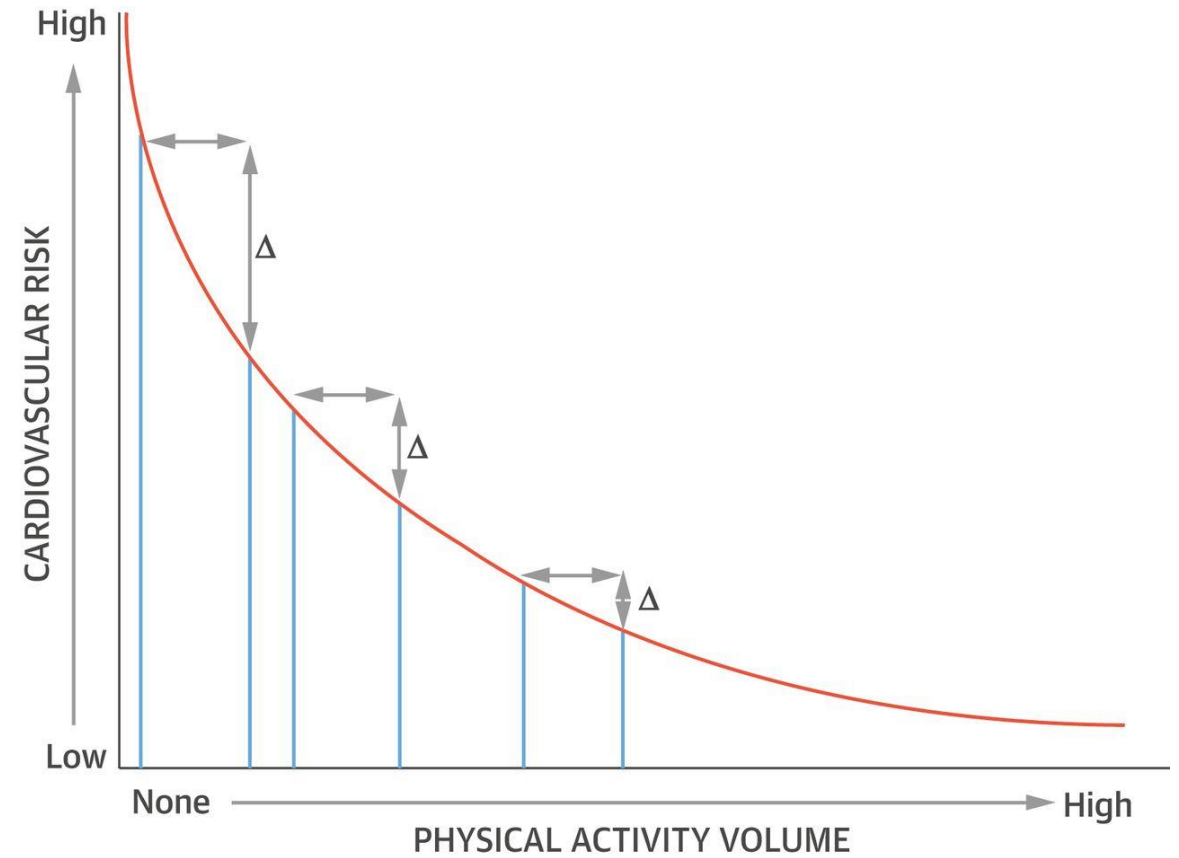


Figure 4. Effect of intervention on diastolic function.



Peter Kokkinos et al. *JACC* 2022; 80:598-609.



Thijs M.H. Eijvogels et al. *JACC* 2016;67:316-329

From: **Association of Cardiorespiratory Fitness With Long-term Mortality Among Adults Undergoing Exercise Treadmill Testing**

JAMA Netw Open. 2018;1(6):e183605. doi:10.1001/jamanetworkopen.2018.3605

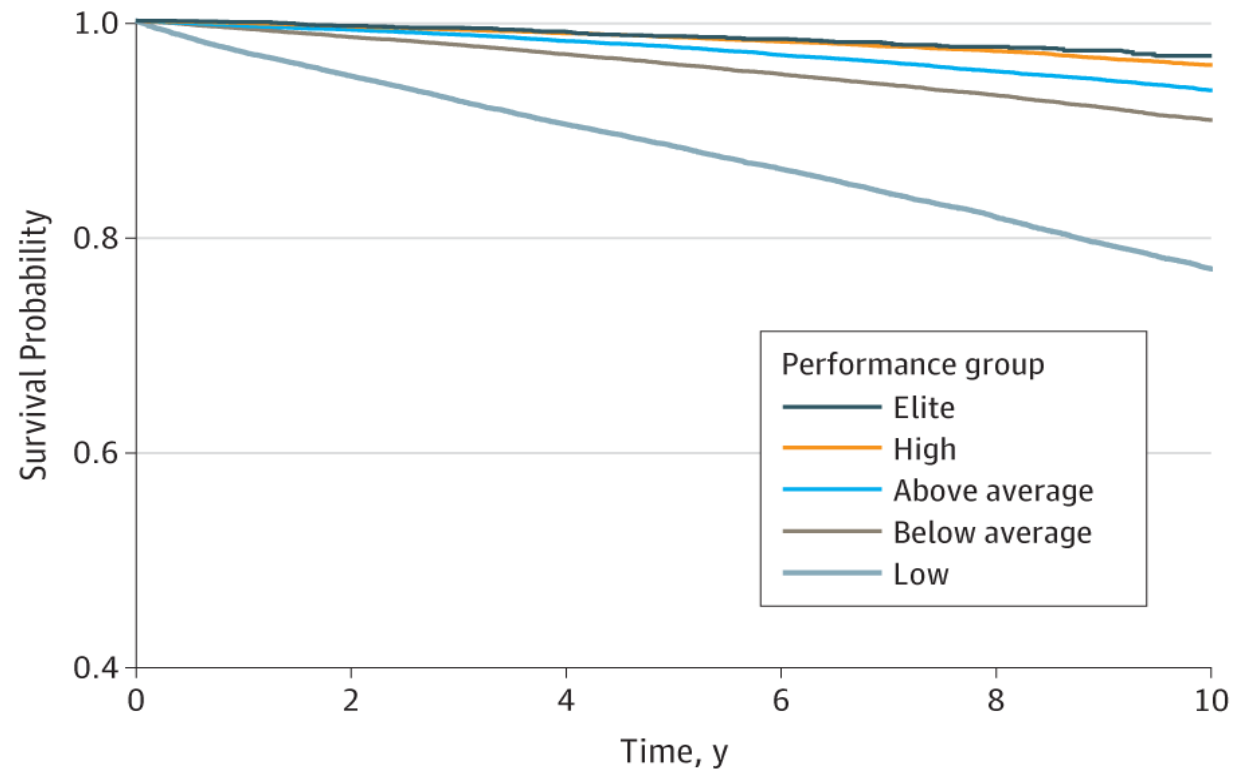
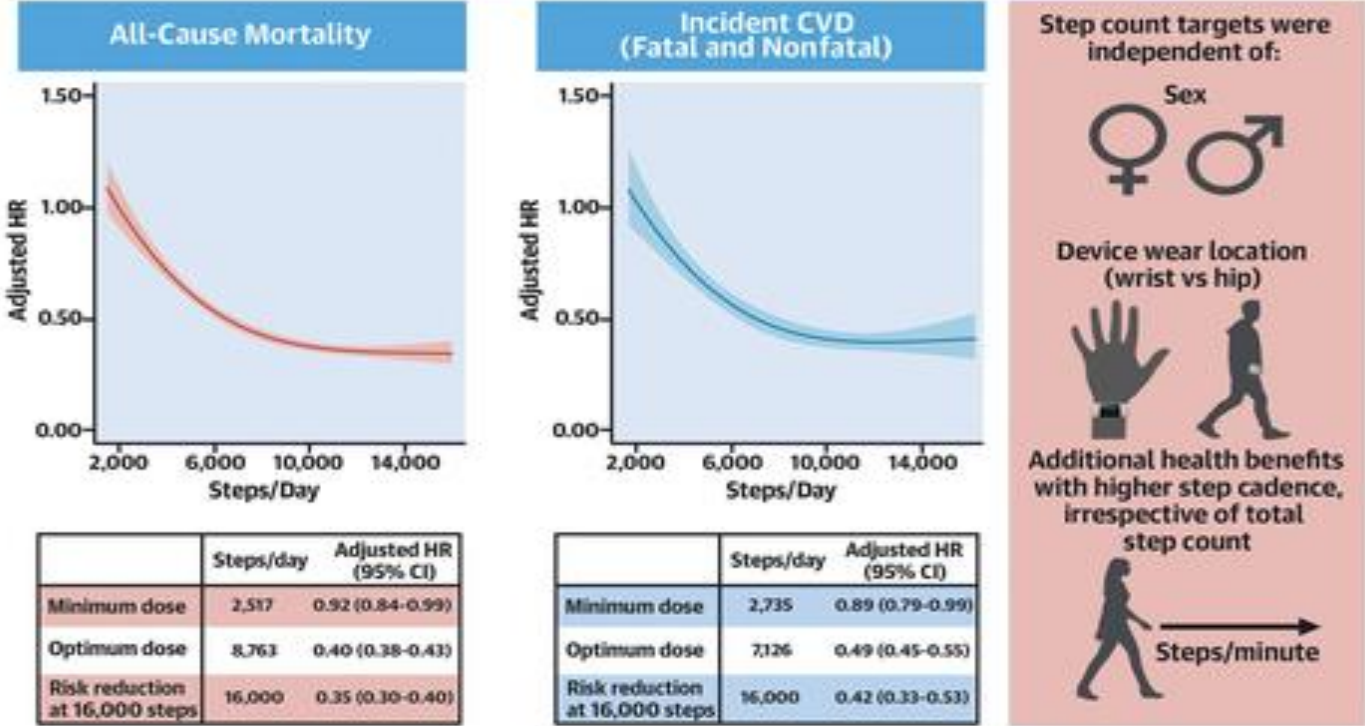


Figure Legend:

Patient Survival by Performance Group Log-rank $P < .001$ for all groups, except elite vs high performers (log-rank $P = .002$). Performance group classifications by cardiorespiratory fitness are defined in Table 2.

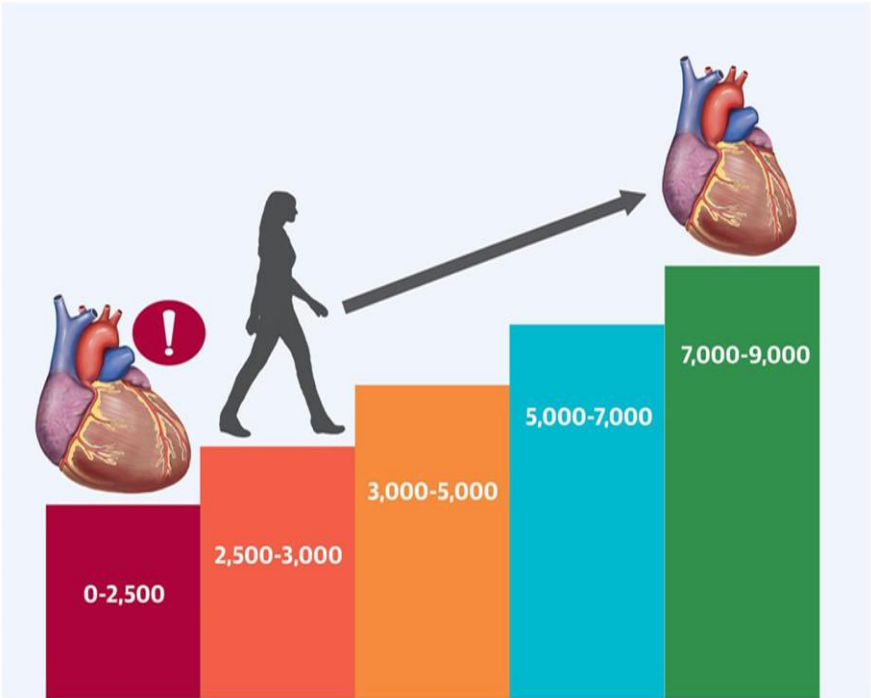
CENTRAL ILLUSTRATION: Dose-Response Associations of Daily Step Count With Clinical Outcomes

This systemic review and meta-analysis of 12 cohorts including 111,309 individuals from the general population identified minimal and optimum step count targets for reducing adverse health outcomes.



Stens NA, et al. J Am Coll Cardiol. 2023;82(15):1483-1494.

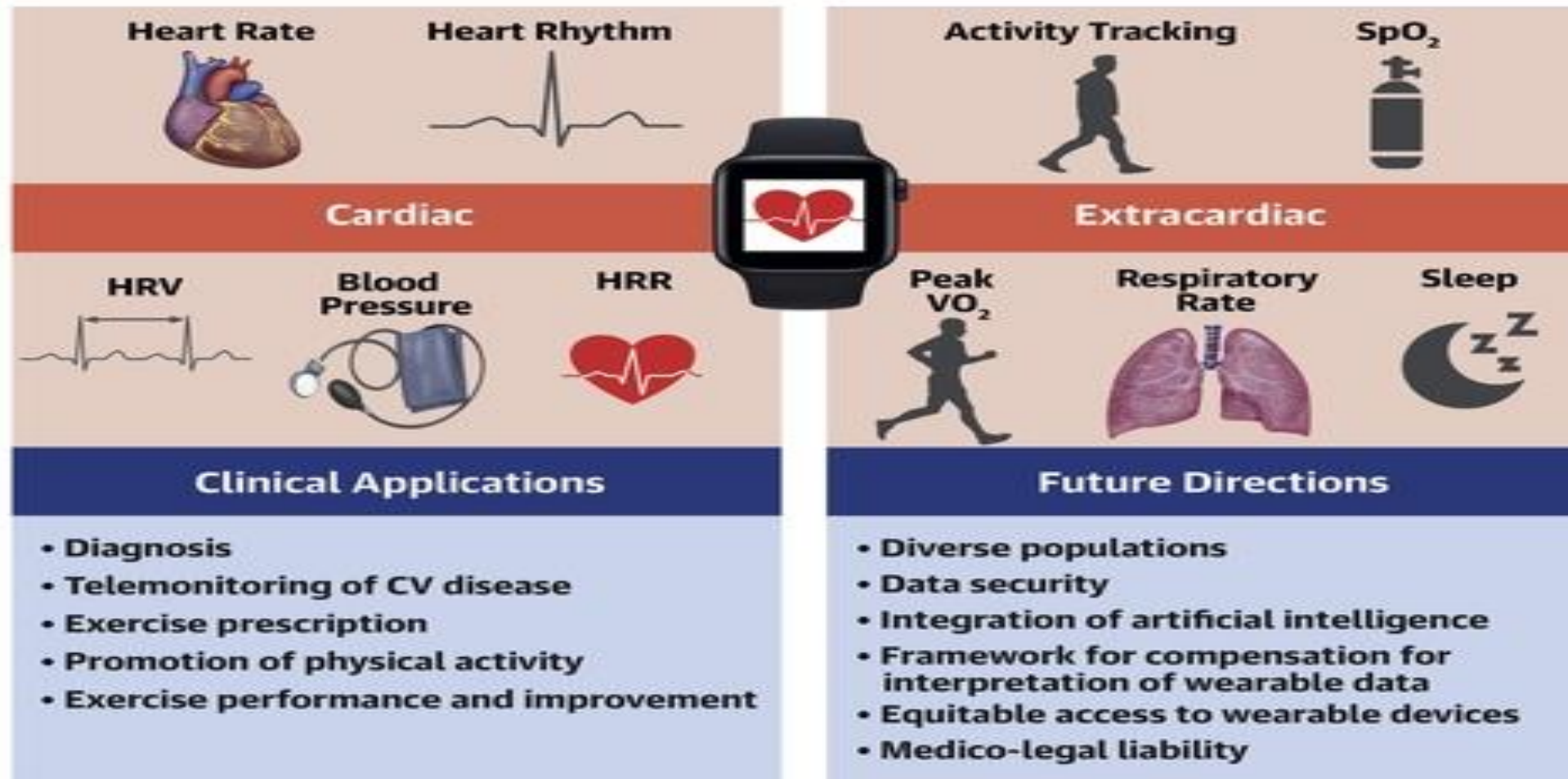
Niels A. Stens et al. JACC 2023; 82:1483-1494.



TITLE: RESISTANCE EXERCISE TRAINING IN PROSTATE CANCER PATIENTS ON ANDROGEN DEPRIVATION THERAPY (ADT)

- **Objective:** Evaluate 20-week resistance exercise training effects, with/without protein supplementation, on muscle mass, strength, body composition, and aerobic capacity in prostate cancer patients on ADT.
- **Participants:** 126 prostate cancer patients on ADT; 96 completed the study.
- **Methods:**
 - Randomized into three groups: Exercise + Protein (EX + PRO), Exercise + Placebo (EX + PLA), Control (CON).
 - Measures: Muscle mass (DXA, CT), strength (1RM tests), performance (Timed Up and Go, 30-Second Chair Stand), and aerobic capacity (VO₂ peak).
- **Results:**
 - **Muscle mass and strength:** Increased in EX + PRO and EX + PLA, decreased in CON.
 - **Body fat:** EX + PLA showed less fat increase than EX + PRO and CON.
 - **Aerobic capacity:** Maintained in EX + PLA, reduced in other groups.
 - **Protein supplementation:** No additional benefits observed beyond exercise.
- **Conclusion:** Resistance exercise effectively counters ADT side effects on muscle and body composition; protein supplementation adds no further benefits.
- Med Sci Sports Exerc. 2022 Dec 14;55(4):614–624.

CENTRAL ILLUSTRATION: Common Health Metrics Provided by Consumer Wearable Devices



Petek BJ, et al. J Am Coll Cardiol. 2023;82(3):245-264.

Bradley J. Petek et al. JACC 2023; 82:245-264.

CONCLUSIONS and Take Aways

Cardiovascular Risk Factors Are Prevalent

23% of prostate cancer patients have pre-existing cardiovascular disease, and 51% have poorly controlled cardiovascular risk factors.

ADT and Newer Hormonal Therapies May Negatively Impact Cardiovascular Health

ADT is associated with increased risk of heart failure, arrhythmias, and conduction disorders, particularly in patients with pre-existing cardiovascular disease. Newer hormonal therapies like abiraterone and enzalutamide also increase the risk of cardiovascular events.

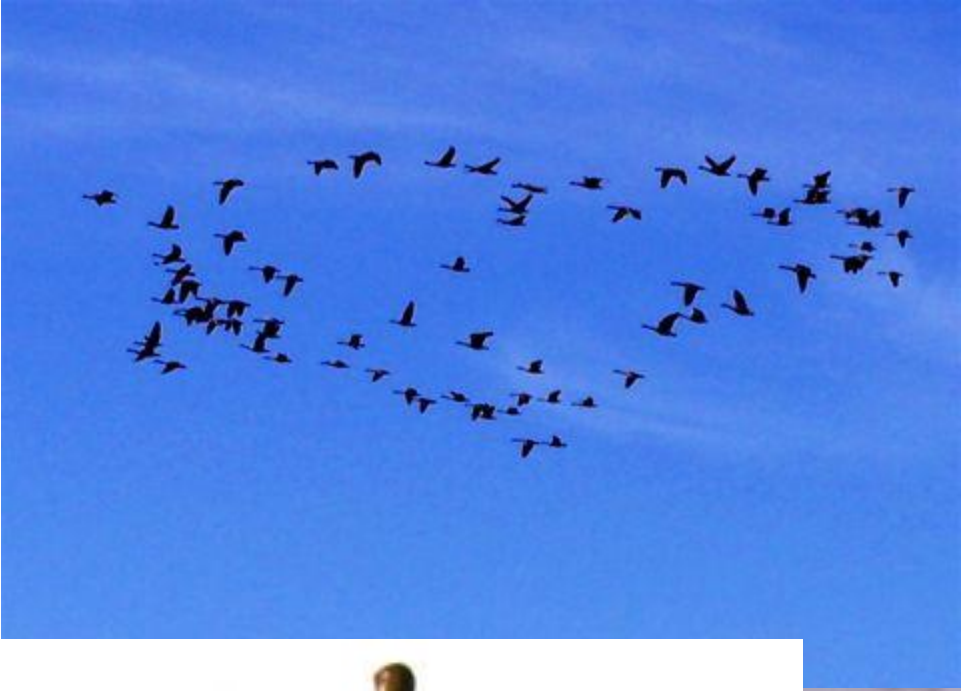
Comprehensive Cardiovascular Risk Management is Essential

A multidisciplinary approach involving the oncology team, primary care providers, and cardiologists is needed to systematically address cardiovascular risk factors in prostate cancer patients undergoing hormonal therapies. Stress Lifestyle based therapies

Personalized Treatment Decisions are Important

When selecting hormonal therapies, oncologists should carefully consider the patient's cardiovascular history and risk factors to mitigate potential adverse cardiovascular effects. However most importantly Rx risk factors and use the best Rx for the patient's cancer.

○



Thank you

