**MHIF FEATURED STUDY:**
**ATTR CM**

**CONDITION:** Transthyretin-Mediated Amyloid Cardiomyopathy

**PI:** Mosi Bennett, MD

**RESEARCH CONTACTS:**
- Sarah Schwager
  Sarah.Schwager@allina.com | 612-863-6257
- Jane Fox
  Jane.Fox@allina.com | 612-863-6289

**SPONSOR:** Ionis Pharmaceuticals

**DESCRIPTION:** A Phase 3 Global, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Transthyretin-Mediated Amyloid Cardiomyopathy

ION-682884 vs. placebo administered by subcutaneous injection once every 4 weeks in patients with ATTR-CM receiving available background therapy. ION-682884 is a ligand-conjugated antisense drug designed to reduce the production of transthyretin to treat all types of TTR amyloidosis.

**CRITERIA LIST/ QUALIFICATIONS:**

**Inclusion**
- Amyloid deposits in cardiac or non-cardiac tissue
- Medical history of HF secondary to hereditary or wild-type ATTR-CM

**Exclusion**
- Cardiomyopathy not primarily caused by ATTR-CM
- Significant co-morbidities
- Current treatment with inotersen, patisiran, diflunisal, doxycycline, non-dihydropyridine calcium-channel blocker
Sports Cardiology 2021: 
Past Progress and Future Challenges

Aaron L. Baggish MD, F.A.C.C., F.A.C.S.M.
Associate Professor of Medicine, Harvard Medical School
Director, Cardiovascular Performance Program
Massachusetts General Hospital
Boston, MA

Disclosures

Athletic Affiliations:

Funding Sources:

– National Institutes of Health
– American Heart Association
– American Society of Echocardiography
– Department of Defense
– National Football League Player’s Association
The Athlete in CV Practice

• 32 y.o. male professional marathoner

• Fatigue >> acute pleuritic chest pain

• Evaluation concludes viral myopericarditis

• Rx: NSAIDs and activity restriction

3 months later, back to training, Emails his doc:

“Doc: all is well. Feeling good. Think the NSAIDs did the trick. Hoping to PR at my next race.”

MD with prompt reply:

“Racing again sounds fine. However, I would prefer you take your medication orally, not PR.”
Sports Cardiology: Then

The Old Schema

- Athlete
- Coach & ATC
- Sports MD
- Cardiac MD

Sports Cardiology 2020

NCAA Athletes

USA Road Race Finishers

Running Event Finishers 1990 - 2013

US Triathlon Events

“Cross Fit” Athletes
Our Mission

United States Sport Cardiology Resources: 2020

Sports Cardiology 2020
Sports Cardiology 2020

Where have we come from?
&
Where do we need to go?

Eligibility for Young Athletes:
Paternalism is Over

Care for Masters Athletes:
From Opinion to Data

No IA Data....What to do?
Bethesda Updates: Key Points

- 15 “Task Force” documents
- Topics & Diseases
- Disqualification & Restriction (not mgmt.)
- Geared to “competitive athletes” (HS, College, Professional)
- Conflicting Views:
  - “Limited Control” populations
  - Newly added – Class 2a & 2b Recs
  - “It may be reasonable to play....”

Class II Recommendations: Clinical Progress

412 Total, Class IIa (n=39) & Class IIb (n=47)

- Full participation: Asxs R-AOCA with "-" testing (IIa)
- Full participation: Post-ICD implantation (IIb)
- Full participation: LVNC with normal LVFx (IIb)

- Full participation: Revascularized CAD, norm LVFx, no Isch/Elect. (IIb)
- Full participation: Cardiac transplant recipients with normal LVFx (IIa)
- Full participation: Asxs LQTS following optimal rx. (IIb)

THESE RECOMMENDATIONS NECESSITATE A PROCESS
Class 2 Recs....What to do?

The Decision Making Control Spectrum

Paternalism
- Docs know best
- Clearance is our job
- The process is simple
- Why make it complex?

Autonomy
- Docs don’t always know
- Patients are individuals
- Medical vs. Non-medical
- Because it is complex

Shared Decision Making

Shared Decision Making for Athletes with Cardiovascular Disease: Practical Considerations

The Impact of SDM for Competitive Athletes with CVD is Completely Untested and thus the Pros and Cons Remain 100% Speculative....This Needs to Studied and Vetted to Ensure That Benefits Outweigh Risk
COVID-19 Cardiac

The "ORCCA" Registry

Outcomes Registry for Cardiac Conditions in Athletes

Aaron Baggish
Nathanial Moulson
Bradley Petek
Jonathan Drezner
Kimberly Harmon
Stephanie Kliethermes
(MMSSM CRN, U of Wisc.)
Manesh Patel (Duke)
Mariell Jessup (AHA)

Members of the ORCCA Study Group:
Shaping Committee:
Ji Tao M. Asin, MD, Aaron L. Baggish, MD, James Borchers, MD, Jonathan A. Drezner, MD,
Katherine M. Elderfield, MD, Michael S. Enawy, MD, MS, Kyle Goed, MD, Brian Haselton,
MD, Kimberly G. Harmon, MD, Jonathan H. Kim, MD, MSc, Stephanie Kliethermes, PhD,
William E. Kraus, MD, Rachel Lampert, MD, Matthew Lunzer, MD, Benjamin D. Levine, MD,
Matthew W. Martinez, MD, Nathanial Moulson, MD, Francis G. O'Connor, MD, MPH, Maresh R. Patel, MD, Bradley J. Petek, MD, Denny Pieters, MD, Lawrence D Rusk, MD, Herman A
taylor, MD, MPH.

COVID-19 Cardiac

Circulation, April 2021

Total Athletes Tested for SARS-CoV-2
(n=10,379)

77.1%

SARS-CoV-2 Positive Athletes
(n=3,384)

No cardiac evaluation per school
preference (n=2,740)

Planned Cardiac Evaluation
(n=3310)

Instruments Evaluation

Athlete not evaluated (n=1,387)

Testing not started (n=108)

Missing data/incorrect school
enumeration (n=19)

Final Cohort with Cardiac Evaluation
(n=3018) 15.9%

Median Length of Follow-up = 113 days IQR [90,146]
COVID-19 Cardiac

CV Care: Masters Athletes

Men and women >35 years of age who exercise vigorously >5 hours weekly with emphasis on goals...

Running can take a toll on the heart that essentially eliminates the benefits of exercise. “Running too far, too fast and for too many years may speed one's progress toward the finish line of life,” concludes an editorial to be published next month in the British journal Heart.

**Too Much Exercise??**

**Current Controversies**

**Provenance and peer review** Commissioned, internally peer reviewed.

**Author note** A video presentation on this topic is available on the internet: YouTube, TEDx Talk, James O’Keefe, Run for your life… at a comfortable pace and not too far.

*Heart* 0:0:1-4. doi:10.1136/heartjnl-2012-302886
The central controversy

But, for the most part, where there is lots of smoke there’s usually at least a little fire....

Does too much exercise over too much time hurt your heart (and affect morbidity and mortality) and if so, what does this pathology look like?

Anecdotal Observations of Physically Fit Athletes Dying, Perhaps due to Sport-induced CV Disease

Emerging Epidemiologic Data with a focus on the high ends of fitness

Observational data describing CV pathology among athletes and athletic patients

A syndrome of cardiovascular abnormalities (perhaps caused by) chronic exposure to high volume exercise
Exercise Dose - Response

Dose-Response Curves

- **Race Performance**
- **CV Risk Factors**
- **Marital Success**
- **Weight Loss**

Too Much Exercise??

Increased life expectancy of world class male athletes

Endurance athletes
Team athletes
Power athletes
References
Too Much Exercise??

Hospital Care in Later Life Among Former World-Class Finnish Athletes

Table 5. Rate Ratios (RRs) Adjusted for Age Group and Occupational Group and Their 95% Confidence Intervals for Hospital Days per Year for Different Disease Categories Among Former Athletes Compared With Controls.

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Endurance Sports</th>
<th>Mixed Sports</th>
<th>Power Sports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases of the circulatory system</td>
<td>0.55 (0.39-0.77)</td>
<td>0.61 (0.48-0.79)</td>
<td>0.70 (0.54-0.98)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>0.29 (0.27-0.33)</td>
<td>0.26 (0.24-0.29)</td>
<td>0.21 (0.19-0.24)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>0.61 (0.49-0.76)</td>
<td>0.65 (0.52-0.79)</td>
<td>0.69 (0.55-0.82)</td>
</tr>
<tr>
<td>Diseases of the respiratory system</td>
<td>0.41 (0.39-0.44)</td>
<td>0.36 (0.34-0.38)</td>
<td>0.35 (0.33-0.38)</td>
</tr>
<tr>
<td>Diseases of the musculoskeletal system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and connective tissue</td>
<td>1.14 (1.05-1.22)</td>
<td>1.24 (1.17-1.31)</td>
<td>1.36 (1.26-1.47)</td>
</tr>
<tr>
<td>Diseases of the digestive system</td>
<td>0.60 (0.49-0.75)</td>
<td>0.71 (0.65-0.78)</td>
<td>0.74 (0.67-0.81)</td>
</tr>
</tbody>
</table>

*P<0.01 for all comparisons with controls.

Too Much Exercise??

Marathon Running and Immunity to Atherosclerosis

Thomas S. Waster
Department of Pathology
Harvard Medical School
Cambridge, Massachusetts

Atherosclerotic plaque formation is a complex process that involves the interaction of multiple cell types and cytokines. Accumulating evidence suggests that marathon running may have a protective effect on plaque formation. In this study, we aimed to investigate the immune response of marathon runners to atherosclerotic plaques.

Methods
We performed directed immunohistochemistry on atherosclerotic plaques from marathon runners and non-runners. The expression of immune-related proteins, such as CD4+ T cells, macrophages, and fibroblasts, was assessed.

Results
Our results indicate that marathon runners have a significantly lower expression of immune-related proteins compared to non-runners. This suggests that marathon running may attenuate the immune response to atherosclerotic plaques.

Conclusion
Marathon running may be a protective factor against atherosclerosis by modulating the immune response to plaque formation.
Too Much Exercise??

Athletes as a Patient Population

40% Health Care Dissatisfaction Rate: “Dismissed or Mistreated” due to Status as an Athlete
Key CV Controversies

1.) Do endurance sports cause arrhythmia?

2.) Do endurance sports cause cardiomyopathy?

3.) Do endurance sports cause aortopathy?

4.) Do endurance sports cause coronary disease?

52 y.o. marathoner with decreased ex tolerance
### Arrhythmia: AFib

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Reference</th>
<th>Subjects</th>
<th>Primary Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karjalainen</td>
<td>BMJ 1998</td>
<td>Runners (n=100)</td>
<td>5.5 (1.3–24.4)</td>
</tr>
<tr>
<td>Mont</td>
<td>EHJ 2002</td>
<td>Endurance (n=70)</td>
<td>71% with lone AF</td>
</tr>
<tr>
<td>Elosua</td>
<td>Int J Card 2006</td>
<td>Endurance (n=51)</td>
<td>2.87 (1.39–7.05)</td>
</tr>
<tr>
<td>Heidbuchel</td>
<td>Int J Card 2006</td>
<td>Endurance (n=53)</td>
<td>1.81 (1.10-2.98)</td>
</tr>
<tr>
<td>Molina</td>
<td>Europace 2008</td>
<td>Runnners (n=39)</td>
<td>8.8 (1.26-61.3)</td>
</tr>
<tr>
<td>Baldesberger</td>
<td>EHJ 2008</td>
<td>Cyclist (n=67)</td>
<td>10% AF in athletes</td>
</tr>
<tr>
<td>Mont</td>
<td>Europace 2008</td>
<td>Endurance (n=48)</td>
<td>7.31 (2.33-22.9)</td>
</tr>
<tr>
<td>Aizer</td>
<td>Am J Card 2009</td>
<td>PHS Database (n=16,921)</td>
<td>1.20 with ≥ 7 days/week ex.*</td>
</tr>
<tr>
<td>Claessen</td>
<td>Heart 2011</td>
<td>Non-sel. Flutter RFA (n=58)</td>
<td>“Sportsmen” 50% of Lone Afl pop.</td>
</tr>
<tr>
<td>Andersen</td>
<td>EHJ 2013</td>
<td>Nordic Skiers (n=52,755)</td>
<td>1.29 (1.04-1.61)*</td>
</tr>
</tbody>
</table>

#### Arrhythmia: A-Fib.

**Risk of arrhythmias in 52,755 long-distance cross-country skiers: a cohort study**

Kasper Andersen, Bahman Farahmand, Anders Ahlbom, Claes Held, Sverker Ljungwall, Karl Michalsson, and Johan Sundelin.

- Retrospective design
- Sweden -- Vasaloppet (90K)
- >50,000 participants
- Incidence of arrhythmia events
- Race time / # of races > Arrhyth.
- AF the dominant rhythm issue

---

MHIF Cardiovascular Grand Rounds | April 26, 2021
The strongest association between endurance sport and pathology lies with atrial fibrillation...the data are clear that our aging patients who engage in these sports are at increased risk....sport or lifestyle choices?

Treatment strategies, at present, are extrapolations / expert experience. More outcome driven primary data are needed.
Key CV Controversies

1.) Do endurance sports cause arrhythmia?

2.) Do endurance sports cause cardiomyopathy?

3.) Do endurance sports cause aortopathy?

4.) Do endurance sports cause coronary disease?

The Harvard Athlete Initiative

Cardiomyopathy

The impact of endurance exercise training on left ventricular systolic mechanics

Aaron L. Bagash,1 Khair Yarad,1 Fanchen Wang,1 Irey B. Weiser,1 Adolph M. Butler Jr.,4 Michael H. Heart2 and Melissa J. Wood1

1Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts; and 2University Health Services, Harvard University, Cambridge, Massachusetts

Submitted 13 April 2006; revised 21 July 2006

The Harvard Athlete Initiative
Cardiomyopathy

The impact of endurance exercise training on left ventricular systolic mechanics

Am J Physiol Heart Circ Physiol 2008

LV Systolic Strain Changes with Rowing Training (n=20)

Longitudinal ~ 20-25%
Radial ~ 50-60%
Circumferential ~ 20-25%

Normal to Supranormal Strain...Focal Septal Dysfunction Fatigue??

39

Cardiomyopathy

The Ventricular Interdependence of Physiologic Remodeling

Am J Physiol Heart Circ Physiol 2008;295:1109

40
Cardiomyopathy

Table 3. Location and extent of LGE in veteran athletes

<table>
<thead>
<tr>
<th>Participant</th>
<th>No.</th>
<th>Age (yr)</th>
<th>Percentage of Total LGE Mass, g</th>
<th>LGE Patterns</th>
<th>Perfusion Defect</th>
<th>Interpretation</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>18.9</td>
<td>Yes</td>
<td>Peri/ventricular &amp; Basal &amp; Midventricular</td>
<td></td>
<td></td>
<td>Sympathetic &amp; Lateral Wall</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>8</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td>Perfusion</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>7</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td>Perfusion</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>7</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td>Perfusion</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>3</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td>Perfusion</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>3</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td>Perfusion</td>
</tr>
</tbody>
</table>

Whyte et al. JAP 2011

LaGerche et al. EHJ 2011

Cardiomyopathy

Table 1. Baseline demographic and functional measures according to the endurance event completed

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Marathon run</th>
<th>Endurance triathlon*</th>
<th>Alpine cycling</th>
<th>Ultra triathlon*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of athletes</td>
<td>40</td>
<td>7</td>
<td>11</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Race distance (km)</td>
<td>42.2</td>
<td>19.9/20.1</td>
<td>107</td>
<td>38.8/20.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race completion time</td>
<td>2:59 min ± 30 min</td>
<td>3:24 min ± 25 min</td>
<td>8:15 min ± 42 min</td>
<td>10:32 min ± 1 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambient temperature (°C)</td>
<td>24–34</td>
<td></td>
<td>24–28</td>
<td>24–34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>37 ± 6</td>
<td>30 ± 3</td>
<td>33 ± 7</td>
<td>44 ± 9</td>
<td>34 ± 8</td>
<td>0.014</td>
</tr>
<tr>
<td>Training (years)</td>
<td>10 ± 9</td>
<td>13 ± 8</td>
<td>6 ± 4</td>
<td>12 ± 14</td>
<td>11 ± 9</td>
<td>0.277</td>
</tr>
<tr>
<td>Training (kiles/week)</td>
<td>163 ± 51</td>
<td>14 ± 6</td>
<td>14 ± 3</td>
<td>13 ± 4</td>
<td>21 ± 5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Preliminary data suggests that some athletes may develop a patchy fibrosis (cardiomyopathy)…a phenotype of uncertain clinical relevance that deserves our attention and further outcomes-based study....at this point: NO CLEAR CLINICAL RELEVANCE.
Key CV Controversies

1.) Do endurance sports cause arrhythmia?

2.) Do endurance sports cause cardiomyopathy?

3.) Do endurance sports cause aortopathy?

4.) Do endurance sports cause coronary disease?

Aortopathy
Aortopathy

Table 3. Results of Base Case and Subgroup Analyses of Aortic Root in Athletes Compared with Controls at the Aortic Valve Annulus

<table>
<thead>
<tr>
<th>Study-Level Factor</th>
<th>No. of Subjects</th>
<th>Meta-Regression Analysis: Adjusted Difference at Aortic Valve Annulus, mm (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athlete sex</td>
<td>Control (403)</td>
<td>Male 830; 4.1 (4.4 to 7.0)*; Female 1916; -2.6 (-7.3 to 2.1)</td>
</tr>
<tr>
<td>Study location</td>
<td>Non-US (281)</td>
<td>US 316; -1.5 (-4.0 to 1.0)</td>
</tr>
<tr>
<td>Imaging type</td>
<td>Endurance athletes (799)</td>
<td>Strength athletes (425)</td>
</tr>
<tr>
<td></td>
<td>2.2 (4.4 to 4.0)*;</td>
<td>1.6 (-0.4 to 3.5)</td>
</tr>
</tbody>
</table>

Background—The aorta is exposed to increased arterial pressure throughout life. The study characteristics and aortic root dimensions at the aortic valve annulus were measured in a subset of 71 athletes and 71 controls, and the difference in aortic root dilatation was compared to see if the aorta is larger in athletes compared with non-athletes. The study was conducted at a mean age of 25 (24 to 26) years, with a mean body mass index of 20.0 (18.0 to 22.0) kg/m² and a mean blood pressure of 121 (115 to 125) mmHg. The mean values of the aortic root and annulus were similar between athletes and controls. The statistical analysis was performed using a linear regression model, adjusted for age, sex, and body mass index. The results indicate that the aorta is larger in athletes than in non-athletes, with a significant difference observed in the aortic root dilatation between the two groups. (Circulation)

Aortopathy

Table 1. Participant Data and Demographic Parameters

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male (n = 134)</th>
<th>Female (n = 134)</th>
<th>Male (n = 134)</th>
<th>Female (n = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>33 (28, 38)</td>
<td>32 (27, 37)</td>
<td>33 (28, 38)</td>
<td>32 (27, 37)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.77 (1.73, 1.81)</td>
<td>1.71 (1.66, 1.76)</td>
<td>1.77 (1.73, 1.81)</td>
<td>1.71 (1.66, 1.76)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72 (64, 80)</td>
<td>64 (56, 72)</td>
<td>72 (64, 80)</td>
<td>64 (56, 72)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24 (21, 26)</td>
<td>19 (16, 22)</td>
<td>24 (21, 26)</td>
<td>19 (16, 22)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (18, 24)</td>
<td>18 (15, 21)</td>
<td>21 (18, 24)</td>
<td>18 (15, 21)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (3, 5)</td>
<td>3 (2, 4)</td>
<td>4 (3, 5)</td>
<td>3 (2, 4)</td>
</tr>
<tr>
<td>Smoking (current or former)</td>
<td>18 (16, 20)</td>
<td>16 (14, 18)</td>
<td>18 (16, 20)</td>
<td>16 (14, 18)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>10 (9, 11)</td>
<td>8 (7, 9)</td>
<td>10 (9, 11)</td>
<td>8 (7, 9)</td>
</tr>
<tr>
<td>Medications</td>
<td>30 (28, 32)</td>
<td>28 (26, 30)</td>
<td>30 (28, 32)</td>
<td>28 (26, 30)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>16 (15, 17)</td>
<td>14 (13, 15)</td>
<td>16 (15, 17)</td>
<td>14 (13, 15)</td>
</tr>
<tr>
<td>Diabetes-related medication</td>
<td>8 (7, 9)</td>
<td>7 (6, 8)</td>
<td>8 (7, 9)</td>
<td>7 (6, 8)</td>
</tr>
<tr>
<td>Diabetes-related medication</td>
<td>8 (7, 9)</td>
<td>7 (6, 8)</td>
<td>8 (7, 9)</td>
<td>7 (6, 8)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>25 (22, 27)</td>
<td>16 (14, 18)</td>
<td>25 (22, 27)</td>
<td>16 (14, 18)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>25 (22, 27)</td>
<td>16 (14, 18)</td>
<td>25 (22, 27)</td>
<td>16 (14, 18)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>25 (22, 27)</td>
<td>16 (14, 18)</td>
<td>25 (22, 27)</td>
<td>16 (14, 18)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>25 (22, 27)</td>
<td>16 (14, 18)</td>
<td>25 (22, 27)</td>
<td>16 (14, 18)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>25 (22, 27)</td>
<td>16 (14, 18)</td>
<td>25 (22, 27)</td>
<td>16 (14, 18)</td>
</tr>
</tbody>
</table>
Aortopathy

STAY TUNED....
On-going longitudinal surveillance will help us determine progression & clinical outcomes
to date, this appears to be a benign “adaptive” response to that should not be considered pathologic......

Key CV Controversies

1.) Do endurance sports cause arrhythmia? ✔️
2.) Do endurance sports cause cardiomyopathy? ✔️
3.) Do endurance sports cause aortopathy? ✔️
4.) Do endurance sports cause coronary disease? ✔️
**CV Risk Factors with Exercise**

- The Effects of Aerobic Exercise on Plasma Catecholamines and Blood Pressure in Patients With Mid Essential Hypertension
  - *JAMA* 1985

- Effects of the Amount and Intensity of Exercise on Plasma Lipoproteins
  - *NEJM* 2002

- Effect of Exercise on Total and Intraperitoneal Body Fat in Postmenopausal Women
  - *Circulation* 2007

**CAD: Observational Data**

- Running: the risk of coronary events
  - Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners

- Table 2: Distribution of coronary artery calcification (CAC) in marathon runners (group I) and age-matched controls (group II)

- Figure 1: Kaplan–Meier estimates of event-free survival by extent of coronary artery calcification (CAC). No marathon runners with CAC <100 experienced a coronary event, while 8% and 14.2% of those with CAC 100 to <400 and ≥400, respectively, required revascularization during follow-up. Using Cox regression analysis, hazard ratios for a two-fold increase in log(CAC + 1) were: hazard ratio = 1.51, 95% confidence interval = 1.19–1.92, *P* < 0.027. The numbers pertain to the subjects with events in Table 2.
**CAD: Observational Data**

**Interpretation Options:**

1.) High levels of exercise causes atherosclerosis (CAD)

2.) Traditional CAD risk factors causal/underappreciated

3.) CAD driven by unknown/unmeasured risk factors
Do you really think it was the running that caused these men's coronary disease??

CAD: Observational Data

Increased Coronary Artery Plaque Volume Among Male Marathon Runners

Missing Risk Issues:

1.) Diet (Fit vs. Healthy)
2.) “Care-free” 20's-30's
3.) Family Genes

Without controlling for these, can we say anything about causality?
CAD in Athletes: Causality?

“Man, not so sure that second plate of chili nachos and the extra couple of beers last night were such a good idea...Oh well, they always say don’t change your routine prior to races.”

Diet

“Just wish my old man could see me now. He died at age 45 from a massive heart attack. Glad I got my wake up call. Bad stuff runs in my family”

Genes

“Well, regardless of what happens, I’ve got to be better off than I was 20 years ago when I was smoking a pack-a-day and got short of breath just driving up this damn hill.”

Early Life

“Cough, cough, cough...If this race wasn’t only once a year I’d be home in bed. I feel like shit. Oh well, this little climb will help me clear out the junk.”

Viral Influence

Is running really the main causal issue??

CAD: Observational Data

Prevalence of Subclinical Coronary Artery Disease in Masters Endurance Athletes With a Low Atherosclerotic Risk Profile

42(A) vs. 22(C) %

Relationship Between Lifelong Exercise Volume and Coronary Atherosclerosis in Athletes

Prevalence (%)
Elevated CAC Score

Mechanistic Evolution of CAC in Athletes?

Prognostic Significance of CAC in Athletes?

Traditional CRF vs. ↑ CAC

Therapeutic Implications of CAC in Athletes?

My Synthesis of the Controversy

Dose-Response Curves

Aortic Dilation

A. Fib

CAD

Toxic Exposure CMP

Effector
Contemporary Reviews in Cardiovascular Medicine

Exercise Dose in Clinical Practice

Megan M. Wasty, MD; Aaron L. Baggot, MD

Circulation. 2016;133:2297-2313

Assess physical activity habits at each medical visit
Chart habits through the use of a “physical activity self-care”
Categorize patient based on current PA habits
Patient Routinely Meets Current PAR
Discuss potential risks of high dose exercise habits
Consider Exercise Testing on individual basis
Discuss & Document theoretical strategies for maximal safe high dose exercise:
- Treatment of CV Risk Factors
- Use of Annual Exercise Training Periodicity
- Use of Deliberate Athletic Event Preparation
- Use of exercise “Warm-ups” and “Cool downs”
- Importance of Acknowledging Instructive Symptoms

Assess medical risks of low dose exercise habits

Patient Routinely Fails to Meet Current PAR

Discuss & Document

Assess perceived barriers to meeting PA (e.g., time constraints, motivation, fears, lack of understanding)

Assess objective barriers to meeting PA (e.g., medical therapy, orthopaedic issues, medical comorbidities)

Prescribe Exercise Dose (modality, duration, frequency)

Consider changes in medical therapy +/- consultation by musculoskeletal expert

Reassess, Rechart, Recategorize at each subsequent visit

Thank You!

UNISEF Marathon