Atherosclerotic Heart Disease, Conduction Disturbances, and Arrhythmias

Case-Based Risk Stratification for Common Cardiovascular Impairments

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Cliff Hale MD MBA FACP DBIM
Case 1: Jack, a 44 year-old male wants $1mil term

- Paroxysmal atrial fibrillation with a “general ill feeling” for three years; no syncope.
- Exacerbated by exercise, especially with training and competing in Ironman competitions.
- 72”; 206 lbs.; P53; BP 100/60
- Never smoked; no alcohol concerns; no illicit drug use
- Echocardiogram: normal chambers, valves, pressures, walls, and relaxation. Normal EF.
- Negative high level TM.
Jack, continued.

- Event monitor: sinus bradycardia with occasional PVCs with episodic paroxysmal atrial fibrillation with rates around 140 BPM
- No medications prescribed for atrial fibrillation
- One brother with atrial fibrillation at early age
- Saw electrophysiologist and ablation was contemplated but not done
- Has been to urgent care and hospital twice with spontaneous conversion both times and all labs normal

Does this atrial fibrillation influence Jack’s mortality risk?
Lone Atrial Fibrillation

- Atrial fibrillation under age 60 with no cardiopulmonary disease including hypertension. (idiopathic if age > 60)
- Controversial designation; heterogeneous cohort due to subtle subclinical pathology and genetics.
- Generally favorable mortality risk relative to normal
- Primary mortality risk is stroke, beginning at age 55 and increasing over time
- Risk increases if left atrial volume exceeds 32ml/m²
- About a third are familial with an incidence rate ratio of 3.48 with a first or second-degree relative with lone AF.
- Typically there are triggers, sleep, exercise, alcohol
Olmstead county; first episode AF < age 60 with no heart disease or hypertension. Followed up 25.2 ± 9.5 years.

Of 3,623 with AF 76 had lone atrial fibrillation (34 paroxysmal, 37 persistent, and 5 permanent) with mean age of 44.

Of 71 without permanent AF 22 progressed to permanent AF, most often older with QRS abnormalities.

Survival at 15 and 30 years was 92% and 68% compared with 86% and 57% for age and sex-matched controls.
Case 1: Jack’s Risk?

- After 30 years the risk for lone AF is about same as general population.
- Stroke risk correlates with age and the appearance of hypertension, DM, CHF, and ASCHD. No excess mortality for the AF in the absence of these factors.
Case 2 Jill

- 64 year-old woman diagnosed with atrial fibrillation six months ago. It is persistent
- Initially cardioverted with relapse. One attempt at ablation failed after five weeks.
- Hypertensive with borderline blood pressure on medications but no other cardiovascular risk factors.
- ECG voltage increased with lateral lead T-wave flattening
- Echo shows mild LVH, grade 1 diastolic dysfunction, and mild atrial enlargement (LAD 42 mm).
- NT-proBNP 865 during atrial fibrillation
Historically we used “acute” and “chronic” atrial fibrillation. Since 2014 we use these classes:

- **Paroxysmal**: terminated spontaneously or with medication within seven days
- **Persistent**: Fails to self terminate in seven days and requires drugs or cardioversion to restore sinus rhythm
- **Long-standing persistent**: Lasting longer than 12 months
- **Permanent**: patient and physician have stopped trying to convert to sinus rhythm.

Atrial fibrillation typically progresses through these stages over time.
Mechanisms of Mortality (Long-Term Outcomes)

- Embolization, particularly stroke, is the primary cause of death *directly* related to atrial fibrillation.

- *However*, a minority of deaths in those with AF are due to cerebral vascular disease.

- AF is associated with a twofold increase of silent cerebral ischemia (SCI) in those without stroke. This condition leads to cognitive dysfunction and dementia.
Mortality and Rhythm and Rate Control for AF

Follow-up Study of the AFFIRM Study

- Baseline variables were significantly associated with death.
  - Age, CAD, CHF, DM, CVA/TIA, tobacco use, LV dysfunction, mitral regurgitation
- Sinus rhythm correlated with lower mortality
- Those on warfarin had lower mortality risk
- Antiarrhythmic’s benefits were offset by adverse effects
Fifty-three patients with lone atrial fibrillation

NT-proBNP measured before cardioversion and four weeks later

Of the 33 who remained in sinus rhythm, the interquartile NT-proBNP fell from a mean of 759 before cardioversion to a mean of 318 four weeks later.

Of the 19 who relapsed into AF the interquartile NT-ProBNP was 1,124 before cardioversion and 1,256 four weeks later).

In terms of using NT-ProBNP to predict successful cardioversion with lone AF, the area under the ROC curve was 0.80 (between fair and good)
Atrial Fibrillation and the Risk of Death

A Prospective Population Study, The Framingham Heart Study

- 5,209 people
- 296 women and 325 men developed atrial fibrillation over 40 year observation
- Mortality adjusted for Age, HTN, smoking, diabetes, LVH, myocardial infarction, CHF, valvular disease, CVA, and TIA
- The overall risk of death in those with atrial fibrillation was
  - Men: 1.5
  - Women: 1.9

Circulation. 1998;98:946
Atrial Fibrillation and the Risk of Death
A Prospective Study in Women, The Women’s Heath Study

- 34,722 women
- 15.4 years
- 1,011 developed atrial fibrillation

Hazard ratios for new onset atrial fibrillation using multivariate models

- All-cause death 2.14
- Cardiovascular death 4.18
- Non-cardiovascular death 1.19

JAMA. 2011;305(20):2080
Pulmonary Vein Ablation Vs. Drug Therapy for PAF

- 198 patients aged 56 ± 10 years with PAF of 6 +/- 5 years duration who failed antiarrhythmic drug therapy were randomized to
  1. Circumferential pulmonary vein ablation (CPVA)
  2. Maximal doses of another drug (sotalol, flecainide, amiodarone)

- Percentage free of atrial tachyarrhythmias at one year:
  - 93% CPVA (9% had repeat procedure)
  - 35% Antiarrhythmic drug therapy

J Am Coll Cardiol. 2006;48(11):2340-7
Recurrences of Atrial Fibrillation After Ablation

- 445 patients with no atrial fibrillation for one year after successful ablation were followed 66+ months.
- At 60 months 16.3% had a recurrence of atrial fibrillation.
- At 10 years 29.8% had a recurrence of atrial fibrillation.
- Independent hazard risks for recurrence were persistent AF (HR 3.08) and hypertension (HR 1.08).
- If both were present (like Jill) 37.6% recur by 5 years and 68.8% recur at 10 years.

Heart Rhythm 2014 May; 11(5): 771-776
Case 2: Questions About Jill

- What is the likely etiology of atrial fibrillation?
- Is there value in seeking to establish sinus rhythm?
- What were Jill’s odds that the ablation would be successful one year?
- Does another attempt at ablation seem reasonable?
- What is the prognostic significance of her NT Pro-BNP level (865)?
- From what cause is she most likely to die?
Case 3: 33 year-old male applying for $500K

- HTN since age 26 in Air Force. Found to have LVH and received service-connected 70% disability.
- Continued with diastolic pressures of 90-100 despite medication
- A repeat echo in Air Force showed normalization of LVH
- Had one episode pericarditis at age 23
- Continues with resting chest pain during sleep, especially supine. It lasts 10 minutes
Also while in Air Force years ago he had some dizziness while hiking and with intercourse. No syncope
At age 26 had coronary angiogram: 20% LM and 30% LAD
Blood pressure is treated with ACE inhibitor. No beta blocker and no EP study
He claims to have quit smoking after 12 pack years, but cotinine positive (later admits to using e-cigarettes)

VS: Ht. 72”; Wt. 211 lbs.; BMI 28.7; P 68-91; BP 132/90 and 143/93
Exam normal except for BP, cotinine and benzodiazepines
Stress Echocardiogram

- Maximum blood pressure 220/84 and max HR 176
- DP (double product) 38720
- METS 12.7
- Some PVC’s
- Duke ST deviation 1.2 mm
- No wall motion abnormality
- Normal Doppler measures
Case 3: What’s the best course of action at this juncture?

1) He clearly had left main and LAD CAD at age 26, and with persistent BP elevations and nicotine he is unlikely to have improved and probably worsened. Decline.

2) He has a negative high level 12.7 MET stress echo now, despite the evidence for CAD seven years ago. This risk can be accepted.

3) I need more information to decide. If so, what would you like to see? Another angiogram? A CTA? Holter monitor, another urine drug screen?

What is the Risk?
- None
- Mild
- Moderate
- High
Case 4: 76 year-old female for $100K term

- Mild blood glucose elevations with HbA1c 6.1
- BP control on two drugs 150-180/60-90 in APS but normal on our exam
- Lipids TC 240-260 range and LDL’s in 170+ range
- Unwilling to take statins
- During preoperative exam for planned surgery for postmenopausal bleeding (apparent fibroid tumor) the physician examines records from three years earlier:
  - CIMT from a vascular surgeon (to follow)
  - EKG from PCP (to follow)
  - Coronary Calcium score from PCP (to follow)
Carotid intima-media thickness measurement and coronary calcium score

- CIMT right 1.1 mm (>75\textsuperscript{th} percentile for age) and left 0.9 mm (= 75\textsuperscript{th} percentile for age)

- Coronary calcium score 173 (mainly LAD and RCA) or 70\textsuperscript{th} percentile for age
Is there “excess vascular risk for age”?

- If you only had the CIMT, would it change your risk assessment over and above the History/APS/labs?

- If you only had the EKG, is it sufficient? With or without the other two tests?

- If you only had the Coronary Calcium score, would it change your risk assessment over and above the History/APS/labs?

- Are there any other tests you feel that you need to see for risk assessment prior to offering?

- Would you offer prior to the hysterectomy for fibroid uterine tumor? If there were no CV risk assessment tests available to you, would you offer prior to the planned hysterectomy?
Carotid Intima-Media Thickness (CIMT)

Normal Values

- Example: Age 10 - 0.4-0.5 mm
- Example: Age 50 - 0.7-0.8 mm

2010 ACC/AHA guidelines give CIMT a level IIa for asymptomatic adults with intermediate levels of risk?

- Requires highly trained US techs with experience
- Requires offline analysis with dedicated software
- Value in risk stratification and prediction of future CV events is not assured over and above traditional risk models
Meta-analysis of CIMT value in CV Risk Prediction

- 14 population-based cohorts: 45,828 patients
- Mean follow-up 11 years
- 4,007 first-time strokes or MIs.
- Does inclusion of common CIMT enhance Framingham risk assessment?

- > 90% ended up in same risk category with or without the CIMT. The CIMT only reclassified 0.8% correctly
- In intermediate risk patients, 88% classified correctly with or without the CIMT. Only 3.6% reclassified correctly w/CIMT

_JAMA. 2012;308(8):796_
CTA and Coronary Artery Calcium Score (CACS)
Prognosis: CAC Score vs. CT Angiography

- 4,425 outpatients with suspected CAD risk but no events
- Identifying major adverse cardiac events (MACE) such as death, non-fatal MI, and revascularization
- Followed over 1,081 days mean (> 3 years)

Area under ROC curve:
- Using clinical factors only for prediction ➞ 0.71
- Using CACS score + clinical ➞ 0.82
- Using CTA descriptive characteristics ➞ 0.93

363 (8.2%) had MACE
- CACS = 0 ➞ 2.1% CTA no plaque ➞ 0.8%
- CACS = 1-100 ➞ 12.9% CTA nonobstr. ➞ 3.7%
- CACS = 101-400 ➞ 16.3% CTA 1 vessel ➞ 27.6%
- CACS > 400 ➞ 33.8% CTA 2 vessel ➞ 35.5%
  ➞ 57.7%

JACC Imaging. 2012;5(10):990-9
153 patients with MI over one year ago and 52.3% with siblings aged 30-60 and no known CAD.

42.5% sibs enrolled, almost all with low Framingham score (90.7%) and Heartscore (97.7%)

Only one sib with + stress echo

CCTA showed stenosis in 59.1% sibs; 38.6% mild nonobstructive; 20.5% with moderate to severe obstructive
Prospective 5-year mortality study in 1,884 patients with suspected CAD but no modifiable risks (BP, DM, lipids, smoking).

Coronary CT Angiography and major adverse cardiac events (MACE) in five years

- No CAD (0 lesions) 5.6%
- Nonobstructive CAD (1-49% lesions) 13.2%
- Obstructive CAD (50%+ lesions) 36.3%

Hazard ratios for MACE
- Obstructive 6.62
- Nonobstructive 2.20
Zero CAC Score Confers 15-Year 'Warranty' Against CAD

A Most Useful Insurance Medicine Underwriting Tool

- CACS = 0 gives a 15 yr. “warranty” against CAD mortality (<1% in both men and women).
  - 9,715 asymptomatic patients without known CAD
  - 4,864 patients with CACS = 0
  - Followed for 14.6 years
  - CACS 0 4.7% died; CACS >0 14.6% died
  - Independent of Framingham score or NCEP-ATP III score

- Low risk of CACS of 0 persisted 15 years under age 60 and 14 years over age 60.

- A different JACC article cited three series of patients with scores of zero have been studied and all ultimately had a <1% chance of significant coronary stenosis.*

- This study went on to show that The frequency of converting from a score of zero to a meaningful score over four years is 25% and is associated with age, diabetes, and smoking

## Correlating CACS to Other Risk Models

<table>
<thead>
<tr>
<th></th>
<th>Multivariable HR adjusted for Framingham Risk Score (95% CI; ( P ))</th>
<th>Multivariable HR adjusted for NCEP-ATP III (95% CI; ( P ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC 0</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>CAC 1–99</td>
<td>2.08 (1.74–2.48; &lt;0.001)</td>
<td>2.03 (1.70–2.42; &lt;0.001)</td>
</tr>
<tr>
<td>CAC 100–399</td>
<td>3.42 (2.83–4.14; &lt;0.001)</td>
<td>3.32 (2.74–4.02; &lt;0.001)</td>
</tr>
<tr>
<td>CAC 400–999</td>
<td>4.93 (3.98–6.12; &lt;0.001)</td>
<td>4.81 (3.87–5.97; &lt;0.001)</td>
</tr>
<tr>
<td>CAC ≥1000</td>
<td>6.79 (5.29–8.72; &lt;0.001)</td>
<td>6.99 (5.46–8.95; &lt;0.001)</td>
</tr>
</tbody>
</table>

JACC Imaging. 2015;8(8):900-909
Quantification of CAD Calcium Using Ultrafast CT

- Began with Agatston Score*
- Significant difference in scores ($p < 0.0001$) in those without and those with CAD by decade

<table>
<thead>
<tr>
<th>Age</th>
<th>Without CAD</th>
<th>With CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>5</td>
<td>132</td>
</tr>
<tr>
<td>40-49</td>
<td>27</td>
<td>291</td>
</tr>
<tr>
<td>50-59</td>
<td>83</td>
<td>462</td>
</tr>
<tr>
<td>60-69</td>
<td>187</td>
<td>786</td>
</tr>
</tbody>
</table>

*JACC 1990; 15(4): 827
Ages 40-49: CACS of 50 is 71% sensitive and 91% specific for CAD
Ages 50-59: CACS of 50 is 74% sensitive and 70% specific for CAD
Ages 60-69: CACS of 300 is 74% sensitive and 81% specific

Negative predictive value of zero CACS is:
98% ages 40-49
94% ages 50-59
100% ages 60-69
CAC is “reasonable” for risk assessment in asymptomatic adults at Framingham intermediate risk (10-20% ten yr. risk) and “may be reasonable” for low to intermediate risk (6-10 % ten year risk).

CAC is useful as a marker of extent of risk, better than individual lesion severity.

Generally cross sectional plaque area is five times greater than calcification area!
Hazard Ratios Independently Increase with CACS

Especially in Ages <45 and >75

<table>
<thead>
<tr>
<th>CACS</th>
<th>Hazard Ratio &lt; Age 45</th>
<th>Hazard Ratio &gt; Age 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-100</td>
<td>2.3</td>
<td>7.0</td>
</tr>
<tr>
<td>101-400</td>
<td>7.4</td>
<td>9.2</td>
</tr>
<tr>
<td>&gt;400</td>
<td>34.6</td>
<td>16.1</td>
</tr>
</tbody>
</table>

A zero CACS represents a 5.6 year survival of 98-99% regardless of age.
Case 4: 76 year-old female for $100K

- Mild blood glucose elevations with HbA1c 6.1
- BP control on 2 drugs 150-180/60-90 in APS but normal on our exam
- Lipids TC 240-260 range and LDL’s in 170+ range
- Unwilling to take statins

During preoperative exam for planned surgery for postmenopausal bleeding (apparent fibroid tumor) the physician examines records from three years earlier:

- CIMT
- EKG
- Coronary Calcium score

Risk?
- None
- Mild
- Moderate
- High.
Case 5: Woman, 58, with a LBBB on insurance ECG

- Admits to controlled hypertension otherwise “healthy”.
- Mildly overweight
- Lipids high normal. Otherwise no other risk factors
- Do we order an APS or make an offer?
- If chose to go with the information we have:

What is the Risk?

- None
- Mild
- Moderate
- High
Conduction Blocks

Causes

- Congenital
- Infection
- Infarction (possibly silent)
- Myocarditis
- Hypertension
- Cardiomyopathy
Newly Acquired LBBB in Community Population

Framingham Study Population

- Eighteen years of observation; 55 new LBBBs in 5,209 people
- Average age of onset 62
- Most LBBBs occurred with HTN, CAD, and cardiac enlargement
- 48% developed CAD or CHF at or after onset
- Within 10 years 50% died from cardiovascular disease
- LBBB contributed independently to increased risk of cardiovascular death

Annals of Internal Medicine 1979 90;(3):303
Risk of LBBB in a Community Population Over Age 55

- Community cohort, 1,688 participants free of known CHF or MI (SPPARCS) > age 55
- LBBB at enrollment or within 2 years (42 of 1,688)
- Recorded CHF and cardiovascular death at years 4 and 6.
- 70 (4.8%) developed new CHF.
- Odds ratio for CHF with LBBB after adjusting for confounders was 2.85
- Odds ratio for mortality after adjustments
- LBBB in the absence of a clinically detectable heart disease is associated with new-onset CHF and death from cardiovascular diseases.

Cardiology Research 2012:3(6):258-263
Exercise Induced LBBB

- 17,277 exercise tests
- Follow-up 3.7 years
- 70 Exercise induced LBBB
- 25 patients with cardiac events
  - 17 with Exercise Induced LBBB
  - 8 in control group
- 7 deaths
  - 5 with exercise induced LBBB
  - 2 in control group

Among 17,277 patients who underwent exercise stress testing, patients who developed left bundle branch block (LBBB) during exercise testing had a significant reduction in cardiac event-free survival during follow-up.


J Cardiovasc Electrophysiol 2009; 20:781
LBBB and RBBB in Women with and without CVD

- Women’s Health Initiative population, 66,450
- 714 LBBB and 832 RBBB

Women with cardiovascular disease
- Hazard ratio for CV death: 2.92 for LBBB
- Hazard ratio for CV death 1.62 for RBBB
- Only LBBB increased HR for all-cause death: 1.43

Women without cardiovascular disease
- LBBB predicted CV death risk: HR 2.17
- RBBB did not elevate CV death risk
- Neither LBBB, nor RBBB increased all-cause mortality

Am J Cardiol 2012;110:1489-1495
Case 5: Woman, 58, LBBB on insurance ECG

- Admits to controlled hypertension otherwise “healthy”.
- Mildly overweight
- Lipids high normal. Otherwise no other risk factors

What is the Risk?
- None
- Mild
- Moderate
- High
Case 6: 62 year-old man applies for $1 mil

- Full information including APS
- Qualifies for best class but has this ECG . . .

Axis -30 through -90
RS in II, III, and aVF
Q in aVL

Any risk?
Outcomes of LAFB in Those 65 and Older Without Manifest Cardiac Disease

- Cardiovascular Health Study (CHS). A prospective cohort of 1,664 aged ≥ 65, 39 of which had a left anterior hemiblock (-45 through -90) at baseline
- Median follow-up 15.7 years
- Diabetes, HTN, CAD, and myocardial infarction excluded
- ECG findings of LVH, inferior MI, and ventricular pre-excitation excluded
- Adjusted for age, race, gender, BMI, SBP, tobacco, alcohol use, income, and study center
- HR for atrial fibrillation: 1.89; HR for CHF 2.43; HR for death 1.57

JAMA. 2013;309(15)1587
LAFB, Stress Echocardiogram and Cardiac Death
Patients referred for stress echo to rule out CAD

- 1,187 patients with suspected CAD but no MI had a dobutamine stress test.
- 159 had LAHB at baseline ECG
- Five-year follow up
- Excluded those with MI, pacemaker, pathologic Q waves, LBBB, and RBBB.
- Cox adjustment for age, tobacco, history of CHF, DM, and ischemia
- HR for LAFB:
  - 1.8 with normal DES
  - 1.7 with abnormal DSE

Normal Stress Echo
Abnormal Stress echo

Figure 2. Kaplan-Meier survival curves (end point of cardiac death) in the presence and in the absence of left anterior hemiblock (LAHB) in patients with normal dobutamine stress echocardiogram (A) and in patients with abnormal dobutamine stress echocardiogram (B).

Axis -30 through -90
RS in II, III, and aVF
Q in aVL
Reconsider Case 6: 62 year-old man

- Full information including APS
- Qualifies for best class but has this ECG . . .

What is the Risk?
- None
- Mild
- Moderate
- High
Case 7: A 71 year-old woman; $750K

- Type II DM for 4 years; controlled hypertension; BMI 29; borderline lipids
- APS obtained. No other pertinent history
LPFB: A bit uncommon but worth spotting

- Right axis deviation (> +90 degrees; some say +100)
- Small R waves with deep S waves I and aVL
- Small Q waves with tall R waves II, III and aVF
- QRS duration normal or slightly prolonged
- No evidence of right ventricular hypertrophy
- No evidence of any other cause for right axis deviation
LPFB Usually Carries Meaning for Risk

- The posterior division is the least vulnerable segment of the whole system.
- It is thicker than the others.
- Located in the inflow tract of the left ventricle, which is a less turbulent region than the outflow tract,
- It has a double blood supply (from the anterior and posterior descending coronary arteries.)
- If it’s in trouble, the heart is probably in some sort of trouble.
- High correlation with inferior MIs.*

Case 7: A 71 year-old woman; $750K whole life

- Type II DM for 4 years (HbA1c 6.3); controlled hypertension; BMI 29; borderline lipids
- APS obtained. No other pertinent history
- LPHB on routine 12-lead ECG

How much risk beyond her CV risk factors?

- None
- Mild
- Moderate
- High
Case 8: 45 year-old man

- Application is clean as a whistle.
- Labs are good.
2013 Copenhagen City Heart Study

- 18,441 participants free from MI, CHF, and LBBB
- Prospective random sampling from residents of Copenhagen ≥20 years of age (1976-2003)
- 119 M and 47 women with RBBB
- Endpoints were all-cause mortality and cardiovascular outcomes
- Hazard risk for MI 1.67
- Hazard risk for pacemaker insertion: 2.17 (but low numbers)
- Overall RBBB was associated with increased all-cause mortality. HR 1.31 due to cardiovascular mortality. Non-cardiovascular mortality was not increased.

Europ Heart J. 20013;34:138-147
Case 8: 45 year-old man with a RBBB on his exam ECG

- Application is clean as a whistle.
- Labs are good.

What is the Risk?
- None
- Mild
- Moderate
- High
Case 9: 69 year-old woman

- HbA1c 6.2 with no history DM
- BMI 35
- No admitted syncope or pre-syncope

- Lipids okay
- No cardiovascular history

What is the Risk?
- None
- Mild
- Moderate
- High
Mortality Risk Bifascicular Block (Older People)

- 108 patients with bifascicular block (age 74 ± 10 years, 69% male) and 108 age and sex-matched control patients with normal conduction.
- Clinical characteristics were similar initially except for more congestive heart failure in patients with block.
- After omitting patients with moderate or severe congestive heart failure the mortality risk ratio 1.47.
- Compared with controls, the group of patients with bifascicular block had more sudden death and deaths of unknown cause, but a similar number of noncardiac and diagnosed cardiac deaths.
- More patients with bifascicular block developed new second and third degree atrioventricular block or new overt coronary artery disease, but this finding did not support prophylactic pacing in asymptomatic patients.

JACC. 1983;1(5):1207-1212
Case 9: Woman, 69, with bifascicular block

- HbA1 6.2 with no history DM
- BMI 35
- No admitted syncope or pre-syncope
- Lipids okay
- No cardiovascular history

What is the Risk?

- None
- Mild
- Moderate
- High
Case 10: Tom, a 44 year-old male, previously declined

- Angina at age 35. Angiogram: 100% mid LAD and 95% proximal LCx
- 2VCABG with LIMA to LAD and free right radial artery graft to LCx, OM1
- 3 Treadmills since at ages 36, 41, 44 (current)
- Father had percutaneous coronary intervention in his early 50’s
- Applicant has no hypertension or diabetes
- Lipids TC 131, TG 72, HDL 44, LDL 86 on a “statin”.
- Current Nuclear stress test: 12.9 METS, 85% max HR, no ST changes, 59% EF, TID 0.73, and no nuclear deficits
- Carotid US with 20% bilateral soft plaques
1968-75 1,698 patients with mean age 54 received vein grafts and were followed for 20 years.

### Survival

<table>
<thead>
<tr>
<th>Vessels Grafted</th>
<th>Percentage of All</th>
<th>Percent 20-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single vessel</td>
<td>18%</td>
<td>40%</td>
</tr>
<tr>
<td>Double vessel</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>Triple vessel</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Left Main</td>
<td>25%</td>
<td>20%</td>
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</tbody>
</table>

### Graft Patency

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>0-5 years</td>
<td>81% patent</td>
</tr>
<tr>
<td>6-10 years</td>
<td>68% patent</td>
</tr>
<tr>
<td>11-15 years</td>
<td>60% patent</td>
</tr>
<tr>
<td>16-20 years</td>
<td>46% patent</td>
</tr>
</tbody>
</table>

What About Those Grafts?

- Vein grafts fail high and fast—perhaps 25% in the first 12 months
- LIMA has an excellent track record for long term patency
- RIMAs do nearly as well as LIMAs
- Radial artery grafts do nearly as well as LIMAs
- Average vein graft life is 7 years
- Primary graft closure risks are: small diameter of recipient coronary, males, “jump” grafts, and smoking
- Oddly DM is not proven in risk closure for grafts like it is for native disease.
- Graft closure doesn’t routinely cause an MI! (Collaterals?)
- There are underwriting clues in the cath report and the op report (if you have them).

Neth Heart J. 2010 Jan; 18(1): 7–11
Circulation 2004; 110:e40-e46
Case 10: Tom’s Risk?

Tom had advanced disease at age 35, but he is now, at 44, an exemplary cardiovascular risk otherwise. Based upon the information at hand, would you make an offer?
Case 11: Dick, a 49 year-old male

- Out of town on a business trip Dick had chest pain. He walked 1.5 miles to urgent care with no change in the pain.
- Sent to cardiologist’s office for a treadmill, which was stopped for chest pain.
- Sent to ER. Two ECGs 3 hours apart with transient slight ST elevation. Two normal troponins.
- No change of pain with Nitroglycerine. TIMI score = 0 (i.e. felt 5% risk within the next 14 days)
- No medical history otherwise, but his father had a triple bypass at age 80
- Released from ER and told “get a TM with his own doctor in home state in two days”. Does not comply.

Case continued . . .
Case 11, Dick, continued

- Offer postponed until TM produced
- Gets an exercise ECG without imaging
- Has 13 METS with no chest pain but ST changes are documented (next slide).
- Referred then for exercise perfusion scan and again goes 13 METS with no chest pain, and this time no ST changes. Perfusion is normal.
- Continues to have episodes of CP despite proton pump inhibitor
- Reapplies for life insurance.
Yes, over and above ST segment analysis, the measure of heart function as a whole as measured by METS is a very powerful predictor of mortality.

N ENGL J MED 2002; 346:793–801
Do METS Matter?

- Prospective study of 3100 females (pink) and 10,000 males (blue) and age-adj.
  all cause mortality per 10,000 person-years

- Aerobic Center
  Longitudinal Study in healthy men and women

Cleveland Clinic J Med June 2008 Vol.75.6, 424-430 also JAMA 1989: 262:2395-2401
Dick’s Mortality Risk?

What is the Risk?
- None
- Mild
- Moderate
- High
Case 12: Harry, a 61 year-old male

- At age 56 Harry had angina pectoris and abnormal TM
- Angiogram: 100% Diag 1; 50% mid LAD; 100% mid LCx; and mild RCA disease
- Attempted PTCA of 100% LCx not successful, so he was prescribed medical treatment and sent home
- Two years later at age 58 he had more angina and more medical treatment
- Then at age 60 he had a cardiac perfusion scan with pharmacologic “stress” (next slide) with a comment: “stable AP”
- A1C 6.0; Trig. elevations without treatment; says he quit smoking just before application but cotinine positive
REPORT AND INTERPRETATION

PHARMACOLOGIC STRESS PROTOCOL IV LEXISCAN

Resting Electrocardiogram: RSII, PRWT V1-V3, NSST T wave abnormalities

Pharmacologic stress:
A total of 0.4mg IV Lexiscan was infused. The baseline heart was 90; the heart rate at maximal vasodilation was 133. The baseline blood pressure was 142/80, the blood pressure at maximal vasodilation was 120/76.

ECG changes with Lexiscan infusion: Indeterminate
Arrhythmias with Lexiscan infusion: None
Symptoms with Lexiscan infusion: Burning in chest

MYOCARDIAL PERFUSION IMAGING:
During one-day protocol, patient was injected with 9.52 millicuries of Myoview for rest and 27.2 millicuries for Stress intravenously. Sixty minutes later resting tomographic images were obtained, followed by stress tomographic images using SPECT gamma camera.

Results: A significant infero-lateral perfusion defect was noted with moderate but not complete reperfusion.
Stress gated SPECT images revealed normal contractility without wall motion abnormalities.

The calculated EF was: 53%

Conclusions:
1. Indeterminate Lexiscan stress study without definitive EKG changes but with chest burning.
2. Myocardial perfusion SPECT images consistent with a mixed anterior inferolateral wall MI with moderate peri-infarction ischemia.
3. Stress gated SPECT images revealed gravely normal contractility.
### Myocardial Perfusion Imaging
with Exercise or Pharmacologic Stress

#### Indications for Pharmacologic Stress
- Unable to exercise
- Aortic stenosis
- LBBB
- Pacemaker
- Recent MI
- Severe HTN

#### Imaging agents
- Thallium-201 ($\text{K}^+$)
- Tc-99m sestamibi ($\text{Ca}^{++}$) (e.g., Cardiolite)
- Tc tetrofosmin (e.g., Myoview)
- Tc teboroxime (e.g., Cardiotec)

#### Pharmacologic Stress
- Vasodilators ("stealers")
  - Adenosine and analogs
  - Dipyridamole (Persantine)
- Inotropic/Chronotropic
  - Dobutamine
Meta-analysis of 24 studies and 14,918 patients comparing exercise and chemical nuclear stress tests and subsequent CV event rates

- ROC curve showed no difference in discrimination
- Chemical stress-tested patients have more poor prognostic factors of which the most important was worse exercise capacity

Event rates with normal test results: Pharm. Vs. Exercise
- Pharm. 1.78%
- Exercise 0.65%

Event rates with Abnormal test results: Pharm. Vs. Exercise
- Pharm. 9.98%
- Exercise 4.3%

A Word about Transient Ischemic Dilation Ratio (TID)

**Table 1.** Distribution of the Study Population 1 by Quartiles of TID Ratio

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of Patients</th>
<th>Mean ± SD of TID Ratio</th>
<th>Range of TID Ratio (Minimum-Maximum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st quartile</td>
<td>361</td>
<td>0.93 ± 0.06</td>
<td>0.80-0.99</td>
</tr>
<tr>
<td>2nd quartile</td>
<td>400</td>
<td>1.02 ± 0.02</td>
<td>1.00-1.07</td>
</tr>
<tr>
<td>3rd quartile</td>
<td>409</td>
<td>1.13 ± 0.04</td>
<td>1.08-1.20</td>
</tr>
<tr>
<td>4th quartile</td>
<td>390</td>
<td>1.35 ± 0.14*</td>
<td>1.21-1.79</td>
</tr>
</tbody>
</table>

*p = 0.001 across the groups. TID = transient ischemic dilation.

**JACC 2003; 42:1818-1825**

TID ratios > 1.22 with exercise or > 1.36 with pharmacologic stress suggest extensive CAD, even in presence of normal MPI.

(71% sensitivity and 95% specificity)


**Figure 1.** Annual rates of first future cardiac events (total events) and hard events in patients with normal myocardial perfusion single photon emission computed tomography distributed by quartiles of transient ischemic dilation (TID) ratio. *p < 0.001 across the groups; †p = 0.006 for highest quartile versus all others. Open bars = total events; solid bars = hard events.
Selective Risk Adjustments after Interventions from AHA Statistics from 2010 Survey

Metabolic Syndrome

- Have increased DM risk 2.1-3.6 x
- Have increased risk CAD 1.5-2 x
- Have increased CAD mortality 1.2-1.6 x
- Type 1 vs 2 DM pts.
- Type 2 have a 95% lifetime chance of some vascular disease
- Type 1 have 35% chance of MI by age 55

Smokers

- 1.3 billion smokers in the world
- Males who smoke have 6 x chance of MI of nonsmokers
- Females who smoke have 3 x chance of MI of nonsmokers
- Risk of mortality increases 15 x if continue to smoke after MI
Case 12: Harry’s Mortality Risk?

- At age 56 Harry had angina pectoris and abnormal TM
- Angiogram: 100% Diagonal 1; 50% mid LAD; 100% mid LCx and mild RCA disease
- Attempted PTCA of 100% LCx not successful. Prescribed medical Rx and sent home
- Two years later, age 58, more angina and more medical Rx
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- A1C 6.0; Trig. elevations without treatment; says quit smoking just before application but cotinine positive

What is the Risk?
- None
- Mild
- Moderate
- High
Case 13: A 48 year-old female CEO

$5 million term application in competition

- History PVCs and NSVT with normal cardiac evaluation
- Doctor told her not to worry about it; she could take meds or have an ablation if it bothered her.
- PVCs on insurance exam ECG (next slide)
- High stress job
- No other admitted health issues
- Exam BP 138/90 62” and 135#
Case 13: A 48 year-old female CEO

5 in ten seconds = 30 per minute = 1800 per hour
Contrary to what many of us were taught, prognosis correlates poorly with complexity of PVCs but highly to the presence of structural heart disease and left ventricular dysfunction.

Evaluation should be aimed at documenting ectopy and assessing for structural heart damage with:

- 24 hour Holter Monitor or equivalent
- Echocardiography for structure and function
- Exercise ECG to evaluate ectopy with exercise

It’s not always possible for us to get full evaluation, right?
Ventricular Ectopy in Apparently Healthy Subjects

- Cohort: 70 apparently healthy subjects with frequent or complex ventricular ectopy.
- Ectopy at least 60 per hour; 78 – 1,994; group mean 566.
- Mean age 46 ± 13.3; Mean follow-up 6.5 years
- Evaluated with Holter, vectorcardiography, maximal stress ECG, and echocardiography; and subjects with positive results were excluded.
- Thirty-one of the seventy allowed coronary angiography.
  - 18 had entirely normal arteries
  - 7 < 50% lesions (given beta blockers)
  - 6 > 50% lesions (given beta blockers)

Expected deaths (Monson's US white and non-white death rate table) for 448 person-years was 7.4, whereas only 2 study subjects died. Those with angiograms were included!

2 PVCs per 10-sec strip = 720/hr.
5 PVC per 10-sec strip = 1,800/hr

Figure 1. Distribution of Frequencies of Mean Ventricular Ectopic Beats in 72 Subjects.

Figure 2. Life-Table Survival Experience of the Study Cohort as Compared with That of Patients with Normal Coronary Arteries or Mild Coronary Artery Disease (CAD), Moderate Coronary Artery Disease, and Unrecognized Myocardial Infarction (MI).

The data in the present study were analyzed by the Kaplan–Meier method because of the small sample size, and the results are independent of the follow-up time. The data of Proudfoot et al. and Kannel et al. permitted only a life-table analysis.
2,425 men and 3,064 women (age in early fifties) with no clinical evidence for CAD.
302 men and 242 women had clinically apparent CAD
Followed for four to six years.
For men with frequent or complex ventricular ectopy and without apparent CAD, the age and covariate-adjusted risk for all cause death was 2.3. It was 2.12 for MI or death from MI.
There were statistically insignificant increases in risk for men with CAD and women with and without CAD. It is likely that the ventricular ectopy in men is a marker for subclinical CAD.
If we do not have a cardiac workup . . .

- Of 15,070 community-based subjects ages 45-64, 940 had PVCs and were followed up > 10 years.
- Cardiovascular mortality 3X higher in those with PVCs vs. those without.
- After controlling for CV risk factors there was a 2X increase in cardiovascular death with PVCs.
- Risk was increased in those with and without baseline coronary heart disease, but structural heart disease was not excluded.
- No gender distinction.

Figure 2. Age-adjusted survival function estimates for CHD events and/or death among participants with and without baseline VPCs.
PVCs: Sudden and Total Cardiac Death

Meta-analysis 2013 (Structural Heart Disease not Excluded)

- Eleven studies included with 106,195 participants from general populations
- ≥ 1 PVC during an ECG or ≥ 30 over one-hour recording
- Overall adjusted relative risk for sudden cardiac death comparing those with PVCs to those without was 2.64
- For total cardiac death the relative risk was 2.07
- Most studies tried to exclude cardiovascular disease, but participants were not tested for structural heart disease.

Am J Cardiol. 2013;112(8):1263-1270
Case 13: Underwriter requests cardiac records, and

- Echocardiogram was normal except borderline LVH
- Six months ago exercise ECG to 12.0 METs with mild hypertensive response to exercise
- 10% unifocal PVCs in resting phase with one 3-beat run NSVT. Ectopy resolved midway through Stage I.
- Pre-exam ectopy reappeared four minutes into recovery period.
- No family history of syncope of sudden death

What about the NSVT?
A Word About Outflow Tract Idiopathic Ectopy and NSVT

- By definition assumes a full cardiovascular evaluation otherwise normal and no evidence for genetic channelopathies (e.g., Brugada, LQTS)
- Repetitive uniform PVCs
- Repetitive monomorphic NSVT (resolves with exercise)
- Adrenergically mediated (respond to verapamil or adenosine)
- 70% - 80% originate RVOT (LBBB pattern)
- 20% - 30% originate LVOT (RBBB pattern)
- Drugs or ablation work well
Underwriting NSVT in Apparently Healthy People

**Applicant under age 40**

Consider:
- Idiopathic VT
- Cardiomyopathy
- Valvular disease
- Early CAD
- Genetic channelopathies

**Applicant over age 40**

Consider:
- CAD
- Idiopathic VT
- Cardiomyopathy
- Hypertension
- Valvular disease
- Genetic channelopathies

- If a cardiac condition is present, conservatively rate for cause
- If no cardiac condition is present, exercise testing is needed
  - Exercise testing causes NSVT, risk is elevated
  - Exercise testing suppresses ectopy, risk is minimal
Regarding NSVT

- NSVT in the presence of structural heart disease, ischemic heart disease, or other cardiac abnormalities may be associated with increased mortality.
- In the documented absence of heart disease, spontaneous NSVT does not appear to carry any adverse prognostic significance.
- Exercise induced or post-exercise NSVT may predict the future development of CAD and increased cardiac mortality. (HR 2.5 for CV death 23 years out*)

Eur Heart J. 2004;25:1093-1099

* Circ.1977;56(6):985-989
Case 13: A 48 year-old female CEO

- History PVCs and NSVT with normal cardiac evaluation
- Doctor told her not to worry about it; she could take meds or have an ablation if it bothered her.
- PVCs on insurance exam ECG (next slide)
- High stress job
- No other admitted health issues
- Exam BP 138/90 62” and 135#

What is the Risk?

- None
- Mild
- Moderate
- High
Case 14: 50 year-old man with exercise-induced PVCs

- 55 year-old mildly overweight man with occasional palpitations and “chest awareness” is scheduled for an exercise ECG.
- Hypertension and hyperlipidemia controlled with meds. Build upper end of normal. Father had an MI at age 63.
- Resting ECG is normal except for a single PVC on a ten-second strip.
- Exercised one minute into Stage 4 (protocol requirements met.) Peak systolic blood pressure was 190 and peak HR was 160. No chest pain. ECG tracing showed no ST deviations, but revealed monomorphic PVCs accelerating through exercise and resolving in the recovery period.

Physician stated exercise ECG was negative, and offered to treat palpitations with a beta blocker if the patient wished.

Is there additional risk?
Exercise-Induced Ventricular Ectopy: Long-term Outcomes

- 6,101 asymptomatic French men aged 42-53, free of detectable cardiovascular disease (ECG, labs, and BP, but no assessment for ventricular function). Followed for 23 years.
- Frequent ventricular ectopy defined as *one run of two or more PVCs or 10% PVCs on 30-sec ECG*.
- Before Exercise:
  - 48 had frequent PVCs before exercise
  - 121 had infrequent PVCs before exercise
  - 5,932 had no PVCs before exercise
- *There were no significant differences in all-cause, non-cardiovascular, and cardiovascular death for ventricular ectopy before exercise.*

NEJM. 2000;343:826-33
During exercise:
- 138 had frequent PVCs
- 520 had infrequent PVCs
- 5,443 free of PVCs

During Recovery:
- 174 with frequent PVCs
- 448 with infrequent PVCs
- 5,497 had no PVCs

Mortality with PVCs During Exercise and in Recovery

Long-Term All-Cause and Cardiovascular Mortality with PVCs During Exercise

During Exercise:
- Frequent PVCs: 41.3%
- Infrequent PVCs: 27.9%
- No PVCs: 26.3%

Long-Term All-Cause and Cardiovascular Mortality with PVCs During Recovery

During Recovery:
- Frequent PVCs: 35.0%
- Infrequent PVCs: 27.7%
- No PVCs: 26.5%

NEJM. 2000;343:826-33
3% of 271 subjects with a positive exercise test had frequent PVCs.

6% of subjects with frequent PVCs had a positive stress test.

Mortality for frequent PVCs is similar to that for ST depression.

What is the mortality risk for this man?

NEJM. 2000;343:826-33
Communication regarding slide deck, studies, etc.

- Jfino@allstate.com
- Cliff.hale.tx5a@statefarm.com
Long-Term Mortality Risk in Individuals with Atrial or Ventricular Premature Complexes

- 7,504 community population without known CVD (NHANES)
- 89 had any PACs on 12-lead ECG
- 110 had any PVCs on 12-lead ECG
- Outcomes: all-cause mortality, cardiovascular disease (CVD) mortality, and ischemic heart disease (IHD) mortality
- 18 years follow-up
- PACs HR 1.41 for all cause death
- HR 1.78 for CVD death
- HR 2.4 for IHD death
- No significant associations for PVC with all-cause, CVD, or IHD death

Am J Cardiol. 2014;114(1):59
Frequent PACs Predict New Occurrence of Atrial Fibrillation and Adverse Cardiovascular Events.

- 428 without atrial fibrillation or structural heart disease had 24-hour monitoring.
- 107 had >100 PACs/day (top quartile)
- 29% developed atrial fibrillation vs. 9% in those with < 100 PACs/day.
- Cox regression analysis revealed HR for AF was 3.2 for those with >100 PACs/day.
- HR for composite endpoints of ischemic stroke, CHF, and death, was 1.95 for those with >100 PAC/day.