Update in the Literature 2012

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Chief, Hospital Medicine Section
Associate Chief, Medical Service
Denver VA Medical Center

Associate Professor of Medicine
University of Colorado
Update in the Literature 2012

- Case based format
- Multiple articles per case
- For each:
  - Research question asked
  - Design
  - Results/Conclusions/Comments
- Summary of practice changes
Objectives

- Take away a bottom line message from each study reviewed today
- Reflect on whether your practice might be altered by this information
Disclosures

- Oakstone publishing
- American Board of Internal Medicine
- No PEDs…
Acknowledgements

- Jeffrey J. Glasheen, MD
  University of Colorado School of Medicine
- Joseph Li, MD
  Harvard Medical School
- Anneliese Schleyer, MD
  University of Washington, Seattle
- Brad Sharpe, MD
  UCSF School of Medicine
Case

A 66 y/o woman sees you for routine follow-up of medical problems. She notes a sense of an “irregular” heartbeat.

PMHx includes PVD/claudication. Takes lisinopril and aspirin.

Normotensive, HR 100 and irregular, no features of CHF.

EKG shows atrial fibrillation.
Which of the following are true?

A. Her CHADS\textsubscript{2} score is 0 and you should recommend aspirin for stroke prevention.
B. Her CHA\textsubscript{2}DS\textsubscript{2}-VASc score is 3 and you should recommend anticoagulation.
C. If you recommend dabigatran, her risk of acute coronary syndrome will also decline.
D. I hope there aren’t more questions on “new oral anticoagulants…”
Impact of the CHA\textsubscript{2}DS\textsubscript{2}-VASc Score on Anticoagulation Recommendations for Atrial Fibrillation

Pamela K. Mason, MD, Douglas E. Lake, PhD, John P. DiMarco, MD, PhD, John D. Ferguson, MBChB, MD, J. Michael Mangrum, MD, Kenneth Bilchick, MD, Liza P. Moorman, RN, ACNP-BC, J. Randall Moorman, MD

University of Virginia Health System, Charlottesville.

Question: How does the adoption of a newer stroke risk assessment tool (CHA$_2$DS$_2$-VASc) affect anticoagulation recommendations?

Design: Prospective cohort

Patients: 1664 patients

1° Outcome: CHADS$_2$ versus CHA$_2$DS$_2$-VASc scores and rates of anticoagulation recommendation
CHADS₂

- CHF
- HTN
- Age ≥ 75
- DM
- Stroke (2 points)
- Anticoagulate for 2, “consider for 1”…

*JAMA* 2001;285:2864-2870.
CHA$_2$DS$_2$-VASc

- Age $\geq$ 75 (2 points)
- Vascular Disease
- Age $\geq$ 65-74 (1 point)
- Sex Category F
- Anticoagulate for 2

*Chest* 2010;285:2864-2870.
## Adjusted risk of stroke, %/year

<table>
<thead>
<tr>
<th>Score</th>
<th>CHADS$_2$</th>
<th>CHA$_2$DS$_2$-VASc</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
<td>0</td>
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<tr>
<td>1</td>
<td>2.8</td>
<td>1.3</td>
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<tr>
<td>2</td>
<td>4.0</td>
<td>2.2</td>
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<tr>
<td>3</td>
<td>5.9</td>
<td>3.2</td>
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<td>4</td>
<td>8.5</td>
<td>4.0</td>
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<tr>
<td>5</td>
<td>12.5</td>
<td>6.7</td>
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<tr>
<td>6</td>
<td>18.2</td>
<td>9.8</td>
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<td>…</td>
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</tr>
<tr>
<td>9</td>
<td>…</td>
<td>15.2</td>
</tr>
</tbody>
</table>
Results: CHA₂DS₂-VASc

- Average score increased from 1.1 to 1.8
- Recommendation for anticoagulation increased from 33% to 53%
- Elderly women especially
- CHA₂DS₂-VASc better identifies low risk

Case

A 66 y/o woman sees you for routine follow-up of medical problems. She notes a sense of an “irregular” heartbeat.

PMHx includes PVD/c Claudication. Takes lisinopril and aspirin.

Normotensive, HR 100 and irregular, no features of CHF.

EKG shows atrial fibrillation.

\[
\text{CHADS}_2 = 0 \\
\text{CHA}_2\text{DS}_2\text{-VASc} = 3
\]
Dabigatran is associated with an increased risk for ACS according to a meta-analysis of the randomized controlled non-inferiority trials which led to its approval, NNH about 250.

Ann Intern Med 2012;157:66-68
Dabigatran was misused in the majority of prescriptions in the US – only 36% were for atrial fibrillation stroke prevention.

Within 12 weeks of marketing approval in 2010, it was responsible for more serious adverse events than 97.8% of other medications, including fatalities associated with misuse.
FDA Adverse Events 2011:

Warfarin: 1106 adverse events (72 deaths)
Dabigatran: 3781 adverse events (542 deaths)
Which of the following are true?

A. Her CHADS\textsubscript{2} score is 0 and you should recommend aspirin for stroke prevention.

B. Her CHA\textsubscript{2}DS\textsubscript{2}-VASc score is 3 and you should recommend anticoagulation.

C. If you recommend dabigatran, her risk of acute coronary syndrome will also decline.

D. I hope there aren’t more questions on “new oral anticoagulants…”
Case

A 62 y/o man sees you for advice about his anticoagulation.

Unprovoked DVT 1.5 years ago, on warfarin in the interim, asx. Getting tired of the blood draws and wants to know if it can be safely stopped.

What do you recommend?
You recommend:

A. Warfarin cessation.
B. Continue warfarin indefinitely.
C. Decrease dose of warfarin goal INR 1.5.
D. Replace warfarin with aspirin
Aspirin for Preventing the Recurrence of Venous Thromboembolism

Cecilia Becattini, M.D., Ph.D., Giancarlo Agnelli, M.D., Alessandro Schenone, M.D., Sabine Eichinger, M.D., Eugenio Bucherini, M.D., Mauro Silingardi, M.D., Marina Bianchi, M.D., Marco Moia, M.D., Walter Ageno, M.D., Maria Rita Vandelli, M.D., Elvira Grandone, M.D., and Paolo Prandoni, M.D., Ph.D., for the WAFASA Investigators

Question: What is the clinical benefit of aspirin after completion of anticoagulation therapy for first unprovoked venous thromboembolism?

Design: Multicenter randomized trial

Patients: 403 patients followed for 2 years

1° Outcome: Recurrent VTE, major bleeding, death

## WARFASA Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>ASA</th>
<th>NNT</th>
<th>p</th>
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<tbody>
<tr>
<td>Recurrent VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bleeding</td>
<td></td>
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<tbody>
<tr>
<td>Recurrent VTE</td>
<td>21.8%</td>
<td>13.7%</td>
<td>12</td>
<td>0.02</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
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<td>12</td>
<td>0.02</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2.0%</td>
<td>1.9%</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*WARFASA Results*  

Low-Dose Aspirin for Preventing Recurrent Venous Thromboembolism

Question: What is the clinical benefit of aspirin after completion of anticoagulation therapy for first unprovoked venous thromboembolism?

Design: Multicenter randomized trial

Patients: 822 patients followed for 3 years

1° Outcome: Recurrent VTE, major bleeding, MI, stroke, death

## ASPIRE + WARFASA Results

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<th>NNT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>19.1%</td>
<td>13.8%</td>
<td>19</td>
<td>0.007</td>
</tr>
<tr>
<td>Major Vascular</td>
<td>22.4%</td>
<td>15.9%</td>
<td>14</td>
<td>0.002</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.9%</td>
<td>2.9%</td>
<td>NS</td>
<td>NS</td>
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</table>

You recommend:

A. Warfarin cessation.
B. Continue warfarin indefinitely.
C. Decrease dose of warfarin goal INR 1.5.
D. Replace warfarin with aspirin
Obesity Trends* Among U.S. Adults
BRFSS, 1990, 2000, 2010
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)

1990

2000

2010

No Data  <10%  10%-14%  15%-19%  20%-24%  25%-29%  ≥30%

Source: Behavioral Risk Factor Surveillance System, CDC.
Updates in Prevention 2012

- Lifetime CV risk
- Ideal Health Metrics
- Think about bariatric surgery
Lifetime Risks of Cardiovascular Disease

Jarett D. Berry, M.D., Alan Dyer, Ph.D., Xuan Cai, M.S., Daniel B. Garside, B.S., Hongyan Ning, M.D., Avis Thomas, M.S., Philip Greenland, M.D., Linda Van Horn, R.D., Ph.D., Russell P. Tracy, Ph.D., and Donald M. Lloyd-Jones, M.D.
CV Lifetime Risk Pooling Project

Question: What are the lifetime risks of cardiovascular disease across a broad age spectrum?

Design: Patient-level meta-analysis of 18 cohort studies: age, blood pressure, cholesterol level, smoking status, and diabetes status

Patients: 257,384 women, men, black, white

1° Outcome: Remaining lifetime risk of cardiovascular events

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Risk Factors Optimal</th>
<th>≥1 Risk Factor Not Optimal</th>
<th>≥1 Elevated Risk Factor</th>
<th>1 Major Risk Factor</th>
<th>≥2 Major Risk Factors</th>
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</thead>
<tbody>
<tr>
<td><strong>Risk at 45 yr of age</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fatal coronary heart disease or nonfatal myocardial infarction</td>
<td>1.6 (0.4–3.3)</td>
<td>9.3 (3.0–15.6)</td>
<td>9.3 (5.0–13.7)</td>
<td>12.7 (10.3–15.0)</td>
<td>21.5 (17.5–25.5)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>8.3 (3.8–12.8)</td>
<td>8.9 (6.5–11.3)</td>
<td>9.1 (7.5–10.9)</td>
<td>9.1 (7.9–15.9)</td>
<td>11.5 (9.5–13.5)</td>
</tr>
<tr>
<td>Death from cardiovascular disease</td>
<td>4.8 (0.8–8.7)</td>
<td>4.9 (3.1–6.7)</td>
<td>6.9 (5.4–8.8)</td>
<td>11.2 (9.9–12.5)</td>
<td>21.9 (19.4–24.5)</td>
</tr>
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<td>Total events related to atherosclerotic cardiovascular disease</td>
<td>4.1 (0.8–8.2)</td>
<td>12.2 (4.6–19.7)</td>
<td>15.6 (10.3–20.9)</td>
<td>20.2 (17.2–23.2)</td>
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<tr>
<td><strong>Risk at 55 yr of age</strong></td>
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<tr>
<td>Fatal coronary heart disease or nonfatal myocardial infarction</td>
<td>0</td>
<td>6.5 (0.7–12.2)</td>
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<td>18.3 (15.9–20.8)</td>
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<td>Fatal or nonfatal stroke</td>
<td>5.3 (0–11.3)</td>
<td>8.3 (5.3–11.4)</td>
<td>6.0 (4.8–7.2)</td>
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<td>6.4 (0–13.3)</td>
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<td><strong>Risk at 65 yr of age</strong></td>
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<td>Fatal coronary heart disease or nonfatal myocardial infarction</td>
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<td>17.6 (11.3–23.9)</td>
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<td>12.4 (2.8–22.0)</td>
<td>25.0 (15.4–34.5)</td>
<td>29.3 (23.8–34.7)</td>
<td>31.9 (28.8–34.9)</td>
<td>38.7 (35.3–42.1)</td>
</tr>
<tr>
<td><strong>Risk at 75 yr of age</strong></td>
<td></td>
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## CV Lifetime Risk Pooling Project

### Women

<table>
<thead>
<tr>
<th>Total CV events, age 45</th>
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<th>≥ 2 major</th>
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<tbody>
<tr>
<td>Total CV events, age 55</td>
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<td>12.4%</td>
<td>29.3%</td>
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</tr>
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</table>

Consistent across birth cohorts, and among blacks and whites
CV Lifetime Risk Pooling Project

- **Lowest risk** --
  - 45 y/o woman with optimal RF
  - 1.6% lifetime risk of MI or cardiac death!

- **Highest risk** –
  - 65 y/o man with 2+ RF
  - 49.5% lifetime risk of any CV

CV Lifetime Risk Pooling Project

Question: What are the lifetime risks of cardiovascular disease across a broad age spectrum?

Design: Patient-level meta-analysis of 18 cohort studies: age, blood pressure, cholesterol level, smoking status, and diabetes status

Patients: 257,384 women, men, black, white

1° Outcome: Remaining lifetime risk of cardiovascular events

Conclusion: Marked and consistent differences in risk factor burden → markedly different risk

“...Efforts to lower the burden of cardiovascular disease will require prevention of the development of risk factors (primordial prevention) rather than the sole reliance on the treatment of existing risk factors (primary prevention).”
Epidemiology and Prevention

Ideal Cardiovascular Health Predicts Lower Risks of Myocardial Infarction, Stroke, and Vascular Death Across Whites, Blacks, and Hispanics
The Northern Manhattan Study

Chuanhui Dong, PhD; Tatjana Rundek, MD, PhD; Clinton B. Wright, MD, MS; Zane Anwar; Mitchell S.V. Elkind, MD, MS; Ralph L. Sacco, MD, MS

Circulation 2012;125:2975-2984
Question: What is the relationship between “Ideal CV Health Metrics” and CV risk?...

Design: Prospective observational cohort median 11 yrs

Patients: 2981 patients without baseline MI

1° Outcome: Risk of cardiovascular disease – MI, stroke, and vascular death

*Circulation* 2012;125:2975-2984
AHA Ideal Health BEHAVIORS

1. Smoking: never or quit > 1 year
2. BMI < 25
3. Moderate activity 150+ min/wk; vigorous 75+ min/wk
4. 4-5 healthy diet components:
   1. ≥ 4.5 cups fruit/vegetables per day
   2. ≥ 2 servings (3.5 oz) fish per week
   3. ≥ 3 servings (1 oz) whole grains per day
   4. ≤ 1500 mg Na+ per day
   5. ≤ 450 kcal sugar sweetened beverage per week
5. [and normal BP, total cholesterol, and fasting glucose]

_Circulation_ 2010;121:586-613
Northern Manhattan: Results 3D!
Northern Manhattan

Question: What is the relationship between “Ideal CV Health Metrics” and CV risk?

Design: Prospective observational cohort median 11 yrs

Patients: 2981 patients without baseline MI

1° Outcome: Risk of cardiovascular disease – MI, stroke, and vascular death

Conclusion: Strong and consistent relationship between ideal CV health metrics and individual cardiovascular risk, clear implications for individual risk estimates and public health emphasis.
Bariatric Surgery and Prevention of Type 2 Diabetes in Swedish Obese Subjects

Lena M.S. Carlsson, M.D., Ph.D., Markku Peltonen, Ph.D., Sofie Ahlin, M.D., Åsa Arveden, M.D., Claude Bouchard, Ph.D., Björn Carlsson, M.D., Ph.D., Peter Jacobson, M.D., Ph.D., Hans Lönnroth, M.D., Ph.D., Cristina Maglio, M.D., Ingmar Näslund, M.D., Ph.D., Carlo Pirazzi, M.D., Stefano Romeo, M.D., Ph.D., Kajsa Sjöholm, Ph.D., Elisabeth Sjöström, M.D., Hans Wedel, Ph.D., Per-Arne Svensson, Ph.D., and Lars Sjöström, M.D., Ph.D.
Question: To determine whether surgery can prevent diabetes

Design: Prospective case control

Patients: 3429 obese subjects, 1658 surgery, 1771 not

1° Outcome: Rate of incident Type II diabetes

Results: Usual care – 22.1% diabetic
         Surgery – 6.6% diabetic
         About 70% relative risk reduction, NNT 7
         p < 0.001

Conclusion: Bariatric surgery is markedly more effective than usual care in preventing DM
Primum non nocere...
Despite heterogeneity among trials and patients, probiotics were found to be safe and effective for preventing antibiotic associated diarrhea (NNT 13) and *C Diff* in particular.

*Arch Intern Med* 2012;172:922-928
Probiotics for the Prevention of *Clostridium difficile*-Associated Diarrhea

A Systematic Review and Meta-analysis

Bradley C. Johnston, PhD; Stephanie S.Y. Ma, MD; Joshua Z. Goldenberg, BSc; Kristian Thorlund, PhD; Per O. Vandvik, MD, PhD; Mark Loeb, MD; and Gordon H. Guyatt, MD

**Conclusion:** Moderate-quality evidence suggests that probiotic prophylaxis results in a large reduction in CDAD without an increase in clinically important adverse events.
consultations
Elevated post-op troponin levels were detected in over 10%, identifying patients with between a 1 in 25 and a 1 in 6 risk of 30 day mortality.
Perioperative statins reduce the risk of post-op atrial fibrillation (NNT 6), post-op MI (NNT 23), and reduced LOS by 0.3 days – but had no effect on ICU LOS. We should do it (mostly vascular surgery), and probably high dose.

Arch Surg 2012;147:181-189
Practice Summary

Things to Do:

1) Use CHA$_2$DS$_2$-VASc to assess stroke risk in a fib to guide risk reduction strategies

2) Venture into new oral anticoagulants very cautiously…

3) Prescribe aspirin for secondary VTE prevention after initial course of anticoagulation

4) Communicate lifetime CV risk
Practice Summary

Things to Do:

5) Encourage AHA “ideal” health behaviors

6) Prescribe probiotics to limit the risk of antibiotic associated diarrhea and C diff in particular
Practice Summary

Things to Consider:

1) Referral for bariatric surgery among seriously obese patients for prevention of Type II DM
2) Post-op troponin if it will alter management
3) Prescribe perioperative high potency statin therapy around vascular surgery
Practice Summary

Things to Stop:

1) Use of dabigatran outside FDA indication of stroke risk reduction in atrial fibrillation
Thank you!

Melver.Anderson@va.gov