The Risky Business of Risk Factor modification
It’s Just a Numbers Game And So Much More

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Objectives

Be able to explain what is meant by the various cardiovascular/fracture endpoints which drug therapy is aimed at improving.

Be able to select and use an appropriate risk estimation tool to help a patient understand their level of risk and chance of benefit.

Be able to conceptualize how this information could be applied to pharmacotherapeutic decision-making.
Risk ...

Risk markers - associated with a bad outcome
Risk factors - modifiable?
Risky behaviors - smoking, nutrition, activity
Risk of disease - CVD, MI, strokes, fractures
Risk of treatment - harms, costs
Risk of over diagnosis - inconvenience, labelling, worry
Risk Factors versus Clinical Endpoints

“a risk factor/marker is a variable associated with an increased risk of disease”

<table>
<thead>
<tr>
<th>Not As Important</th>
<th>Very Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood pressure</td>
<td>symptoms</td>
</tr>
<tr>
<td>cholesterol</td>
<td>heart attacks</td>
</tr>
<tr>
<td>glucose/diabetes</td>
<td>strokes</td>
</tr>
<tr>
<td>bone density</td>
<td>heart failure</td>
</tr>
<tr>
<td>heart rate</td>
<td>death</td>
</tr>
<tr>
<td>CRP</td>
<td>dialysis</td>
</tr>
<tr>
<td>proteinuria</td>
<td>amputation</td>
</tr>
<tr>
<td>family history</td>
<td>fractures</td>
</tr>
<tr>
<td>age</td>
<td>blindness</td>
</tr>
<tr>
<td>gender</td>
<td>revascularization</td>
</tr>
<tr>
<td>race</td>
<td>angina</td>
</tr>
<tr>
<td>FEV1</td>
<td>TIAs</td>
</tr>
</tbody>
</table>
Conditions requiring risk assessment

The main ones are hypertension, cholesterol, glucose/diabetes, osteoporosis/BMD, atrial fibrillation, cancer

Figure out risk

Then figure out benefit

Include harm and costs and inconvenience
We are knowledge brokers.
“Choice is a gift from the patient to the doctor, not the other way around”
It’s all about figuring out

The Chance
WITH NO TREATMENT

vs

The Chance
WITH TREATMENT
We need minimally disruptive medicine

The burden of treatment for many people with complex, chronic, comorbidities reduces their capacity to collaborate in their care. Carl May, Victor Montori, and Frances Mair argue that to be effective, care must be less disruptive.
Risky Adjectives

HOW

low is low

moderate is moderate

high is high
Treatment thresholds are arbitrary

Not based on patient preferences

Not based on cost/benefit

Seem to be primarily emotionally-based
What Will You Do?

You are approximately 50 y/o

You have been diagnosed “properly” with elevated blood pressure

You have tried non-drug measures for 6 months and still your blood pressure remains elevated

QUESTION

ABOVE what systolic blood pressure would YOU take a drug every day for the next 5 years?
What is your “scary” number?

130
140
145
150
155
160
165
170
175
Numbers VS NUMBERS

Risk factor numbers

vs

CVD

Risk/benefit/harm
Misguided beliefs

Patients believe CVD “prevention” drugs produce a 70% absolute benefit over 5 years when at most only ~ 20-30% benefit is possible over a lifetime

Clin Med 2002;2:527-33
Risk of future illness

CVD risk/benefit

(most people don’t benefit despite a lifetime of treatment)

Assume a person’s lifetime risk of CVD is that of a male with two CVD risk factors - roughly 50% (NEJM 2012;366:321-9)

Assume that with multiple risk factor modification we can reduce that risk relatively by 60% (VERY optimistic)

Risk goes from 50% ➔ 20%

30% of individuals BENEFIT

70% DO NOT despite a LIFETIME of treatment
20 "NEGATIVE" STUDIES IN A ROW

**LIPIDS**

AIM-HIGH, HPS2-THRIVE (niacin)

dalOUTCOMES (dalcetrapib)

STABILITY (darapladib)

ACCORD (fibrates)

**DIABETES**

ACCORD, ADVANCE, VADT (aggressive A1c lowering)

ROADMAR (olmesartan)

ORIGIN (insulin)

SAVOR-TIMI 53 (saxagliptin)

EXAMINE (alogliptin)

ALECARDIO (alectinazar)

**BLOOD PRESSURE**

ALITIREN (aliskiren)

AMRIDE (amlodipine)

ALECARDIO (alectinazar)

VISTA-16 (varespladib)

EMPA-REG OUTCOME (empagliflozin)

SPRINT (120mmHg vs 140mmHg) - 1.6% ARR for CVD events, 1.8% ARR for kidney events over 3.3 years

HOPE 3 - statins YES 1.4% ARR for CVD events over 5.6 years

BUT blood pressure no benefit

182,000+

patients
Patient

Activity
Nutrition

Measure - BP (SBP) - Chol?

Risk of cardiovascular disease

Patient decision

Treatment
Thiazides
ACE inhibitors
Statins etc

EVIDENCE FOR, AND MAGNITUDE OF, THE reduction in cardiovascular outcomes

Side effects

Repeat BP and chol??

Reevaluate need
Relative Risk and Absolute Benefit - recap

Baseline Risk of a heart attack = 50% over 5 years
RR - Relative benefit = 0.8 or 20% reduction
With Treatment = 40%
Absolute difference = 10%
NNT = 10

Baseline Risk of a stroke = 2% per year
RR - Relative benefit = 0.25 or 75% reduction
With Treatment = 0.5%
Absolute difference = 1.5%
NNT = 67

Baseline risk of cancer = 10% lifetime
RR - Relative harm = 2.5 or 150% increase
With Treatment = 25%
Absolute difference = 15%
NNH = 7
Evidence-based risk communication

“There is likely no single best method of communicating probabilities to patients but rather several good options with some better suited to certain risk scenarios.”

Ann Intern Med 2014;161:270-80
Recommended approaches

GENERAL SUGGESTIONS - these are “relative”
use percentages or natural frequencies (numerator/denominator)
use absolute terms
add bar graphs or icon arrays
use incremental risk format with icon arrays in the same array

• avoid use of NNTs
if use relative risks add baseline risks

Ann Intern Med 2014;161:270-80
Cardiovascular Endpoints
Risk of What and over How Long

WHAT

CVD is cardiovascular disease

Typically = CHD + cerebrovascular

CHD = coronary heart disease = fatal and non-fatal MIs and sometimes angina

Cerebrovascular disease = fatal and non-fatal strokes - and sometimes TIAs

CVD sometimes includes other conditions - heart failure, peripheral vascular disease

HOW LONG - 5 or 10 years
How accurately can we predict risk?

“Non-traditional” Risk Factors

C-reactive protein
ankle–brachial index
leukocyte count
fasting blood glucose
periodontal disease
carotid intima–media thickness
coronary artery calcification score on CT
homocysteine
lipoprotein(a)

“There is at present no place for adding additional risk factors to the present risk prediction models”
Circulation 2013;127:1948–56

Oswald Chesterfield Cobblepot
AKA The Penguin
60 years old
Loves birds
Lives a luxurious lifestyle
Relatively inactive
PMH - Conduct disorder
Smoker
A1c 8
BP 150/90 mm/Hg
Total cholesterol 6 (240)
HDL 1 (40)

10 year risk
Framingham (HA, angina, HF, stroke, int claud) = 53%
ASCVD (HA, stroke) = 41%
Bruce Banner
AKA The Hulk
Age 45
Scientist
Easily agitated, and emotionally withdrawn
SBP 160 mm/Hg
Non-smoker
Non-diabetic
Total cholesterol 4.4 (180)
HDL 1.5 (60)
AM testosterone: 330 nmol/L (N 6.7-29)
Urine catechol: +ve (no urine found)

10 year risk
Framingham (HA, angina, HF, stroke, int claud) = \(8\%\)
ASCVD (HA, stroke) = \(2\%\)
Wonder Woman
Age 40 (OK she ages well)
BP 120/70 mmHg
Total cholesterol 6.8 (270)
HDL 1.6 (65)
LDL 5.0 (200)
Trigs 1
Diet mostly caiman and anaconda (rich in cholesterol)
Non-diabetic
Not a smoker (but still smokin’)
PMH: Charles Bonnet Syndrome
(suffers from visual hallucinations that are pleasant: in this case, a jet)
Wears bracelets as a defence but otherwise dresses more than appropriately!

10 year risk
Framingham (HA, angina, HF, stroke, int claud) = 2%
ASCVD (HA, stroke) = 1%
S.M. + W.W
45 years old
Diabetics A1c 8.5
SBP 140 mm/Hg
Non smokers
Total cholesterol 4.5 (180)
HDL 1.2 (55)

10 year risk
Framingham (HA, angina, HF, stroke, int claud) = 12%/12%
ASCVD (HA, stroke) = 4%/2%
Superman  
Age 74  
Still quite physically active  
BP 150/90 mmHg  
Total cholesterol 5.2  
HDL 1.4  
BMI 35  
A1C 15 = 5.4 on Krypton so OK  
Prostate exam: very hard throughout  
… almost steel-like?  

10 year risk  
Framingham (HA, angina, HF, stroke, int claud) = 33%  
ASCVD (HA, stroke) = 29%
Risks over short time periods

Assume a 5% (5/100) reduction in CVD over 5 years

~ 1% (1/100) reduction over one year

~ 0.1% (1/1000) per month

~ 0.02 (1/5000) per week
10 year risk
Framingham (HA, angina, HF, stroke, int claud) = 53%
ASCVD (HA, stroke) = 41%

Smoker - stop ~15% absolute
A1c 8 ?
BP 150/90 mm/Hg - 30-50% RR
Total cholesterol 6 (240) - 25% RR
HDL 1 (40)

10 year risk
Framingham (HA, angina, HF, stroke, int claud) = 8%
ASCVD (HA, stroke) = 2%

Non-smoker
Non-diabetic
SBP 160 mm/Hg - 30% RR
Total cholesterol 4.4 (180) -25% RR
HDL 1.5 (60)

10 year risk
Framingham (HA, angina, HF, stroke, int claud) = 2%
ASCVD (HA, stroke) = 1%

Smokin’ - NO TREATMENT
BP 120/70 mmHg - 0%
Total cholesterol 6.8(270) - 25% RR
HDL 1.6 (65)
LDL 5.0 (200)
1. CVD = death, MI, stroke, CHF, and coronary revascularisation including CABG and PTCA

2. 1/2-2/3 are hard endpoints - fatal/nonfatal MI or stroke

[Table]

<table>
<thead>
<tr>
<th>AGE</th>
<th>SBP</th>
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<th>MEN</th>
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<tr>
<td>C</td>
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<td>55-64</td>
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<tr>
<td>A</td>
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<td></td>
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<tr>
<td>B</td>
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<tr>
<td>C</td>
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<td>45-54</td>
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<td></td>
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<tr>
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<td></td>
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<td>B</td>
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<td>C</td>
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<td></td>
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<tr>
<td>C</td>
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\[ ≃ 5\text{-year CVD}^1 \]

<table>
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<th>risk (%)^2</th>
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<tbody>
<tr>
<td>&gt;30</td>
</tr>
<tr>
<td>20-30</td>
</tr>
<tr>
<td>10-20</td>
</tr>
<tr>
<td>5-10</td>
</tr>
<tr>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

- Smoking or diabetes approx. doubles the risk

1. "normal" BMI - 20-25
2. "overweight" BMI 25-30
3. "obese" BMI - >30

Lancet 2008;371:923–31
Baseline 10-year risk (%) of CVD, blindness, amputation and ESRD (lifetime) based on A1c (1-3)
(all numbers are ballpark approximations but provide at least a starting point for discussion)

1) CVD from UKPDS risk engine calculator - v3.0b2 - unreleased beta - 2012
3) ESRD from Ann Int Med 1997;127:788-95 - lifetime risk and authors didn’t break down numbers based on gender or other risk factors

* does not imply a reduction in risk as most individual studies of medications that lower glucose don’t show reductions in risk of CVD endpoints - a meta-analysis suggests glucose control reduces major CVD by 5%(0.95RR) Lancet Diabetes Endocrine 2015;3:356–66
* hypoglycaemia risks vary between medications but are roughly 1-2%/year (severe) and 5-10%/year (overall)
<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Key RCTs (patients/years)</th>
<th>MA (# of studies)</th>
<th>Additional Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL LOWER GLUCOSE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RED</strong> - no effect on clinical outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>METFORMIN</strong> - Glucophage, Glumetza, generic</td>
<td></td>
<td>700/11 7% 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SULFONYLUREAS</strong> - Gliclazide (Diamicron, generic), Glimepiride (Amaryl), Glyburide (Diabeta, Euglucon, generic)</td>
<td></td>
<td>4,000/10 4-11 3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INSULIN</strong></td>
<td></td>
<td>12,000/6 4,000/10 None done</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DPP4s</strong> - Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Trajenta), Alogliptin (Nesina)</td>
<td></td>
<td>5,000/1.5 16,000/2 1,500/2 None done</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GLITAZONES</strong> - Pioglitazone (Actos), Rosiglitazone (Avandia)</td>
<td></td>
<td>4,400/4 5,200/3 42 ?CHF harm ? ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GLPs</strong> - Exenatide (Byetta), Liraglutide (Victoza), Dulaglutide (Trulicity)</td>
<td></td>
<td>? - not studied ? ? ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MEGLITINIDES</strong> - Nateglinide (Starlix), Repaglinide (GlucoNorm)</td>
<td></td>
<td>? - not studied ? ? ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SGLT2</strong> - Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance)</td>
<td></td>
<td>Empag (7000/3) 1.6% Others? ? ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tight control</strong></td>
<td></td>
<td>10,000/3.5 1,800/5.5 11,000/5 ?Mortality harm 3 2% 2% 2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### T2DM - Lifetime Treatment Benefits - absolute risk reduction

<table>
<thead>
<tr>
<th>Age</th>
<th>ESRD</th>
<th>Vision Loss</th>
<th>Amputation</th>
<th>First MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>6.5</td>
<td>2.1</td>
<td>2.7</td>
<td>2.6</td>
</tr>
<tr>
<td>55</td>
<td>4.2</td>
<td>1.6</td>
<td>2.2</td>
<td>4.0</td>
</tr>
<tr>
<td>65</td>
<td>2.1</td>
<td>1.0</td>
<td>1.5</td>
<td>3.7</td>
</tr>
<tr>
<td>75</td>
<td>0.7</td>
<td>0.5</td>
<td>0.8</td>
<td>2.7</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>ESRD</th>
<th>Vision Loss</th>
<th>Amputation</th>
<th>First MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>1.3</td>
<td>0.4</td>
<td>0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>55</td>
<td>0.7</td>
<td>0.2</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>65</td>
<td>0.3</td>
<td>0.1</td>
<td>0.2</td>
<td>0.6</td>
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<tr>
<td>75</td>
<td>0.1</td>
<td>0</td>
<td>0.1</td>
<td>0.3</td>
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</tbody>
</table>

**Metformin at diagnosis**

**Switch to Insulin after 10 years**

UKPDS - most optimistic

10 mmHg reduction in SBP

<table>
<thead>
<tr>
<th>Event</th>
<th>NNT over ten years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>32</td>
</tr>
<tr>
<td>CVD events</td>
<td>26</td>
</tr>
<tr>
<td>CHD events</td>
<td>55</td>
</tr>
<tr>
<td>Stroke events</td>
<td>25</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>45</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>11</td>
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</tbody>
</table>

*JAMA 2015;313(6):603-615. doi:10.1001/jama.2014.18574*
Relative risk reductions with different interventions in DM2

<table>
<thead>
<tr>
<th></th>
<th>Treat BP</th>
<th>Treat Lipid</th>
<th>Treat Sugar</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD events</td>
<td>~ 50%</td>
<td>~20-25%</td>
<td>~ 12.5%</td>
</tr>
<tr>
<td>Mortality</td>
<td>16%</td>
<td>8%</td>
<td>NSS</td>
</tr>
</tbody>
</table>

Afib
Stroke Endpoints
Age 76
A fib
150/70 mmHg
No CHF
No Prev stroke/TIA
No diabetes
# SPARC - Stroke Prevention in Atrial Fibrillation Risk Tool

for estimating risk of stroke and benefits & risks of antithrombotic therapy in patients with chronic atrial fibrillation

**References/Notes**

version 7, January 2015

Developed by Peter Loewen, ACPR, Pharm.D., FCSHP

peter.loewen@ubc.ca

## Percent per Year

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Stroke / Embolism</th>
<th>Major Bleeding</th>
<th>HAS-BLED</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CHADS2</td>
<td>CHA2DS2-VASc</td>
<td>Pop.Avg.</td>
</tr>
<tr>
<td>NO THERAPY</td>
<td>3.6%</td>
<td>4.3%</td>
<td>0.6%</td>
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<tr>
<td>ASPIRIN</td>
<td>2.8%</td>
<td>3.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>ASPIRIN+CLOP</td>
<td>2.0%</td>
<td>2.4%</td>
<td>3.8%</td>
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<tr>
<td>WARFARIN</td>
<td>1.2%</td>
<td>1.4%</td>
<td>3.8%</td>
</tr>
<tr>
<td>DABIGATRAN 110</td>
<td>1.2%</td>
<td>1.4%</td>
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<tr>
<td>DABIGATRAN 150</td>
<td>0.8%</td>
<td>0.9%</td>
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<tr>
<td>RIVAROXABAN</td>
<td>1.2%</td>
<td>1.4%</td>
<td>3.8%</td>
</tr>
<tr>
<td>APIXABAN</td>
<td>0.9%</td>
<td>1.1%</td>
<td>2.6%</td>
</tr>
<tr>
<td>EDOXABAN 30</td>
<td>1.2%</td>
<td>1.4%</td>
<td>1.8%</td>
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<tr>
<td>EDOXABAN 60</td>
<td>1.2%</td>
<td>1.4%</td>
<td>3.0%</td>
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**Additional Table:**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>CHADS2</th>
<th>CHA2DS2-VASc</th>
<th>Pop.Avg.</th>
<th>HAS-BLED</th>
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<tr>
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<td>1.2%</td>
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<tr>
<td>APIXABAN</td>
<td>0.3%</td>
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<td>0.8%</td>
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<tr>
<td>EDOXABAN 30</td>
<td>0.4%</td>
<td>0.2%</td>
<td>1.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>EDOXABAN 60</td>
<td>0.4%</td>
<td>0.2%</td>
<td>3.0%</td>
<td>1.0%</td>
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</tbody>
</table>

http://www.sparctool.com
An easy A fib table

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; Score</th>
<th>No therapy</th>
<th>ASA</th>
<th>OAC</th>
<th>Difference in benefit between ASA and OAC</th>
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<tr>
<td>0</td>
<td>1.9</td>
<td>1.5</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
<td>2.2</td>
<td>0.9</td>
<td>1.3</td>
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<td>2</td>
<td>4</td>
<td>3.1</td>
<td>1.3</td>
<td>1.8</td>
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An even easier A fib table

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