Moving Novel Biomarkers (Genetic or Non-Genetic) From the Lab to the Clinic:

A Translational Cardiologist’s Perspective (And A Cautionary Tale)

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Dr. Ridker is listed as a co-inventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneca and Siemens.
Prediction in Not Prevention

Many Clinicians Will Not Act Even After There is Hard Evidence That Knowing Something New Improves Care

Guidelines Usually Lag Clinical Data By Many Years and Rarely Are Evidence Based (Particularly Those that Claim to Be)

Physician Obstacles to Translation Are Large and Very Difficult To Surmount

“All Change is For the Worse, Including Change For the Better”
G1691A Mutation in Coagulation Factor V and Risks of Future Arterial and Venous Thrombosis

PREVENT: NHLBI’s First Pharmacogenetic Clinical Trial

Hazard Ratio, 0.36 (95% CI, 0.19 to 0.67); P<.001

Cumulative Event Rate

Placebo
(7.2/100 person-years)

64%

Low-Intensity Warfarin
(2.6/100 person-years)

PREVENT: Recurrent VTE by Clinically Important Subgroups

Number of prior VTE *
- >2
- 1

Factor V Leiden or prothrombin mutation *
- Present
- Absent

Gender
- Male
- Female

Age, y
- 30-44
- 45-64
- 65-89

Time after randomization
- ≤1 year
- >1 year

Hazard Ratio (95% CI)
- Favors Placebo
- Favors Low-Intensity Warfarin

Association Between a Literature-Based Genetic Risk Score and Cardiovascular Events in Women

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Daniel I. Chasman, PhD
Guillaume Paré, MD, MS
Julie E. Buring, ScD
Nancy R. Cook, ScD
Joseph P. Miletich, MD, PhD
Paul M. Ridker, MD, MPH

Context While multiple genetic markers associated with cardiovascular disease have been identified by genome-wide association studies, their aggregate effect on risk beyond traditional factors is uncertain, particularly among women.

Objective To test the predictive ability of a literature-based genetic risk score for cardiovascular disease.

Design, Setting, and Participants Prospective cohort of 19,313 initially healthy white women in the Women’s Genome Health Study followed up over a median of 12.3 years (interquartile range, 11.6-12.8 years). Genetic risk scores were constructed from the National Human Genome Research Institute’s catalog of genome-wide association study results published between 2005 and June 2009.

Main Outcome Measure Incident myocardial infarction, stroke, arterial revascularization, and cardiovascular death.

Results A total of 101 single nucleotide polymorphisms reported to be associated with cardiovascular disease or at least 1 intermediate cardiovascular disease phenotype at a published P value of less than 10^{-7} were identified and risk alleles were added to create a genetic risk score. During follow-up, 777 cardiovascular disease events occurred (429 myocardial infarction, 260 stroke, 107 revascularization, and 81 cardiovascular death). Compared with the lowest quintile of risk score, the incidence of cardiovascular events was higher across increasing quintiles of risk score (P = 3.3×10^{-12}). After adjustment for age, high blood pressure, diabetes, smoking, and total cholesterol, a 1-point increase in the risk score was associated with a 14% increase in the incidence of cardiovascular events (95% CI, 11%-16%; P < 0.001).

JAMA 2010;303:631-637
Will Panels of Previously Validated SNPs Improve CVD Risk Prediction?

WGHS: Women’s Genome Health Study

101 SNP GRS

Event-Free Survival

Years

Family History

Years

JAMA 2010;303:631-637
Moving A Biomarker From The Bench to the Clinic
Four Crucial Questions

Is there evidence that individuals identified by the biomarker of interest are at high risk even when other risk factors are acceptable?

Is there evidence that individuals identified at increased risk due to the biomarker of interest benefit by receiving a therapy they otherwise would not have received?

Is there evidence that individuals identified at increased risk due to the biomarker of interest benefit by avoiding a therapy they otherwise would have received?

Is there evidence that altering the biologic pathway reflected by the biomarker of interest reduces clinical event rates?
IL-6 and Risk of Future MI in Apparently Healthy Men

\[ P = 0.01 \]
\[ P = 0.003 \]
\[ P = 0.3 \]

**Quartile of IL-6 (range, pg/dL)**

- Quartile 1: \( \leq 1.04 \)
- Quartile 2: 1.04-1.46
- Quartile 3: 1.47-2.28
- Quartile 4: \( \geq 2.28 \)

**Relative Risk of MI**

- Quartile 1: \( P = 0.3 \)
- Quartile 2: \( P = 0.003 \)
- Quartile 4: \( P = 0.01 \)

**P Trend = 0.001**

*Circulation 2000;101:1767-1772*
RECORD RAINFALL FIGURES
Human fingerprints on the hydrological cycle
VIRTUAL ARCHAEOLOGY
Good science or good game?
BIRDSONG GRAMMAR
It’s almost human

AIMING FOR THE HEART
C-reactive protein as a target for cardioprotective drugs

TECHNOLOGY FEATURE
Gene expression
Event-Free Survival According to Baseline Quintiles of hs-CRP and LDL Cholesterol

Quintiles of hsCRP

Quintiles of LDL

CVD Event-Free Survival Probability

Years of Follow-Up

Meta-analysis of 54 Prospective Cohort Studies
hsCRP concentration and risk of cardiovascular events: 2010

Emerging Risk Factor Collaborators, Lancet January 2010
Meta-analysis of 54 Prospective Cohort Studies: The magnitude of independent risk associated with hsCRP is at least as large, if not larger, than that of BP and cholesterol.

<table>
<thead>
<tr>
<th>Risk Ratio (95%CI) per 1-SD higher usual values</th>
<th>Risk Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
<td>1.37 (1.27-1.48)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.35 (1.25-1.45)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>1.16 (1.06-1.28)</td>
</tr>
<tr>
<td>Non-HDLC</td>
<td>1.28 (1.16-1.40)</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, smoking, diabetes, BMI, triglycerides, alcohol, lipid levels, and hsCRP.
The Reynolds Risk Score is designed to predict the risk of having a future heart attack, stroke, or other major heart disease in the next 10 years. It considers factors such as age, blood pressure, cholesterol levels, smoking status, and family history.

### Factors Considered
- **Age**
- **Smoking**
- **Systolic Blood Pressure (SBP)**
- **Total Cholesterol (TC)**
- **HDL or "Good" Cholesterol (HDLC)**
- **High Sensitivity C-Reactive Protein (hsCRP)**
- **Family History**

### Calculation
To calculate your risk, the score uses information from two other risk factors: a blood test called hsCRP (a measure of inflammation) and whether or not either of your parents had a heart attack before they reached age 60 (a measure of genetic risk). Fill in the information below with your most recent values. Click here for help filling the information.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55</td>
<td>Years (Maximum age must be 80)</td>
</tr>
</tbody>
</table>

- **Do you currently smoke?**
  - Yes
  - No

- **Systolic Blood Pressure (SBP)**: 125 mm/Hg
- **Total Cholesterol**: 230 mg/DL
- **HDL or "Good" Cholesterol**: 42 mg/DL
- **High Sensitivity C-Reactive Protein (hsCRP)**: 4.5 mg/L

- **Did your Mother or Father have a heart attack before age 60?**
  - Yes
  - No

### Results
As shown in the graph below, at Age 68, your chance of having a heart attack, stroke, or other heart disease event at some point in the next 10 years is 29 percent. This risk is approximately 3 times higher than that of a Man the same age who has optimal levels of all modifiable risk factors.

<table>
<thead>
<tr>
<th>current Age</th>
<th>Age 78</th>
<th>Age 68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your 10-year risk (age 68)</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Your 10-year risk (age 68) if</td>
<td></td>
<td></td>
</tr>
<tr>
<td>your blood pressure was 120</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>your cholesterol was 160</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>your hsCRP was 0.5</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>all the above were optimal</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

The graph above also compares your risk to that of a Man of age 68 who has optimal levels for all modifiable risk factors, and shows what your risk would be if you improved your individual risk factors. For young Men, risk may appear to be low over the next 10-years, yet can be very high over a lifetime. Thus, to see what your risk would be as you get older if your risk factors remain the same, click on the buttons above.

### References
- JAMA 2007;297:611-9
- Circulation 2008;118:2243-51
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Is there evidence that altering the biologic pathway reflected by the biomarker of interest reduces clinical event rates?
Inflammation, Statin Therapy, and hsCRP: Initial Observations

![Graph showing relative risk and median hs-CRP levels](image)


**Circulation.** 1999;100:230-235.
JUPITER
Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP

Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Mean LDLC 104 mg/dL, Mean HDLC 50 mg/dL, hsCRP 4 mg/L
JUPITER
Fatal or Nonfatal Stroke

HR 0.52, 95% CI 0.34-0.79
P = 0.002

NEJM 2008;359:2195-2207
HR 0.53, 95% CI 0.40-0.70
P < 0.00001

Placebo (N = 143)
- 47%

Rosuvastatin (N = 76)

Cumulative Incidence

Follow-up (years)

Number at Risk
Rosuvastatin 8,901 8,640 8,426 6,550 3,905 1,966 1,359 989 547 158
Placebo 8,901 8,641 8,390 6,542 3,895 1,977 1,346 963 538 176

NEJM 2008;359:2195-2207
JUPITER
Secondary Endpoint – All Cause Mortality

HR 0.80, 95% CI 0.67-0.97
P= 0.02

Placebo 247 / 8901
- 20%

Rosuvastatin 198 / 8901

Number at Risk
Rosuvastatin 8,901 8,847 8,787 6,999 4,312 2,268 1,602 1,192 683 227
Placebo 8,901 8,852 8,775 6,987 4,319 2,295 1,614 1,196 684 227

Follow-up (years)
## 2009 Canadian Cardiovascular Society (CCS) Guidelines for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease in the Adult

### Primary Goal: LDLC

<table>
<thead>
<tr>
<th>Level</th>
<th>FRS/CRS</th>
<th>LDL</th>
<th>TC/HDLC</th>
<th>hsCRP</th>
<th>Secondary Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>&gt;20%</td>
<td>&lt;2mmol/L or 50% reduction</td>
<td>&lt;5mmol/L</td>
<td>&lt;2 mg/L</td>
<td>TC/HDLC &lt; 4, non HDLC &lt; 3.5 mol/L, hsCRP &lt; 2 mg/L, TG &lt; 1.7 mol/L, ApoB/A&lt;0.8</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>10-19%</td>
<td>&lt;2mmol/L or 50% reduction</td>
<td>Class IIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>&lt;10%</td>
<td>&lt;5mmol/L</td>
<td>Class IIA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Primary Goal:**
  - **High:** CAD, CVA, PVD
  - Most pts with Diabetes
  - FRS > 20%
  - RRS > 20%
  - Level A

- **Moderate:**
  - FRS 10-19%
  - RRS 10-19%
  - LDL > 3.5 mmol/L
  - TC/HDLC > 5.0
  - hsCRP > 2 in men >50 yr, women > 60 yr
  - Level A

- **Low:**
  - FRS < 10%
  - Level A
JUPITER
Achieved LDLC, Achieved hsCRP, or Both?

The Real Controversy:

Is the large benefit observed in the JUPITER trial due to lipid lowering, to inflammation inhibition, or to a combination of these two processes?
JUPITER
LDL reduction, hsCRP reduction, or both?

JUPITER GWAS:

The genetic determinants of rosvastatin-induced LDL-C reduction do not predict rosvastatin-induced CRP reduction

The genetic determinants of rosvastatin-induced CRP reduction do not predict rosvastatin-induced LDL-C reduction

Chasman et al, 2012 Circulation Cardiovascular Genetics
Chu et al, 2012 Circulation Cardiovascular Genetics
Can Targeted Anti-Inflammatory Therapy Reduce Cardiovascular Event Rates and Prolong Life?
## Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

<table>
<thead>
<tr>
<th></th>
<th>Statins</th>
<th>TNF inhibition</th>
<th>IL-6 Inhibition</th>
<th>LDM inhibition</th>
<th>IL-1β inhibition</th>
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</thead>
<tbody>
<tr>
<td>TC</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
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<td>←←</td>
</tr>
<tr>
<td>LDL</td>
<td>↓↓</td>
<td>↑</td>
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<td>←←</td>
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<tr>
<td>HDL</td>
<td>↑</td>
<td>↑</td>
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<td>TG</td>
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<tr>
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</tr>
<tr>
<td>CRP / IL-6</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
</tbody>
</table>
Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA

Persistent Evidence of Inflammation:
Type 2 diabetes or Metabolic Syndrome

LDM 20 mg/week
+ Folate

Placebo
+ Folate

Nonfatal MI, Nonfatal Stroke, Cardiovascular Death

Ridker PM. Thromb Haemost 2009
## LDM and CVD: Observational Evidence

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Group</th>
<th>HR* (95% CI)</th>
<th>Endpoint</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wichita</td>
<td>RA</td>
<td>0.4 (0.2 - 0.8)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td>Choi 2002</td>
<td></td>
<td>0.3 (0.2 - 0.7)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.4 (0.3 – 0.8)</td>
<td>CV Mortality</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td>Netherlands</td>
<td>RA</td>
<td>0.3 (0.1 – 0.7)</td>
<td>CVD</td>
<td>LDM only</td>
</tr>
<tr>
<td>van Helm 2006</td>
<td></td>
<td>0.2 (0.1 – 0.5)</td>
<td>CVD</td>
<td>LDM + SSZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 (0.1 – 1.2)</td>
<td>CVD</td>
<td>LDM + HCQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 (0.1 – 0.5)</td>
<td>CVD</td>
<td>LDM + SSZ + HCQ</td>
</tr>
<tr>
<td>Miami VA</td>
<td>PsA</td>
<td>0.7 (0.6 – 0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td>Pradanovich 2005</td>
<td></td>
<td>0.5 (0.3 – 0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>0.8 (0.7 – 1.0)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6 (0.5 – 0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td>CORRONA</td>
<td>RA</td>
<td>0.6 (0.3 – 1.2)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td>Solomon 2008</td>
<td></td>
<td>0.4 (0.2 – 0.8)</td>
<td>CVD</td>
<td>TNF-inhibitor</td>
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<tr>
<td>QUEST-RA</td>
<td>RA</td>
<td>0.85 (0.8 – 0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td>Narango 2008</td>
<td></td>
<td>0.82 (0.7 – 0.9)</td>
<td>MI</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.89 (0.8 - 1.0)</td>
<td>Stroke</td>
<td>LDM</td>
</tr>
<tr>
<td>UK Norfolk</td>
<td>RA, PsA</td>
<td>0.6 (0.4 – 1.0)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td>0.5 (0.3 – 1.1)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
</tbody>
</table>
Cardiovascular Inflammation Reduction Trial (CIRT)

Primary Aim

- To directly test the inflammatory hypothesis of atherothrombosis by evaluating in a randomized, double-blind, placebo-controlled trial whether LDM given at a target dose of 20 mg po weekly over a three to four year period will reduce rates of recurrent myocardial infarction, stroke, or cardiovascular death among patients with a prior history of myocardial infarction and either type 2 diabetes or metabolic syndrome.
Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

<table>
<thead>
<tr>
<th>Statins</th>
<th>TNF inhibition</th>
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<td>HDL</td>
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<td>↑</td>
<td>←→</td>
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<tr>
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<td>↑</td>
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</tr>
<tr>
<td>CRP / IL-6</td>
<td>↓</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

TNF: Tumor Necrosis Factor
IL-6: Interleukin-6
LDM: Lipoprotein Disruption Mechanism
IL-1β: Interleukin-1β
Cholesterol crystals activate the caspase-1-activating NLRP3 inflammasome to generate IL-1β and initiate atherosclerosis.

Canakinumab (Ilaris, Novartis)

• high-affinity human monoclonal anti-human interleukin-1β (IL-1β) antibody currently indicated for the treatment of IL-1β driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)

• designed to bind to human IL-1β and functionally neutralize the bioactivity of this pro-inflammatory cytokine

• long half-life (4-8 weeks) with CRP and IL-6 reduction for up to 3 months
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation of hsCRP (> 2 mg/L)

Randomized
Canakinumab 50 mg SC q 3 months

Randomized
Canakinumab 150 mg SC q 3 months

Randomized
Canakinumab 300 mg SC q 3 months

Randomized
Placebo SC q 3 months

Primary Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death

Secondary Endpoints: Total Mortality, New Onset Diabetes, Other Vascular Events

Exploratory Endpoints: DVT/PE; SVT; hospitalizations for CHF; PCI/CABG; biomarkers

N = 17,200
FPFV April 2012
Will genetic screening play a role in patient focused thrombosis care?

Will pharmacogenetics matter for cardiovascular disease?
Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to SLCO1B1 rs4149056 Genotype

Risk of muscular complaints by treatment groups and *SLCO1B1* genotypes

**rs4363657**

- **Myalgia (Allelic risk model)**
  - Overall
  - Rosuvastatin
  - Placebo
  - Rosuvastatin Arm (Genotype risk model)
    - CC
    - TC
    - TT (referent)

- **Muscle Weakness/Stiffness/Pain (Allelic risk model)**
  - Overall
  - Rosuvastatin
  - Placebo
  - Rosuvastatin Arm (Genotype risk model)
    - CC
    - TC
    - TT (referent)

- Fewer events associated with “C” allele
- More events associated with “C” allele
- **P-interaction † 0.57**

**rs4149056**

- Fewer events associated with “C” allele
- More events associated with “C” allele
- **P-interaction 0.036**
JUPITER: Rosuvastatin is Equally Effective at Lowering Vascular Risk Among those With and Without the *KIF6* Polymorphism

**KIF6 Non-Carrier**
- KIF-6: Trp/Trp
- Jupiter Caucasian Population
- HR 0.59 (0.39-0.88)
- \( P = 0.009 \)

**KIF6 Carrier**
- KIF-6: Trp/Arg or Arg/Arg
- Jupiter Caucasian Population
- HR 0.61 (0.43-0.87)
- \( P = 0.006 \)

Similar LDL and hsCRP reduction by genotype
Similar absolute event rates by genotype
Similar relative risk reduction by genotype
Some Thoughts About Eric Green’s Density Maps
On the Speed of Translation to Practice

1. Don’t be discouraged. It takes a long time to change practice even when randomized trials exist.

2. Sure, there are bumps, potholes, and u-turns on the Translational Highway, but were else are you going to drive?

3. A true killer app would be nice, but we may not need that since the “average” patient may not be what this is all about. If the cost of screening falls far enough, we don’t need a homerun for all patients, just a clear benefit for some, even if they are rare individuals.

4. It really matters for parents and kids
It must be considered that there is nothing more difficult to carry out, nor more doubtful of success, nor more dangerous to handle, than to initiate a new order of things. For the reformer has enemies in all those who profit by the old order, and only lukewarm defenders in all those who would profit by the new order, this lukewarmness arriving partly from fear and partly from the incredulity of mankind, who do not believe in anything new until they have had an actual experience of it.

Nicolo Machiavelli 1513
Chasman et al, Atherosclerosis 2008

Differential effects of aspirin on vascular outcomes according to polymorphism in the Lp(a) gene