Delivering Personalized Medicine Today: Opportunities and Challenges for Improving Care

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Disclosures

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- **Copyrights/Patents:** SAQ, KCCQ, PAQ, PRISM
- **Equity:** Health Outcomes Sciences, LLC
To deliver Personalized, Evidence-based Medicine at the Point of Care to …

– Improve patients’ experiences with care

– Improve the use of appropriate treatments and outcomes

– Lower Costs
Creating & Applying Evidence-Based Medicine

Outcomes from a Study

Mean Treatment Difference

Risk Stratification
Personalizing Evidence-based Medicine

Outcomes from a Study

Genetics
Pharmacogenomics

Risk Stratification

Proteomics
Biomarkers

Clinical Risk-Stratification

<table>
<thead>
<tr>
<th>GRACE™ ACS Risk Model 0.36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>40-49</td>
</tr>
<tr>
<td>CHF</td>
</tr>
<tr>
<td>Cardiac arrest at admission</td>
</tr>
<tr>
<td>ST-segment deviation</td>
</tr>
<tr>
<td>Elevated cardiac enzymes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Probability of Death or MI</th>
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<tbody>
<tr>
<td>In-hospital</td>
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<tr>
<td>To 6 months</td>
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</table>
Using Registries to Improve Healthcare

Prospective Data Collection → Creation of Predictive Models → Prospectively Improve Health

Requires a Novel IT Solution – ePRISM™

Periodic Benchmark Reports for Quality Assurance
### ePRISM: Clinical Risk Modeling at the Point-of-Care

#### Risk Models

\[
\begin{align*}
\eta &= \beta_0 + \beta_1 x_{T1} + \ldots + \beta_n x_{Tn} \\
\eta &= \beta_1 x_{T1} + \ldots + \beta_n x_{Tn} \\
\eta_i &= \beta_{i0} + \beta_{i1} x_{T1} + \ldots + \beta_{in} x_{Tn} \\
\pi_i &= \begin{cases} 
\pi_i & i = 1 \\
\pi_i - \sum_{j=1}^{i-1} \pi_j & i = 2, \ldots, s \text{ where } \pi_i = \Phi^{-1}(\eta_i) \\
1 - \sum_{j=1}^{s+1} \pi_j & i = s+1
\end{cases} \\
\mu_i &= \begin{bmatrix} \pi_i \\ \pi_i - \sum_{j=1}^{i-1} \pi_j \\ 1 - \sum_{j=1}^{s+1} \pi_j \end{bmatrix} \\
(\eta_{LO}, \eta_{HI}) &= \eta \pm F_{\nu} \left(1 - \frac{\alpha}{2}\right) \sqrt{\varphi^2 + \sigma^2} \\
\sigma^2 &= \begin{bmatrix}
1 \\
x_{T1} \\
\vdots \\
x_{Tn}
\end{bmatrix} \begin{bmatrix}
c_{00} & \ldots & c_{0n} \\
\vdots & \ddots & \vdots \\
c_{n0} & \ldots & c_{nn}
\end{bmatrix} \begin{bmatrix}
x_{T1} \\
x_{T2} \\
\vdots \\
x_{Tn}
\end{bmatrix}
\]

#### Decision Support Tools
Critical Decisions in PCI – and Models to Help

An opportunity to increase the safety and cost-effectiveness of treatment decisions and compliance.

Evidence-based triage between inpatient and outpatient status.

More effective use of bleeding avoidance therapies.

ACC’s Risk Model for Bleeding

Patients with CAD → PCI → Bleeding Avoidance Treatment

ACC Restenosis Model

DES

BMS

Discharge that day

Admit overnight
A Story about Bleeding in PCI

- Most common non-cardiac complication\(^1\)
- Increases risk of death, MI, stroke\(^3\)
- Prolongs length of stay
- Increases hospitalization cost
  - $6500\(^4\) – $8500 for a major bleed
- Patients should be evaluated for bleeding risk
  - AHA/ACC 2011, Class I, Level of Evidence C

1 Kinnaird TD. Am J Cardiol 2003;92:930-5
2 Ndrepepa et al. J Am Coll Cardiol 2008;51:690-97
3 Moscucci M. Eur Heart J 2003;24:1815-23
4 Cohen DJ. J Am Coll Cardiol, 2004; 44:1792-1800
Potential Interventions for High Bleeding Risk

Interventions to Consider:
- Radial Approach
- Use of Bivalirudin
- Use of Closure Device
- Admission as an Inpatient for Observation

Recommendations:
- Therapy should be targeted to higher-risk patients
  » Any benefit with a constant RRR provides the greatest benefits in those at the highest risk.
Bleeding in Patients Undergoing Percutaneous Coronary Intervention

The Development of a Clinical Risk Algorithm From the National Cardiovascular Data Registry

Sameer K. Mehta, MD; Andrew D. Frutkin, MD; Jason B. Lindsey, MD; John A. House, MS; John A. Spertus, MD, MPH; Sunil V. Rao, MD; Fang-Shu Ou, MS; Matthew T. Roe, MD, MHS; Eric D. Peterson, MD, MPH; Steven P. Marso, MD; on Behalf of the National Cardiovascular Data Registry

**Background**—Bleeding in patients undergoing percutaneous coronary intervention (PCI) is associated with increased morbidity, mortality, length of hospitalization, and cost. We identified baseline clinical characteristics associated with bleeding complications after PCI and developed a simplified, clinically useful algorithm to predict patient risk.

**Methods and Results**—Data were analyzed from 302,152 PCI procedures performed at 440 US centers participating in the National Cardiovascular Data Registry. As defined by the National Cardiovascular Data Registry, bleeding required transfusion, prolonged hospital stay, and/or a drop in hemoglobin >3.0 g/dL from any location, including percutaneous entry site, retroperitoneal, gastrointestinal, genitourinary, and other/unknown location. Bleeding complications occurred in 2.4% of patients. From the best-fitting model consisting of 15 clinical elements associated with post-PCI bleeding in a random 80% training cohort, we developed a parsimonious risk algorithm. Predictors of bleeding included age, gender, previous heart failure, glomerular filtration rate, peripheral vascular disease, no previous PCI, New York Heart Association/Canadian Cardiovascular Society Functional Classification class IV heart failure, ST-elevation myocardial infarction, non–ST-elevation myocardial infarction, and cardiogenic shock. The parsimonious model was validated in the remaining 20% of the population (c-statistic, 0.72) and in clinically relevant subgroups of patients. This simplified model was used to derive a clinical risk algorithm, with larger numbers corresponding with greater risk. In 3 categories, bleeding rates were greater in patients with higher estimates (≤7, 0.7%; 8 to 17, 1.8%; ≥18, 5.1%).

**Conclusions**—This report identifies baseline clinical factors associated with bleeding and proposes a clinically useful algorithm to estimate bleeding risk. This model is potentially actionable in altering therapeutic decision making and improving outcomes in patients undergoing PCI. *(Circ Cardiovasc Intervent. 2009;2:222-229.)*

**Key Words:** catheterization ■ hemorrhage ■ risk factors
Gender is an Important Risk Factor for Bleeding

<table>
<thead>
<tr>
<th>Table 2. Most Parsimonious Risk Model Generated in the Training Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimate of the ( \beta ) Coefficient</strong></td>
</tr>
<tr>
<td>Intercept</td>
</tr>
<tr>
<td>ACS type</td>
</tr>
<tr>
<td>ST-elevation MI</td>
</tr>
<tr>
<td>Non-ST-elevation MI/unstable angina</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
</tr>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>NYHA class IV CHF</td>
</tr>
<tr>
<td>Previous congestive heart failure</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Previous PCI</td>
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<tr>
<td>Glomerular filtration rate</td>
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</tbody>
</table>

CHF indicates congestive heart failure; NYHA, New York Heart Association.
Can Physicians Use the Evidence in Practice?

**Risk of In-Hospital Complication**
Ranges of outcome(s) for patients with similar clinical profiles

- **Bleeding**
- **Death**

**Figure 1**
If a vessel is blocked, the doctor may decide to treat the blockage with an angioplasty and/or implant. If the blockage is not improved, the doctor may decide to perform surgery on the coronary artery graft (CABG). This procedure may be performed at a later time.

**Figure 2**
A stent is used to keep arteries open (Figure 3). A stent, which helps keep the artery open, is often implanted after angioplasty. The doctor has explained to me that there are risks with this procedure. It is possible to have a complication that may happen. These risks include, but are not limited to:

- **Bleeding**
- **Death**

**Figure 3**
Possible alternatives to the procedure have been explained to me. This includes not having this procedure at all. Other alternatives might include, but are not limited to:

**Drug Eliking**
the risk of vessel closing within the next year when a drug-eluting stent is used.

**Bare Metal**
the risk of vessel closing within the next year when a bare metal stent is used.

NOTE: These graphs use data from many previously treated patients. It is important to know that your results may differ from those of other patients, even though they had similar medical conditions to you. It is impossible to predict what will happen in your case. The information is not a guarantee of your results.

I understand that I may need blood transfusion during the procedure. I know that there are risks with a transfusion. This might include fever, kidney reaction, hepatitis, acquired Immune Deficiency Syndrome (AIDS), or other infections.

If I get a medical device, my Social Security number can be released to the maker of the device. This is because of the Federal Food and Cosmetic Act section 510(k).

Because this facility is an academic hospital, my medical record may be used for scientific purposes. I understand I may be contacted in the future about my recovery from this procedure.

I consent to any photographing or videotaping of the procedure. The picture or the words describing the procedure will not reveal my identity. I also consent to be a subject of implementation studies being in the procedure room. This is for medical education or to get important product information.
Association Between Use of Bleeding Avoidance Strategies and Risk of Periprocedural Bleeding Among Patients Undergoing Percutaneous Coronary Intervention

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Kevin F. Kennedy, MS
John A. Spertus, MD, MPH
Sunil V. Rao, MD
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for the National Cardiovascular Data Registry

Context  Bleeding complications with percutaneous coronary intervention (PCI) are associated with adverse patient outcomes. The association between the use of bleeding avoidance strategies and post-PCI bleeding as a function of a patient’s preprocedural risk of bleeding is unknown.

Objective  To describe the use of 2 bleeding avoidance strategies, vascular closure devices and bivalirudin, and associated post-PCI bleeding rates in a nationally representative PCI population.

Design, Setting, and Patients  Analysis of data from 1,522,935 patients undergoing PCI procedures performed at 955 US hospitals participating in the National Cardiovascular Data Registry (NCDR) CathPCI Registry from January 1, 2004, through September 30, 2008.

Main Outcome Measure  Periprocedural bleeding.

Results  Bleeding occurred in 30,654 patients (2%). Manual compression, vascular closure devices, bivalirudin, or vascular closure devices plus bivalirudin were used in 35%, 24%, 23%, and 18% of patients, respectively. Bleeding events were reported in 2.8% of patients who received manual compression, compared with 2.1%, 1.6%, and 0.9% of patients receiving vascular closure devices, bivalirudin, and both strategies, respectively ($P<.001$). Bleeding rates differed by preprocedural risk assessed with the NCDR bleeding risk model (low risk, 0.72%; intermediate risk, 1.73%; high risk, 4.69%). In high-risk patients, use of both strategies was associated with lower bleeding rates (manual compression, 6.1%; vascular closure devices, 4.6%; bivalirudin, 3.8%; vascular closure devices plus bivalirudin, 2.3%, $P<.001$). This association persisted following adjustment using a propensity-matched and site-controlled model. Use of both strategies was used least often in high-risk patients (14.4% vs 21.0% in low-risk patients, $P<.001$).

Conclusions  In a large national PCI registry, vascular closure devices and bivalirudin were associated with significantly lower bleeding rates, particularly among patients at greatest risk for bleeding. However, these strategies were less often used among higher-risk patients.

$JAMA. 2010;303(21):2156-2164$

www.jama.com
Benefits of Bivalirudin by Bleeding Risk

- Low Risk (31%): NNT = 227
- Moderate Risk (49%): NNT = 97
- High Risk (20%): NNT = 42

Risk of Major Bleed

- No Bivalirudin
- Bivalirudin
Costs per Patient of Bivalirudin Use

- Detailed hospital’s costs for bivalirudin by bleeding risk at MAHI

A Risk-Treatment Paradox in the Use of Bivalirudin

Marso et al. *JAMA* 2010; 303: 2156-2164

\( n=1,522,935 \)
Replicating the MAHI Experience Nationally

Kaiser-Permanente
San Francisco, CA
Ed McNulty, MD

Mayo Clinic
Rochester, MN
Henry Ting, MD

Henry Ford Hospital
Detroit, MI
Mayra Guerrero, MD

Bay State Medical Center
Springfield, MA
Aaron Kugelmass, MD

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Charles Bethea, MD

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Baylor Health
Plano Heart Hospital
Plano, TX
Bradley Leonard, MD

Washington University
Barnes-Jewish Hospital
St. Louis, MO
Richard Bach, MD

Yale New Haven Hospital
New Haven, CT
Jeptha Curtis, MD

Prairie Heart
St. John’s Hospital
Springfield, IL
Marc Shelton, MD
Addressing Secular Trends in Bleeding

-12
Pre-PRISM
(Standard consent form)

0
Break-in

~2
Post-PRISM
(Enhanced consent form)

14
MD Site Visit

Rest of NCDR

Did Care, Safety and Outcomes Improve?
Change in Processes of Care

- **Bivalirudin Use**
  - Overall OR = 1.24 (1.02, 1.51)
  - OR by Bleeding Risk (interaction p=0.02)
    » Low Risk = 0.94 (0.71, 1.25)
    » Intermediate/High Risk = 1.44 (1.13, 1.84)

- **Any BAS Use**
  - Overall OR = 1.86 (1.45, 2.37)
  - OR by Bleeding Risk (interaction =0.07)
    » Low Risk = 1.38 (0.99, 1.91)
    » Intermediate/High Risk = 1.89 (1.42, 2.52)
Bleeding by Bleeding Risk

Fully-adjusted OR $= 0.55$

($95\% CI = 0.39, 0.77$)
Impact on Women

Female Patients

Rate of Post-PCI Bleeding (%)

- Pre-PRISM
- Post-PRISM

p = 0.05
Interaction p = 0.12

Bleeding Risk
ePRISM-Associated Reduction in Bleeding

Reduction in Bleeding

Rest of US (1135 Hospitals)
Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators*
Enhancing Decision Support for PCI

PCI

Bleeding Avoidance Treatment

DES

BMS

Discharge that day

Admit overnight

Prasugrel

Clopidogrel

TPD
High Expectations for Prasugrel

FDA approves blockbuster blood thinner prasugrel
July 13, 2009 | By John Carroll

Handing a big victory to Eli Lilly and Daiichi Sankyo, the FDA announced on Friday that it approved the blood thinner prasugrel, which is widely considered a likely blockbuster that can go head-to-head with Plavix. One Japanese analyst pegged peak annual revenue at $1.6 billion.

Set For Prasugrel Approval

Full article reprinted from "The Pink Sheet" February 10, 2009
Much Slower Adoption than Expected…
The Need for a TPD Selection Model…

- Weighing benefits and risks of thienopyridines is tough
  - Prasugrel decreases ischemic events
  - Prasugrel increases bleeding risk

- Individualized estimates of benefit and risk may engage patients in a shared decision making process
  - May alter patients’ choice of drug, based on their preferences
  - May alter patients’ compliance
Final Models

**Major Ischemia Risk Model**
c-statistic = 0.63, Hosmer-Lemeshow p = 0.25

- STEMI > 12 hrs vs. UA
- STEMI ≤ 12 hrs vs. UA
- NSTEMI vs. UA
- Hypertension
- Prior PCI
- Prior CABG
- Prior MI
- Chronic heart failure
- Peripheral arterial disease
- Fibrinolytic therapy
- Low molecular weight heparin
- Glycoprotein IIb/IIIa inhibitor
- Glomerular filtration rate (per 10 ml/min)
- Diabetes (prasugrel)
- Diabetes (clopidogrel)
- Killip class ≥ 2 (prasugrel)
- Killip class ≥ 2 (clopidogrel)
- Age (prasugrel, per 10 years)
- Age (clopidogrel, per 10 years)
- Heparin (prasugrel)
- Heparin (clopidogrel)

**Bleeding Risk Model**
c-statistic 0.67, H-L p = 0.28

- Prasugrel
- STEMI > 12 hrs vs. UA
- STEMI ≤ 12 hrs vs. UA
- NSTEMI vs. UA
- Male gender
- Hypertension
- Peripheral arterial disease
- Glycoprotein IIb/IIIa inhibitor
- Radial access
- Age (per 10 years)
- Weight (per 10 kg)

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**OR (95% CI)**

- Prasugrel
  - STEMI > 12 hrs vs. UA
  - STEMI ≤ 12 hrs vs. UA
  - NSTEMI vs. UA
  - Male gender
  - Hypertension
  - Peripheral arterial disease
  - Glycoprotein IIb/IIIa inhibitor
  - Radial access
  - Age (per 10 years)
  - Weight (per 10 kg)

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**Trends**

- Higher Odds of Ischemia
- Lower Odds of Ischemia

- Higher Odds of Bleeding
- Lower Odds of Bleeding
Translating Trials to the Bedside

46yo Man with DM, Prior PCI, PAD & UA

77yo Woman with DM, Prior MI, HF & NSTEMI

Combined Bleed

- Clopidogrel: 2.5%
- Prasugrel: 3.5%

Combined Bleed

- Clopidogrel: 3.8%
- Prasugrel: 5.2%

Probability of Major Ischemic Event

- Clopidogrel: 19.1%
- Prasugrel: 8.5%

Probability of Major Ischemic Event

- Clopidogrel: 14.3%
- Prasugrel: 12.7%
Clinical Models To Be Developed & Tested

- Thrombolytic Therapy for Acute Ischemic Stroke
- ICD Shared Decision-making Tools
- End of life care in HF
- Angina 3-Treatment Model (medicines vs. PCI vs. CABG)
- 30-day Readmission Models – HF, AMI, PCI, Pneumonia
- Anti-thrombotic therapy in PCI and Afib
- New medical disciplines
  - Orthopedics (back pain), Oncology, Obesity, etc.
Summary of Experience in Delivering Evidence-based, Personalized Medicine

- Marked variability in outcomes by patient characteristics
  - Heterogeneity can be modeled and implemented

- Improved patient satisfaction with consent process
  - Increased participation in shared decision-making on stents

- Need new models to support care
  - Ideally developed concurrently with RCTs for FDA Approval

- Need incentives to support evidence-based care and shared decision-making

- Overcoming these challenges can support safer, more cost-effective, personalized care
A Path Forward…

- FDA could encourage tools to support EBM
- FDA could request models of the heterogeneity of treatment benefit with submission of pivotal trials
- These models could be publicly shared
- Innovative tools to implement these models and accelerate adoption of beneficial therapies – in those who most benefit – could be created.
  - Would increase patient engagement in SDM
  - Would improve value in healthcare
  - Would improve clinical outcomes
Implementing PRISM Informed Consents

Cardiac catheterization is a medical procedure to diagnose and treat certain heart conditions. During this procedure, a thin, flexible tube called a catheter is inserted into an artery or vein in your arm, leg, or buttocks and threaded up to your heart through blood vessels. Through the catheter, doctors can perform diagnostic tests or treatments on the heart.

Angioplasty: This procedure involves the use of an inflatable balloon to widen blood vessels. The balloon is inserted through a catheter and then inflated to help the blood flow more freely. After the procedure, the catheter is removed, and you may experience some discomfort, usually for a few days. The risk of complications is low, but it is important to follow your doctor’s instructions for post-procedure care.

Implantation: This procedure involves the placement of a device, such as a pacemaker, to help control the rhythm of your heart. The device is typically placed in a small incision in your chest and connected to wires that are threaded through your blood vessels and attached to your heart. The risk of complications is low, but it is important to follow your doctor’s instructions for post-procedure care.

The catheter is then removed, and you may experience some discomfort, usually for a few days. The patient may be discharged the same day or the next day and can return to normal activities within a few days.

If a vessel is blocked, your doctor may decide to treat the blockage with an angioplasty and/or implant. If your doctor decides that surgery is needed instead of a procedure, a coronary artery bypass graft (CABG) may be done at a later time.
Conceptualizing an Improved Consent Process

Patient Factors:
- Socio-demographics
- Clinical Factors
- Disease Severity

PCI Patients

Informed Consent

Informing Patients

Medical Decision-making

Feedback of Predicted Outcomes

PCI Complications:
- Bleeding
- Death

Outcomes:
- Restenosis
- Need for DAPT

Did the patients read and understand the consent forms?
Did they participate in choosing the stent?

Shared Decision-making:
- Therapeutic options
- Evidence of benefit
- Patient preferences

DES
BMS
Patients’ Experiences of the Consent Process

Original Consent (n=590)  PRISM Consent (n=527)

Reviewed consent form

All p-values from hierarchical models adjusting for site
Knowledge Transfer

Correctly identified purpose of the procedure
Recalled being told of a risk for death
Recalled being told of a risk for bleeding

All p-values from full, site-adjusted models

p=0.02
p=0.09
p=0.08
Discussed Stent Type with Doctor before Treatment

![Graph showing discussed stent type with doctor](image)

**Average OR = 2.7, p=0.02**

- Original Consent (n=590)
- PRISM Consent (n=527)

All p-values from full, site-adjusted models
Participation in Shared Decision-Making

Who Should Decide your Treatment?

Who Decided to Use a DES or BMS?

p=0.43

p=0.05

All p-values from full, site-adjusted models