What we did on our Sabbatical…

Biskupiak JE, Brixner DI

University of Utah College of Pharmacy, Salt Lake City, UT
Presentation Overview

• Where were we again??
• Meetings attended
• Educational Opportunities
• Research Themes
  • Oncology/personalized medicine
  • HCV modeling
  • Health Policy: warfarin generic switching
• OK, we had a little fun too…..
SMDM Europe 2010
May 30 – June 2, UMIT, Hall i.T./Innsbruck, Austria
Where we were....
Where we were....
Where we were....
UMIT

- Founded 2002 as University of the State of Tyrol
- Scientific University for Health Sciences, Medical and Bioinformatics, Nursing Sciences and related Life Sciences Subjects
- 4 Departments, 11 Institutes, 8 Research Divisions/Research Groups
- Currently > 1200 students and 150 employees
Departments

- biomedical computer science & mechatronics
- medical sciences & management
- nursing sciences/gerontology
- public health & hta
- research divisions

www.umit.at
Institute of Public Health, Medical Decision Making and HTA

Core Disciplines

Public Health

Medical Decision Making

IPH

Health Technology Assessment
Important Cooperations
Research & Teaching

**International**
- Harvard School of Public Health
- Massachusetts General Hospital, Harvard Medical School
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Agência Nacional de Vigilância Sanitária Brasil (ANVISA)
- WHO
- University of Utah, Department of Pharmacotherapy

**Europe**
- Ludwig-Maximilians University of Munich (LMU)
- Charité Berlin, TU Berlin
- University Duisburg-Essen
- German Agency for Health Technology Assessment at DIMDI, Federal Ministry of Health (DAHTA@DIMDI)
- Institute for Quality and Efficiency in Health Care (IQWiG)

**National**
- Ludwig Boltzmann Institute for HTA, Vienna (LBI HTA)
- Institute for Sociology, University Graz
- Federal Ministry of Health, Vienna (BMG)
- Austrian Federal Institute for Health Care (ÖBIG)

**Tyrol**
- Medical University of Innsbruck
- Landessanitätsdirektion Innsbruck
- TILAK – Tyrolean Provincial Hospital Company
- District Hospital Hall
Focus on leukemia, breast & prostate cancer

Targeting tumor & stroma

Validation in vitro and in vivo

Utilization & evaluation in diagnostics, therapy & prevention

Area 1

Tumor cell biology & Immunity

Area 2

Bioanalytics & Diagnostics

Area 3

Biomarker-guided Diagnosis, Therapy & Prevention

Area 4

Public Health Decision Modeling, HTA & Health Economics

Area 5 Bioinformatics & Systems Biology

Core Facilities

Tumor Banks, Proteomics, Gene Expression & Function, SNP, Metabolomics, Animal Facility, Clinical Trial Center (CTC)

CEMIT (Center management)
Area 4: Research Program

Methods in Early HTA in Cancer (strategic)
- HTA Cancer Framework
- Value of Innovation
- Surrogate Marker Validation
- Causal Modeling

Outcome & Policy Modeling
- individuals & populations
- clinical & economic
- short- & long-term

Routine Care, Sickness Funds & Cancer Registries
Link results from other areas with "real world" data

e-Health Interface
- combine & integrate
- provide decision support
### AREA 4: Research Groups

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Projekte der AREA 4</th>
<th>KR / PM</th>
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<tbody>
<tr>
<td>4.1</td>
<td>Methodological Framework for Early Health Technology Assessment and Decision Modeling in Cancer</td>
<td>U. Siebert / Team</td>
</tr>
<tr>
<td>4.2</td>
<td>Austrian Myeloma Registry</td>
<td>G. Gastl / W. Willenbacher, E. Willenbacher</td>
</tr>
<tr>
<td>4.3</td>
<td>Development, Validation and Application of a Prostate Cancer Outcome &amp; Policy Model</td>
<td>U. Siebert / N. Mühlberger</td>
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<td>4.4</td>
<td>Development, Validation and Application of a Breast Cancer Outcome &amp; Policy Model</td>
<td>U. Siebert / B. Jahn</td>
</tr>
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<td>4.5</td>
<td>Development, Validation and Application of a Rheumatoid Arthritis Outcome &amp; Policy Model</td>
<td>U. Siebert / NN</td>
</tr>
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<td>4.6</td>
<td>INSYDE – Integration of Health System Data and Exchange</td>
<td>T. Schabetsberger / F. Wozak</td>
</tr>
<tr>
<td>4.7</td>
<td>Austrian CML Registry – Predictive Markers for Response, Outcome and Cost-Effectiveness</td>
<td>G. Gastl / S. Schmidt</td>
</tr>
</tbody>
</table>
Meetings Attended

• Austrian Healthcare Day; held at UMIT
• iGES (Research and Development of Healthcare Infrastructure) Berlin [http://www.iges.de/index_eng.html]
• Switzerland Executive Trade/Study Mission
• European ISPOR Meeting Madrid
• Novo Nordisk Real World Data Workshop
• Basel Switzerland
  • Novartis
  • Actelion
  • Abbott Primary Care Division
Educational Opportunities

• 2 Works in Progress Presentations to Institute
• AGENS Summer School 2011 Lectures
  • Gathering and Use of Secondary Data
• Modeling Week
  • Obesity model
  • CML model
  • Breast cancer model
• Submission of ISPOR Task Force Proposal
  “Good Research Practices for design, conduct, and assessment of personalized healthcare (medicine) for guiding stakeholder decisions.”
Educational Opportunities
Educational Opportunities

• Global Health Policy Course planned for DoP graduate students
• Graduate student and faculty exchange program with UMIT and Oncotyrol
  • UU office at UMIT and PORC
• Ongoing participation in Decision Modeling Course; teaching at UU and DoP
• Clinical Epidemiology Winter School teaching January 2013
Educational Opportunities

- Combined UMIT/University of Utah Fellow

Kim Saverno, RPh, PhD Univ. Arizona

Kim in Budapest December 2011
Grant Submissions

- **PCORI Grant:**
  Disease Registries to Populate Models to Predict Patient Centered Outcomes

- **Sorenson Grant:**
  Proposal on Paradigm Shifts in Approaches to Breast Cancer

- **Cancer Control and Population Sciences**
  Application of Real World Data in CML Patients from the U.S. and Austria to support Decision Analysis for Patients, Providers and Policy Makers

- **Personalized Health Care Program**
  Translating Personalized Medicine into Personalized Health Care by Modeling Risk and Outcomes in Breast Cancer Management of Utah Patients
Research Themes of Collaboration

• Application of Real World Data to Decision Analytical Models
• Applied to Personalized Medicine in Oncology
• Applied to HCV and other selected disease areas
• Utilizing Information towards Health Technology Assessment in Reimbursement Decisions
Submitted:
“Consideration of Generic Distribution Policies of Warfarin Therapy on Patient Outcomes in the United States and Germany” *Annals of Pharmacotherapy*

"Application of Decision-Analytical Models towards Personalized Medicine in CML Treatment Decisions for Payers, Providers and Patients," *Journal of Oncology Practice*

In progress:
“Systematic Assessment of Decision-analytic Models for Chronic Myeloid Leukemia” *International Journal of Health Technology Assessment*

“Personalized decision-making in cancer medicine? Systematic overview of cost-effectiveness thresholds in ten countries across four continents“ *Personalized Medicine*
Submitted:
• Opening the Pipeline to Comprehensive Oncology Outcomes Research Using a Leading and Innovative Regional Health Center’s Electronic Health Record Data linked to State Population Databases ISPOR Madrid workshop; secondarily to ESMDM
• Comparison of Chronic Myeloid Leukemia Registries in Austria and Utah, USA Evidence Based Medicine Hamburg Germany poster; secondarily to HTAi

In progress:
• Application Of Oncology Outcomes Data Towards The Development And Validation Of Decision Analytical Models Across Europe And The United States ESMDM Oslo Workshop
• Validation of a Personalized Medicine Decision Model in Breast Cancer with Real World Data Preliminary Results ESMDM Oslo Poster

Planned:
• Validation of a Personalized Medicine Decision Model in Breast Cancer with Real World Data Final Results E ISPOR Berlin Poster
• Validation of a Personalized Medicine Decision Model in CML with Real World Data Final Results E ISPOR Berlin Poster
Planned Activities

• Continue role as scientific partner to Oncotyrol through three years of continued funding
• Serve on expert panel for development of HTA in oncology personalized medicine
• Develop AHRQ R21 grant proposal based on the breast cancer work
• Compare AT and UT CML registries, apply QoL and compare to NCCN and ELN guidelines
  • David Stenehjem NIH Loan Repayment Grant
  • Kimberly Morley fellowship
  • Grant submission
• Work with Utah Personalized Health Care Program to collaborate with UMIT and Oncotyrol on high visibility projects
### Planned Activities

- Work towards sharing tissue samples for development and validation of biomarkers in breast cancer (Myriad)
- Develop a real world database for application to prostate cancer decision analytical model
- Work with Austrian registry in NSCLC to compare and contrast with HCI NSCLC retrospective registry; consider decision analytical model
- Joint participation on ISPOR Task force for HTA in personalized medicine
Adverse Outcomes Following Substitution of Warfarin Products in Atrial Fibrillation Patients*

Ghate SR¹, Biskupiak JE¹, Ye X¹, Hagan M², Kwong WJ², Fox ES², Brixner DI¹

1. University of Utah College of Pharmacy, Salt Lake City, UT
2. Daichi Sankyo, Inc., Parsippany, NJ

*Annals of Pharmacotherapy 2011 Jun;45(6):701-12
Introduction

- Warfarin is effective anticoagulant for stroke prevention in atrial fibrillation (Afib) patients
  - Narrow therapeutic index
    - In the U.S. there is the brand Coumadin and 8 generic formulations available
      - FDA only requires bioequivalence with the brand product for generic approval
        - Variations in bioavailability and bioequivalence among generic formulations are unknown
        - Limited patient outcomes data available for substitution of 1 generic product for another
Objective

• Assess the risk of adverse outcomes following single or repeated substitution of warfarin formulations in patients with AF whose warfarin therapy may or may not be under close monitoring
Methodology

- **Datasource**
  - Medstat MarketScan
    - Insurance claims (medical and pharmacy)

- **Study population**
  - Adults with a diagnosis of Afib (ICD9 427.31)
    - 16 months continuous eligibility (4 months prior and 12 months after index AF diagnosis)
      - At least 3 warfarin prescriptions during the follow-up period
        - Patients with warfarin prescription during the pre-index period were excluded
First warfarin Rx within 30 days of AF index dx

30-day titration period

Second warfarin Rx

1 year follow-up period

End of follow-up period

Time

AF dx index date

Observation period to evaluate warfarin formulation switching patterns, and the risk of thrombotic and hemorrhagic events
Outcomes and Analysis

• Outcomes
  • Assessment of warfarin substitution patterns and first occurrence of adverse outcomes (GI bleed, IC bleed, PE, DVT and stroke)

• Analysis
  • Cox proportional hazard regression models
    • Control for baseline comorbidities and gender to estimate risk of having a thrombotic or hemorrhagic adverse outcome during periods of exposure to a single formulation and following a switch
### Table 2. Baseline Characteristics and Comorbidities*  

<table>
<thead>
<tr>
<th></th>
<th>Coumadin Only (n = 4,488)</th>
<th>Switchers (n = 12,996)</th>
<th>Only 1 Generic Warfarin Product (n = 20,292)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td></td>
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<tr>
<td>Age, y, mean (SD)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;65</td>
<td>1,376</td>
<td>30.8</td>
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</tr>
<tr>
<td>≥65</td>
<td>3,092</td>
<td>69.2</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
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<tr>
<td>female</td>
<td>1,867</td>
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<tr>
<td>male</td>
<td>2,621</td>
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<td>Plan type</td>
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<tr>
<td>fee for service</td>
<td>2,216</td>
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<tr>
<td>managed health plans</td>
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<td>unknown</td>
<td>172</td>
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<tr>
<td>Charlson comorbidity index</td>
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<tr>
<td>0</td>
<td>523</td>
<td>11.7</td>
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</tr>
<tr>
<td>1</td>
<td>812</td>
<td>18.2</td>
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<tr>
<td>2</td>
<td>1,216</td>
<td>27.2</td>
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<tr>
<td>≥3</td>
<td>1,917</td>
<td>42.9</td>
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</table>

*N = 37,756. Demographic and comorbid characteristics were presented by the 3 mutually exclusive patient groups regardless of the timing of adverse event. Patients were censored at the end of the 1-year follow-up period.

\*p < 0.01 vs Coumadin.

\*p < 0.05 vs Coumadin.

*Managed health plans included, for example, exclusive provider organization health maintenance organization, point of service, preferred provider organization (PPO), PPO with capitation, and consumer-driven health plan.
Forest Plot of Hazard Ratios for Thrombotic Events

- Warfarin DuPont/BMS to Generic
- Generic to Warfarin DuPont/BMS
- Generic to Generic
- One Generic only

Hazard Ratio

- Warfarin (DuPont/BMS) only (reference)
  - Hazard Ratio: 1.51
  - 95% CI: 1.17, 1.93

- Generic to Warfarin DuPont/BMS
  - Hazard Ratio: 1.60
  - 95% CI: 1.23, 2.10

- Generic to Generic
  - Hazard Ratio: 1.74
  - 95% CI: 1.45, 2.11

- One Generic only
  - Hazard Ratio: 1.04
  - 95% CI: 0.88, 1.22
Limitations

- Insurance claims data
  - Cannot rule out other causes of increased risks of adverse outcomes observed in this study
  - Medical records and INR values were not available
  - Level of uncertainty regarding attributing adverse outcomes using diagnosis codes to warfarin therapy, level of anticoagulation or a formulation switching event
Conclusions

• Generic warfarin utilization and switching between formulations are common among patients with Afib.
• Switching warfarin formulations may expose patients with Afib to higher risk of thrombotic and hemorrhagic events.
• Risk-benefit balance of anticoagulation therapy may require maintaining patients on a product with consistent bioavailability.
• Future studies are needed to determine if product standardization, bioavailability and bioequivalence are the problem or if poor patient-physician communication and medication compliance (i.e., fractionated systems of care) are the underlying culprit.
Figure 2. Illustration of five hypothetical generic formulations with their 90% Confidence Intervals (CI) for AUC and Cmax. The 90% CIs must fall within 80%-125% of the brand name drug (100%). Product #1 fails the criteria because the AUC 90% CI falls outside the limits. Product #2 meets the criteria and is quite comparable to the brand name product. Products #3 and #4 would also be approved, but are near the limits of the 80%-125% range and are statistically dissimilar to each other. Product #5, while fulfilling the criteria, is more variable than the other formulations.

Other Contributing Factors?

- In commentary, Haines indicates source of safety issues associated with generic warfarin substitution not likely to be entirely attributed to bioavailability issues.

- Follow-up commentary: Identifying other possible contributing factors to safety issues surrounding generic substitution based on pharmaceutical delivery systems in U.S. and Germany.
  - U.S. pharmacies – in order to get lowest price from their drug wholesalers, pharmacies participate in program that require them to accept the wholesaler’s choice of manufacturing for fulfilling an order.
  - German pharmacies – mandatory substitution is required with the lowest price generic available.

NEW HCV INITIATIVES
New HCV Medications

• Victrelis (boceprevir; Merck)
• Incivek (telaprevir; Vertex)
  • Where there is confusion, there is opportunity! (David Nash)
• Potential projects
  • Merck – incorporate US VA data into their model (Conference call scheduled Feb 2\textsuperscript{nd})
  • Abbott – HCV model development (Initial proposal submitted to them Dec 2011)
  • BMS – recent NEJM 2012;366:216
    • Two new agents in Phase 2 development: daclatasvir and asunaprevir
• HCV protease inhibitor for the treatment of CHC genotype 1 infection in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have failed previous interferon and ribavirin therapy
  • FDA approval – May 2011
  • EMA approval – Aug 2011 (boceprevir) and Sept 2011 (telaprevir)
HCV genotype 1 patient sub-populations studied in RCTs

- Three main factors to consider
  - Histology (cirrhotic vs. non-cirrhotic)
  - Previous treatment (treatment naïve vs. previous treatment)
    - Previous treatment success (partial responder vs. non-responder vs. relapse)
  - This would result in 8 patient sub-groups
- If race / ethnicity added to the mix
  - Black vs. non-black patients
    - A total of 16 patient sub-groups
Response-Guided Therapy

• RCTs were not powered to detect differences in all the various sub-groups
• HCV RNA testing for RGT
  • Treatment duration and early stopping rules
    • Boceprevir: HCV RNA levels at weeks 8, 12 and 24
    • Telaprevir: HCV RNA levels at weeks 4, 12 and 24
Boceprevir

<table>
<thead>
<tr>
<th>Previously untreated patients</th>
<th>HCV RNA levels</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TW8</td>
<td>Undetectable</td>
<td>Complete three-medicine regimen at TW28</td>
</tr>
<tr>
<td>TW24</td>
<td>Undetectable</td>
<td>Continue and finish three-medicine regimen at TW36 and then continue and finish peginterferon/ribavirin to TW48</td>
</tr>
<tr>
<td>Detectable</td>
<td>Undetectable</td>
<td>Complete three-medicine regimen at TW36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous partial responders or relapsers</th>
<th>HCV RNA levels</th>
<th>Recommendation</th>
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<tr>
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<td>Undetectable</td>
<td>Complete three-medicine regimen at TW36</td>
</tr>
</tbody>
</table>

**Treatment futility:**
- If HCV RNA levels \(\geq 100\) IU.mL at TW12, discontinue three-medicine regimen
- If HCV RNA levels detectable at TW24, discontinue three-medicine regimen

Boceprevir Product Information: Extracted from Table 1. Merck, 2011
## Telaprevir

### Treatment Naïve and Prior Relapse Patients

<table>
<thead>
<tr>
<th>HCV RNA levels</th>
<th>Triple therapy</th>
<th>Dual therapy</th>
<th>Total treatment duration</th>
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<tbody>
<tr>
<td>Undetectable at weeks 4 and 12</td>
<td>First 12 weeks</td>
<td>Additional 12 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Detectable at weeks 4 and 12</td>
<td>First 12 weeks</td>
<td>Additional 36 weeks</td>
<td>48 weeks</td>
</tr>
</tbody>
</table>

### Prior Partial and Null Responder Patients

All patients

| First 12 weeks | Additional 36 weeks | 48 weeks |

### Treatment Futility Rules: All Patients

<table>
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<tr>
<th>HCV RNA levels</th>
<th>Action</th>
</tr>
</thead>
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<tr>
<td>Week 4 or Week 12: Greater than 1000 IU/mL</td>
<td>Discontinue triple therapy at 12 weeks</td>
</tr>
<tr>
<td>Week 24: Detectable</td>
<td>Discontinue dual therapy</td>
</tr>
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</table>

*Telaprevir Product Information: Extracted from Tables 1 and 2. Vertex, 2011*