To Test or Not to Test
A Journal Club Discussion on the COAG Trial

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Nothing to disclose relevant to this presentation

Learning Objectives
- Describe the recent journal article entitled Clarification of Optimal Anticoagulation through Genetics, comparing a protocol-based versus genotype-based dosing for warfarin.
- Discuss the results of the COAG trial and its potential impact on clinical practice.
Warfarin: A Case for Genetic Testing?

- Warfarin complexity and interindividual variability is well known
  - Narrow therapeutic window
  - Myriad drug/herbal interactions, disease state interactions
  - Lifestyle influences (alcohol use, smoking, exercise)
  - Genotype variations (CYP2C9*2, CYP2C9*3, VKORC1)

- FDA involvement
  - 55% warfarin dose variability based on age, height, body weight, interacting drugs, indication and VKORC1/CYP2C9 genotypes
  - In 2007, prescribing information (PI) states “Consider lower initial doses in patients with genetic variations in CYP2C9 and VKORC1 enzymes”
  - The 2010 PI revision states “Maintenance dose can be influenced by genetic factors (CYP2C9 and VKORC1 genotypes)”
    - If genotype is known, can assist in selection of starting dose
    - PI contains a table of expected therapeutic range of warfarin doses based on CYP2C9 and VKORC1 genotypes

Barriers to Genetic Testing in Clinical Practice

- Lack of consensus backing
  - American College of Chest Physicians Evidence-based Guidelines: For patients initiating VKA therapy, recommend against the routine use of pharmacogenetic testing for guiding doses of VKA – Grade 1B
  - American College of Medical Genetics: […] routine use of warfarin genotyping is not endorsed by this work group at this time, in certain situations, […] testing may be useful, and warranted, in determining the cause of unusual therapeutic responses to warfarin therapy

- Centers for Medicare and Medicaid Services (2009)
  - Available evidence does not demonstrate that pharmacogenomic testing to predict warfarin responsiveness improves health outcomes
  - Coverage limited to
    - have not been previously tested for CYP2C9 or VKORC1 alleles; and
    - have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered; and
    - are enrolled in a prospective, randomized, controlled clinical study (based on criteria)

COAG Trial: Rationale and Objective

- Identification of a “likely-to-respond” dose at the onset of warfarin therapy could decrease tendency of trial-and-error dosing (sub-therapeutic levels or sequelae of over-anticoagulation)
- Rigorous clinical trials are needed to vet out the role, if any, of genotype-type testing to guide warfarin therapy
- Clarification of Optimal Anticoagulation through Genetics (COAG Trial)
- Objective:
  - Compare two different warfarin dosing strategies: genotype-guided versus clinically-based
  - Strategy implemented in the first 5 days of warfarin treatment initiation
COAG Trial Methods: Inclusion Criteria

- Randomized, multi-center (12 sites), double-blind, U.S.-based trial
- Eligible patients:
  - Need for long-term anticoagulation for various indications
  - Clinical and genotype-data collected for all patients
  - Minimum three month follow-up; up to six months

  Inclusion Criteria
  - Age ≥ 18 years
  - Informed consent
  - Able to be followed in outpatient AC clinic
  - Target INR 2-3
  - Expected duration of warfarin therapy of at least 3 months
  - Inpatient and outpatient clinicians adhere to dosing algorithms and titration regimen within study protocol for AC management
  - Concomitant anti-platelet therapy and bridging anticoagulant therapy permitted

COAG Trial Methods: Exclusion Criteria

- Current or prior warfarin therapy (even 1 dose before enrollment)
- Genotype already known
- Potential complication or interference with therapy
  - Liver disease, Antiphospholipid antibody
  - Contraindication
  - Low life expectancy
  - Pregnancy
  - Non-adherent to follow-up
  - Any factors likely to limit adherence to warfarin
  - Cognitive or other causes of inability to provide informed consent or follow study procedures
  - Participating in another trial that prohibits participation in the COAG trial or planned enrollment in such a trial within the first 6 months of warfarin therapy
  - Requiring blood transfusions within 48 hours prior to randomization
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  - Requiring blood transfusions within 48 hours prior to randomization

COAG Trial Methods: Randomization, Blinding, and Dosing

- Randomization
  - 1:1 ratio assignment of clinical versus genetic-guided dosing strategy
  - Genotyping for CYP2C9 and VKORC1 done at each clinical site immediately after blood sample collection
  - Self-reported: African American or non-African American

- Blinding
  - Double-blind for the first 4 weeks
  - After the 5-day initiation period, clinicians aware of dose change (% ↑ or ↓)
  - After 4 weeks, clinicians were informed of the actual dose; unblinded warfarin therapy thereafter

- Dosing
  - 1st dose: Not based on genetic results in 55% of patients in genotype-arm
  - 2nd and 3rd dose: Genetic-based and clinical-variable based algorithm calculations
  - 4th and 5th dose: Dose revision algorithm employed for titration (up or down)
Primary and Secondary Outcomes

- **Primary**
  - Percentage of time in therapeutic range from Day 4 or 5 until Day 28
    - In all patients
    - In sub-group of patients with absolute difference of ≥1 mg in predicted initial daily dose between the two algorithms
- **Secondary**
  - Composite outcome of any INR ≥4, major bleeding or thromboembolism in the first 4 weeks
  - Time to first therapeutic INR
  - Time to determination of a maintenance dose (first of consecutive two INRs at least 1 week apart in the therapeutic range w/o dose change)
  - Time to an adverse event (death from any cause, major bleeding, thromboembolism, clinically relevant nonmajor bleeding)

Sample size and Power Estimations

- **Targeted >80% power with estimated sample size 1,022 patients**
  - Powered to detect a between-group difference of 5.5% with type I error rate = 0.04 among all patients
  - 9% difference in co-primary subgroup with type I error rate of 0.01
- **However, analytic sample = 955 patients**
  - Withdrawal of 60 patients (30 in each group) before completion of intervention period

Study Flow

- Baseline characteristics comparable between the two arms, especially for those variables incorporated in calculating the dose within each algorithm.
- Age, African American race, Diabetes, Current smoker, Stroke, Meds-8, Amiodarone and/or Fluvastatin use.
Results: Distribution of Time in the Therapeutic Range

- No significant difference in %TTR at 4 weeks
  - 45.2% Genotype-guided arm
  - 44.5% Clinically-guided arm
  - \( P = 0.91 \)
- No difference in co-primary analysis subset
- Among African Americans, mean %TTR less in the genotype group versus clinical group (35.2% vs. 43.5%; \( p = 0.01 \))
- Among non-African Americans, %TTR slightly greater in genotype group (48.8% vs. 46.1%; \( p = 0.15 \))

Results: Range of INRs during the 4-Week Study

- No significant difference above or below mean %TTR
- Better prediction of maintenance dose in non-African Americans in genotype group
- No significant differences in adverse events
- African American patients in the genotype group tended towards INR above therapeutic range
- African American patients in genotype-guided group reached first therapeutic INR later than those in clinical group

COAG Trial Results: Adverse Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Genotype Guided Group (N=100)</th>
<th>Clinically Guided Group (N=100)</th>
<th>Hazard Ratio (HR)( ^* )</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any INR-related major bleeding</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>1.00 (0.49-2.13)</td>
<td>0.98</td>
</tr>
<tr>
<td>Any INR event</td>
<td>4 (4)</td>
<td>4 (4)</td>
<td>1.00 (0.53-1.97)</td>
<td>0.98</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>4 (4)</td>
<td>4 (4)</td>
<td>1.00 (0.50-1.94)</td>
<td>0.98</td>
</tr>
<tr>
<td>Thrombembolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical-related major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>3.00 (0.19-43.21)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

\* Hazard ratio is for the comparison between the genotype-guided arm and the clinically-guided dose group.

\( ^* \) The composite was the clinical outcome outcome.

\( ^\dagger \) The INR at the time of the bleeding event was available for all but one patient (the clinically-guided group). The rate of major bleeding (c) in the genotype-guided group is compared with the rate in the clinically-guided group.

\( ^\ddagger \) The time to first major bleeding event was similar in the genotype-guided and clinically-guided groups. The rate of major bleeding (c) in the genotype-guided group is compared with the rate in the clinically-guided group.
COAG Trial: Discussion and Conclusion

- No benefit of using genotype information to guide warfarin dosing
- Notable difference seen between African American versus non-African American patients
- The trial only addressed the first 4 weeks of therapy
- Would longer duration of genotype-guided therapy improve INR targets?
  - GIFT trial with warfarin in VTE (ongoing)
- Not powered to detect clinical outcomes: rate of bleeding and thrombotic endpoints

EU-PACT Trial: Notable Differences

- European study conducted in UK, Netherlands, Germany, Greece, Austria, and Sweden
- Indications: Atrial fibrillation or venous thromboembolism
- Single-blinded, randomized, clinical trial; 427 patients
- Dosing:
  - Genotype arm: according to algorithm
  - Clinical arm: Fixed dose (<75 years of age – 10 mg, 5 mg, 5 mg [Day 1, 2, 3])
  - (>75 years of age – 5 mg on Days 1, 2, 3)
- Trial Duration: 12 weeks

EU-PACT Trial Results

- Unadjusted %TTR
  - Genotype-group: 67.4%
  - Fixed-dose: 60.3%
  - P<0.001
- Per-protocol analysis
  - 68.9% vs. 62.3%; (p=0.001)
- Difference in mean %TTR noted at week 1 through week 8, but not weeks 9-12
EU-PACT Results

- Time to reach therapeutic INR
  - 21 vs. 29 days (p=0.001)
- Time to reach stable dose
  - 44 vs. 59 days (p=0.003)
- INR >4
  - 27% vs. 37%
- Adverse events not statistically significant

EU-PACT Discussion and Conclusion

- In the European population studied, genotype information positively affected %TTR, time to reach therapeutic INR, and time to achieve a stable dose vs. the fixed dose regimen
- Longer duration than COAG trial
- Limitation noted that clinical outcomes were not assessed
- Conclusion: Genotype-based dosing is superior

FDA Perspective

- Editorial summarizing the information published
- Cited EU-PACT’s fixed dose strategy as “usual care”
- Included an additional EU trial by Verhoef, et al,
  - Genotype and clinical algorithms for dosing acenocoumarol and phenprocoumon in European patients for 12 weeks → NS for %TTR
- Addition of genetic variables to clinical algorithm unlikely to show difference
- Frequent INR checks leading to dose adjustments may have influenced results
- Highlighted less number of bleeding events in genotype groups across all three trials, although bleeding events were generally low in both groups
- Called for studies with methods focused on internal validity, generalizability, and clinical uptake in real world settings
Conclusion

- Use of genetic information to determine course of treatment is part of clinical practice today
- Whether genotype information adds benefit to current practice is debatable
- Experts recommend use of dosing nomograms (e.g., warfarindosing.org) versus trial and error or fixed-dose regimen
- Effect of genotype information on relevant clinical outcomes such as thrombotic events and bleeding endpoints will likely tip the scale towards increased use of pharmacogenetics in the management of warfarin therapy

THANK YOU!