CYP2C19-Proton Pump Inhibitors

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Objectives: *CYP2C19*-PPI Implementation

- Review the pharmacogenetics of PPIs
- Discuss the relationships between PPI pharmacokinetics, intragastric pH, clinical outcomes, and *CYP2C19* genotype
- Consider the medication safety implications for PPI prescribing based on *CYP2C19* genotype
Proton Pump Inhibitor Classification

- First Generation
  - Omeprazole
  - Pantoprazole
  - Lansoprazole

- Second Generation
  - Esomeprazole
  - Rabeprazole
  - Dexlansoprazole
PPIs are metabolized by **CYP2C19**

(rabeprazole to a lesser extent)

Rationale for Implementation: All PPIs are designated CPIC Level B

Gene(s)/drug(s)

- Gene already subject to CPIC guideline
  - Actionable in other professional society guidelines
  - Nominated by CPIC member or recommended by external group (e.g. FDA, EMA)
- Gene not yet subject to CPIC guideline
  - PharmGKB Annotation level 1A, 1B, 2A or 2B
  - Mentioned in professional society guidelines but not actionable

Evaluating alternatives, evidence

- CPIC level A or B: Prescribing action recommended; alternative therapies or dosing are highly likely to be effective and safe
- CPIC level C: No prescribing change based on genetics; alternatives are unclear or evidence is weak but testing is common or gene is CPIC level A or B for other drugs
- CPIC level D: PharmGKB annotation only; no prescribing action recommended; alternatives unclear or evidence is weak; testing is rare

www.cpicpgx.org/
# Dutch Pharmacogenetics Working Group Recommendations for CYP2C19-PPIs

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Prescribing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Omeprazole</strong></td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>No therapeutic recommendation</td>
</tr>
<tr>
<td>IM</td>
<td>No therapeutic recommendation</td>
</tr>
</tbody>
</table>
| UM        | *H. pylori*: ↑ dose by 100-200%  
            | Other: Consider dose ↑ by 100-200% |
| **Pantoprazole** |                          |
| PM        | No therapeutic recommendation |
| IM        | No therapeutic recommendation |
| UM        | *H. pylori*: ↑ dose by 400%   
            | Other: Consider dose ↑ by 400% |

Dutch Pharmacogenetics Working Group
Recommendations for *CYP2C19*-PPIs

<table>
<thead>
<tr>
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<tr>
<td><strong>Lansoprazole</strong></td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>No therapeutic recommendation</td>
</tr>
<tr>
<td>IM</td>
<td>No therapeutic recommendation</td>
</tr>
</tbody>
</table>
| UM | *H. pylori:* ↑ dose by 200%  
   Other: Consider dose ↑ by 200% |
| **Esomeprazole** | |
| PM | No therapeutic recommendation |
| IM | No therapeutic recommendation |
| UM | *H. pylori:* ↑ dose by 50-100%  
   Other: Consider dose ↑ by 50-100% |

Dutch Pharmacogenetics Working Group Recommendations for *CYP2C19*-PPIs

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<tr>
<td><strong>Rabeprazole</strong></td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>No therapeutic recommendation</td>
</tr>
<tr>
<td>IM</td>
<td>No therapeutic recommendation</td>
</tr>
<tr>
<td>UM</td>
<td>No Therapeutic recommendation</td>
</tr>
<tr>
<td><strong>Dexlansoprazole (not addressed in guidelines)</strong></td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>N/A</td>
</tr>
<tr>
<td>IM</td>
<td>N/A</td>
</tr>
<tr>
<td>UM</td>
<td>N/A</td>
</tr>
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</table>

1. RELATING PPI PHARMACODYNAMICS TO CLINICAL OUTCOMES
Increasing intragastric pH to at least 3 for 18 hours a day for 4 weeks is necessary for duodenal ulcer healing.

Contour plots for the predicted relationship between duodenal ulcer healing and acid suppression at 2 (A), 4 (B), and 8 (C) weeks of therapy.

Correlation between the healing rate of erosive esophagitis at 8 weeks and the duration (hr) that intragastric pH is maintained > 4.0

Fig. 1. Relationship between the healing of erosive oesophagitis at 8 weeks and the duration, in hours, out of the 24-hour period, that the intragastric acidity is raised above pH 4.0.


$r = 0.87$ (p < 0.05)
2. CYP2C19 GENOTYPE IS ASSOCIATED WITH SYSTEMIC EXPOSURE
CYP2C19 UM (*17/*17) phenotype associated with lower mean plasma **lansoprazole** concentrations vs. NM (*1/*1)

*17*17: Mean $C_{\text{plasma}}$ 70% lower

*2*2: Mean $C_{\text{plasma}}$ 6.9-fold higher

$p<0.05$, **$p<0.01$
Mean plasma concentrations of omeprazole are significantly lower in CYP2C19 UMs vs. NMs

Plasma concentrations of omeprazole are lower in CYP2C19 NMs compared to IM and PMs.

Mean AUC value in PMs ~13x higher than NM group.

2. *CYP2C19* GENOTYPE IS ASSOCIATED WITH PPI SYSTEMIC EXPOSURE

- **CYP2C19 No Function Allele**
- **CYP2C19 *17 allele**

PPI AUC

References:
3. **CYP2C19 GENOTYPE IS ASSOCIATED WITH INTRAGASTRIC PH VARIABILITY**
Positive correlation between mean intragastric pH and omeprazole AUC

Single dose study of omeprazole 20 mg daily in healthy volunteers

CYP2C19*17 allele carriers with GERD spent more time with esophageal pH < 4 (undesirable outcome)

Retrospective cohort of 74 children who were refractory to PPI therapy

4. RELATING CYP2C19 PHENOTYPE TO CLINICAL OUTCOMES
CYP2C19 NM were at higher risk of being refractory to PPI therapy for erosive esophagitis.
Healing rate of **erosive esophagitis** was significantly lower in NMs compared to PMs after 8 weeks of **LAN** 30 mg daily.

Healing rate (%) by endoscopy after 8 weeks of treatment:

- Total: 89.8% (n=88)
- Homo-EMs: 77.4% (n=31)
- Hetero-EMs: 95.0% (n=40)
- PMs: 100% (n=17)

Treatment dose = **LAN** 30 mg daily x 8 weeks.


CYP2C19 phenotype associated with endoscopic and symptomatic relapse of erosive esophagitis during maintenance therapy with LAN 15 mg daily

Symptomatic recurrence of erosive esophagitis during maintenance therapy with LAN 15 mg/d occurred within 2-4 weeks after step-down of daily dose
4. RELATING CYP2C19 PHENOTYPE TO CLINICAL OUTCOMES

1. CYP2C19 NMNs at increased risk of refractoriness to PPIs for erosive esophagitis treatment
2. CYP2C19 phenotype associated with endoscopic and symptomatic relapse of erosive esophagitis during maintenance therapy with Lansoprazole 15 mg daily
Overview of the safety of PPIs

- Short-term side effects include: HA, diarrhea, nausea
  - Class effect
  - Incidence rates from 1 – 3%
- Safety concerns with long-term PPI use
  - Pulmonary: pneumonia, upper respiratory tract infections
  - GI: *Clostridium difficile*-associated diarrhea
  - Skeletal: osteoporosis, hip and vertebral fracture
  - Neuro: visual disturbances
  - Renal: Interstitial nephritis

5. PPI USE AND RESPIRATORY TRACT INFECTIONS
PPIs-Pneumonia: Proposed Mechanism

↑ intragastric pH

Bacterial colonization of stomach

Pulmonary micro-aspiration

Lung colonization

↑ susceptibility to respiratory tract infections

PPI administration

PPI use associated with increased risk of community-acquired pneumonia in adult patients

Studies: 6 case-control studies

Increased risk of CAP associated with newly prescribed PPIs


Figure 3. Forrest plot evaluating the association between proton pump inhibitor use and risk of community-acquired pneumonia in subgroup analysis.

### 1.2.3 Risk of community acquired pneumonia in newly prescribed proton pump inhibitor users

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laheij et al 2004</td>
<td>0.80647586 (0.23302802 - 3.00)</td>
<td>2004</td>
</tr>
<tr>
<td>Gulmez et al 2007</td>
<td>0.83290912 (0.32558507 - 2.00)</td>
<td>2007</td>
</tr>
<tr>
<td>Sarkar et al 2008</td>
<td>0.89609902 (0.09409576 - 5.10)</td>
<td>2008</td>
</tr>
<tr>
<td>Rodriguez et al 2009</td>
<td>0.19062036 (0.15151544 - 4.20)</td>
<td>2009</td>
</tr>
<tr>
<td>Euirch et al 2010</td>
<td>0.60431597 (0.1985052 - 3.40)</td>
<td>2010</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>17.7% (1.92 [1.40, 2.63])</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 16.25$, df = 4 ($P = 0.003$); $I^2 = 75$

Test for overall effect: $Z = 4.04$ ($P < 0.0001$)

### 1.2.4 Risk of community acquired pneumonia in chronic users of proton pump inhibitor therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laheij et al 2004</td>
<td>0.41871033 (0.20882691 - 3.30)</td>
<td>2004</td>
</tr>
<tr>
<td>Gulmez et al 2007</td>
<td>0.26236426 (0.03932415 - 5.80)</td>
<td>2007</td>
</tr>
<tr>
<td>Sarkar et al 2008</td>
<td>-0.09431068 (0.03670777 - 5.80)</td>
<td>2008</td>
</tr>
<tr>
<td>Rodriguez et al 2009</td>
<td>0.04879016 (0.07760494 - 5.40)</td>
<td>2009</td>
</tr>
<tr>
<td>Euirch et al 2010</td>
<td>-0.05129329 (0.27557733 - 2.50)</td>
<td>2010</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>22.7% (1.11 [0.90, 1.38])</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 47.00$, df = 4 ($P < 0.00001$); $I^2 = 91$

Test for overall effect: $Z = 0.98$ ($P = 0.33$)

**Newly prescribed:** < 30 days

**Chronic user:** ≥ 30 days
Highest risk of CAP occurs within 7 days of starting PPI therapy

Temporal relationship between start of PPI use and CAP risk

**Figure.** Association between current use of proton pump inhibitors (PPIs) and community-acquired pneumonia, according to the timing of first PPI prescription. ORs indicates odds ratios.

Use of acid-suppressive medication was associated with increased risk of hospital-acquired pneumonia in non-ventilated patients.

Primary outcome: hospital-acquired PNA (defined by ICD-9 codes) for bacterial PNA listed as a secondary discharge diagnosis.

Addition of LAN to existing asthma therapy did not improve symptoms, but was associated with higher incidence of respiratory adverse events compared to placebo.

**Design**: randomized, placebo-controlled clinical trial that compared LAN with placebo in children with poor asthma control who were receiving inhaled corticosteroid treatment.

**Table 4. Adverse Events**

<table>
<thead>
<tr>
<th>Treatment Group, No. (%)</th>
<th>Placebo (n=150)</th>
<th>Lansoprazole (n=147)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>74 (49)</td>
<td>93 (63)</td>
<td>1.3 (1.1-1.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Sore throat</td>
<td>59 (39)</td>
<td>77 (52)</td>
<td>1.3 (1.0-1.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Group A Streptococcus</td>
<td>11 (7)</td>
<td>6 (4)</td>
<td>0.8 (0.5-1.1)</td>
<td>.23</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3 (2)</td>
<td>10 (7)</td>
<td>2.2 (0.8-6.1)</td>
<td>.04</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (3)</td>
<td>4 (3)</td>
<td>0.9 (0.5-1.6)</td>
<td>.76</td>
</tr>
<tr>
<td>Otitis media</td>
<td>10 (7)</td>
<td>12 (8)</td>
<td>1.1 (0.7-1.8)</td>
<td>.62</td>
</tr>
<tr>
<td>Acute sinusitis</td>
<td>17 (11)</td>
<td>16 (11)</td>
<td>1.0 (0.7-1.4)</td>
<td>.90</td>
</tr>
</tbody>
</table>

*By Mantel-Haenszel test.*

Association of *CYP2C19* polymorphisms and lansoprazole-associated respiratory adverse effects

**Design**

**Objective**
- Determine whether *CYP2C19* genotype associates with lansoprazole-associated adverse event frequency

**Patients (n = 279; pediatrics)**
- Poor asthma control while on inhaled corticosteroids
- Drug therapy: 1) placebo or 2) LAN (weight-based) x24 weeks
- Research staff conducted structured interviews using a questionnaire to determine the presence of: upper respiratory tract infections, ST, strep throat, bronchitis, PNA, ear infection, and acute sinusitis

CYP2C19 PM+IM, but not NM phenotype was associated with increased risk of upper respiratory tract infections

Mean ± SD plasma concentrations of LAN 30 mg/d were higher in PM+IMs (n = 23) compared with NMs (n = 33)
- PM+IM: 207 ± 179 ng/mL
- NM: 132 ± 141 ng/mL
6. PPI USE AND SKELETAL DISORDERS
Stroke patients who used PPIs had a higher incidence of osteoporosis, hip fracture, and vertebral fracture compared with those who did not use PPIs.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Omeprazole</th>
<th>Lansoprazole</th>
<th>Pantoprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal ulcer</td>
<td>20 mg daily x 4 weeks</td>
<td>15 mg daily x 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>40 mg daily x 4-8 weeks</td>
<td>30 mg daily x 8 weeks</td>
<td></td>
</tr>
<tr>
<td>GERD (symptomatic)</td>
<td>20 mg daily x 4 weeks</td>
<td>15 mg daily x 8 weeks</td>
<td></td>
</tr>
<tr>
<td>Pediatric (1-16 YOA)</td>
<td>5-&lt;10 kg: 5 mg daily x 4 w</td>
<td>&lt; 30 kg: 15 mg daily x12 w</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-&lt;20 kg: 10 mg daily x 4w</td>
<td>10-&lt;30 kg: 30 mg daily x12 w</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 20 kg: 20 mg daily x 4 w</td>
<td>&gt; 30 kg: 30 mg daily x12 w</td>
<td></td>
</tr>
<tr>
<td>Erosive esophagitis</td>
<td>20 mg daily x 4-8 weeks</td>
<td>30 mg daily x 8 weeks</td>
<td>40 mg daily x 8 weeks</td>
</tr>
<tr>
<td>Pediatric (1-16 YOA)</td>
<td>5-&lt;10 kg: 5 mg daily x 4-8 w</td>
<td>&lt; 30 kg: 15 mg daily x12 w</td>
<td>15-&lt;40 kg: 20 mg daily x8 w</td>
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<td>10-&lt;20 kg: 10 mg daily x 4-8 w</td>
<td>10-&lt;30 kg: 30 mg daily x12 w</td>
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<td>&gt; 30 kg: 30 mg daily x12 w</td>
<td>&gt; 40 kg: 40 mg daily x8 w</td>
</tr>
<tr>
<td>Maintenance of healing of erosive esophagitis</td>
<td>20 mg daily</td>
<td>15 mg daily</td>
<td>40 mg daily</td>
</tr>
<tr>
<td>Pediatric (1-16 YOA)</td>
<td>5-&lt;10 kg: 5 mg daily</td>
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**CYP2C19-PPIs: Conclusions**

- **CYP2C19 genotype** is associated with PPI systemic exposure.
- **CYP2C19 RM/UM phenotypes** are associated with undesirable pH outcomes.
- **CYP2C19 NM phenotype** is associated with lower healing rates of erosive esophagitis vs. PM phenotype.
- There may be medication safety implications for **CYP2C19 phenotype-guided PPI prescribing**.
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