Why then, can one desire too much of a good thing?  
William Shakespeare, ‘As You Like It’

The proton pump inhibitors (PPIs) are potent inhibitors of gastric acid production. Omeprazole was the first PPI introduced. Subsequently, lansoprazole, pantoprazole, rabeprazole and the 5-enantiomer of omeprazole became available. As they suppress acid more efficaciously than H2-receptor antagonists, they are now widely used for the treatment of conditions such as peptic ulcer disease,1,2 gastro-oesophageal reflux disease (GERD),3 nonsteroidal anti-inflammatory drug (NSAID)-induced gastrointestinal lesions,4, 5 Zollinger-Ellison syndrome, dyspepsia and, together with two antibiotics, eradication of Helicobacter pylori infection.6

PPIs are more expensive than H2-receptor antagonists; the current difference in price is about 10-fold. Therefore, cost-effectiveness could be an issue. While PPIs are superior to H2-receptor antagonists in the resolution of symptoms and healing of ulceration,7 there are not much significant differences among different PPIs.7, 8 In high risk patients with peptic disease, e.g. a patient with fresh melaena, PPI given intravenously has been shown to be effective in downstaging the endoscopic lesion and decreasing the need for endoscopic intervention.9 Intravenous PPI reduces rebleeding and mortality after endoscopic treatment.9 Complicated peptic diseases should also be treated with a course of PPI for 6-8 weeks. In uncomplicated helicobacter-negative peptic disease, an H2-receptor antagonist may suffice, with PPI as second line treatment if the ulcer fails to heal after 8 weeks. PPI is also used for the prevention of gastrointestinal bleeding in patients on long term NSAIDs and aspirin (table 1).1, 2

In general, PPIs are very well tolerated. Side-effects are uncommon and usually minor. However, there are recent concerns about osteoporotic fractures, susceptibility to infections and interaction with clopidogrel diminishing its antiplatelet effect.

The suppression of gastric acid by a PPI can be up to 99%. While this facilitates the healing of ulcers and reduces the pain due to acid in the stomach or oesophagus, the lack of gastric acid, hypochlorhydria, may affect the digestion of proteins and the absorption of vitamin B12 and calcium. It is also thought that insufficient acid may lead to bacterial overgrowth and increase the risk of pneumonia.10 Therefore, it has been suggested that patients at high risk of pneumonia should be prescribed PPI only when necessary and at a lower dose.11 Similarly, prolonged treatment with a PPI may increase the risk of Clostridium difficile infection substantially.12

| Table 1A. Patients at increased risk of gastrointestinal toxicity due to NSAID |

<table>
<thead>
<tr>
<th>High risk</th>
<th>Moderate risk (1-2 risk factors)</th>
<th>Low risk</th>
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</thead>
<tbody>
<tr>
<td>1. History of a previously complicated ulcer, especially recent</td>
<td>1. No risk factors</td>
<td>1. Age &gt;65 years</td>
</tr>
<tr>
<td>2. Multiple (&gt;2) risk factors</td>
<td>2. High dose NSAID therapy</td>
<td>H. Pylori is an independent and additive risk factor and should be addressed separately.</td>
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<tr>
<td>3. A previous history of uncomplicated ulcer</td>
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<td>4. Concurrent use of aspirin (including low dose), corticosteroids or anticoagulants</td>
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Adapted from American College of Gastroenterology Guidelines for prevention of NSAID-related ulcer complications9

There are also concerns that prolonged use of PPIs might cause osteoporosis and increase the risk of fractures of the hip, wrist, and spine. In a study of 135,000 people aged 50 or above, those taking high doses of PPI for longer than a year were 2.6 times more likely to have sustained a hip fracture.13 The risk of a fracture increases with dose and duration. The precise reasons for this are unclear, but it is thought that a rise in pH may reduce the solubility of calcium and consequently its absorption. The Food and Drugs Administration of the United States has requested a change in the drug labelling to include the possible increased risk of fractures.14
The interaction of PPI with clopidogrel has come under the spotlight recently. Clopidogrel is an antiplatelet agent that has a marginally superior cardiovascular outcome and better gastrointestinal side-effect profile compared to aspirin.  Thus it is used together with aspirin in acute coronary syndrome and after percutaneous coronary intervention. Clopidogrel is inactive and requires metabolism by cytochrome P450 enzymes to achieve its therapeutic effect. People with a variant in CYP2C19 metabolise clopidogrel poorly and therefore the antiplatelet effect is diminished. In Hong Kong, about 18% of the population are poor metabolisers in this respect. Patients on long term clopidogrel, especially those also taking aspirin, may require an acid suppressing agent. In this situation, a PPI could be hazardous as it might block the metabolism of clopidogrel into its active form. This can lead to an increase in the risk of myocardial infarction. Whereas similar findings were observed only in retrospective studies, other post hoc analyses, prospective studies and a randomised controlled trial revealed no increase in major cardiac events related to cotherapy. In the face of conflicting evidence, the current recommendation is not to use PPI in a patient on clopidogrel unless it is essential to do so. If PPI is indicated, then a PPI with a lower likelihood of interaction should be considered, as the potential for interactions among these agents varies. Omeprazole and esomeprazole are metabolised mainly via CYP2C19 and therefore have the highest potential for interaction. Rabeprazole is also metabolised via this isoenzyme, but possesses significant affinity for CYP3A4 resulting in fewer clinically significant interactions. Pantoprazole, on the other hand, is primarily metabolised via CYP2C19 O-demethylation rapidly followed by sulfate conjugation. As a result, pantoprazole has the lowest potential for P450 metabolism and drug-drug interaction and should be the preferred PPI for patients on clopidogrel. Ticagrelor and prasugrel, two new antiplatelet drugs, do not require metabolism to be active and may have an advantage over clopidogrel if they are proven to be clinically as effective.

Like all drugs classified as poisons, PPIs carry risks as well as benefits. In the United States, they are the third best-selling class of drugs, suggesting a large degree of overprescribing. The appropriate use of PPIs should be promoted. This would include using alternative drugs for dyspepsia and uncomplicated peptic ulcer disease, and limiting the duration of PPI treatment.

References