ABSTRACT
Proton pump inhibitors (PPIs) are routinely prescribed for acid peptic diseases (APDs). They are also used in intensive care units as a prophylaxis against aspiration pneumonia. PPIs are often coprescribed with nonsteroidal anti-inflammatory drugs and antiplatelet agents. Although PPIs are safe they are not devoid of their adverse effects which comprises hypo or achlorhydria, interstitial nephritis, gastric tumours, nutritional deficiencies like hypomagnesaemia, hypokalemia, hypocalcemia and that of Vit B 12. A major concern was raised when adverse outcome was observed in patients receiving both PPI and clopidogrel in cases of myocardial infarction. This was attributed to the inhibition of CYP2C19 and failure of activation of clopidogrel which was eventually considered as an effect of genetic polymorphism of CYP2C19. Enhanced cardiovascular mortality was also observed when PPIs were used along with antiplatelet drugs like aspirin and ticagralor which do not require CYP2C19 for their activation. Use of PPIs was thought to be the culprit for adverse cardiovascular outcome due to various possible causes like reduced myocardial contraction (negative inotropy), hypokalemia, hypomagnesaemia and hyperhomocysteinemia. Recently focus is centered on PPI induced inhibition of DDAH causing raised ADMA levels reflecting in to inhibition of eNOS and synthesis of eNO. NO is considered as vasoprotective and is an endogenous antiatherosclerotic substance. Hence PPIs by inhibiting eNOS and eNO are likely to enhance mortality in patients with known cardiovascular diseases and even in healthy individuals when used in high parenteral doses or for prolonged period. Confirmation of association with adverse cardiovascular outcome needs further confirmation by extensive appropriate clinical trials. Till then clinicians need to be warned against indiscriminate use of PPIs.

Keywords: ADMA, cardiovascular risk, proton pump inhibitors

INTRODUCTION
Proton pump inhibitors (PPI) are commonly prescribed for acid peptic diseases (APD) like peptic ulcer, gastro esophageal reflux disease (GERD), helicobacter pylori (H pylori) infection etc. They are also used in intensive care unit as a prophylaxis against APD and aspiration pneumonia. PPIs are routinely co-prescribed with nonsteroidal anti-inflammatory drugs (NSAIDS), anticoagulants and antiplatelet drugs. The medical field has witnessed a substantial rise in the incidence of APD due to various causes like stress, harmful dietary habits, and lack of exercise; smoking, alcohol consumption and use of gastric mucosal unfriendly drugs like NSAIDS. Similarly, there has been a proportional increase in the prescriptions of PPIs. Globally every year about 113 million PPI prescriptions are filled. This along with its over the counter sale amounts to about 13 billion dollars sales worldwide annually. In the year 2009, about 21 million people in USA used one or more prescriptions of PPI. Thus easy availability of PPIs over the counter and its use without medical supervision is a matter of grave concern.

Proton pump inhibitors and cardiovascular risk:

PPIs are substituted benzimidazoles. They are prodrugs which get activated in the acidic pH of the canaliculi of gastric parietal cells and undergo molecular rearrangement to active sulfonamide cations. PPIs block the final step of gastric acid secretion by irreversibly inhibiting hydrogen potassium adenosine triphosphatase enzyme system (H+ K+ ATPase) also known as proton pump. PPIs are considered to be very safe and effective but like other drugs they are also not devoid of adverse reactions. Various adverse effects of this class of drugs include hypo/achlorhydria, nutritional deficiencies like those of Vit B 12, magnesium, calcium and iron, acute interstitial nephritis, gastric tumors, hypocalcemia leading to osteoporosis and bone fractures, enteric infections like clostridium difficile, pneumonia in ICU settings and anaphylactic reactions with intravenous PPI.

It is natural that rise in the intragastric pH by PPI can lead to decreased absorption of non haeme iron. A study by Sarzyski E al showed evidence of decreased iron absorption with chronic PPI therapy leading to anaemia. But it had drawbacks like small sample size and a number of confounders. Hence there is a need for further study for generalizing such an inference.
Concern was raised when enhanced cardiovascular mortality was observed in patients where PPIs were co-prescribed with anti-platelet drugs like clopidogrel. Various studies have noted an adverse clinical outcome in high risk cardiovascular population independent of clopidogrel use also.

Clopidogrel is a prodrug and needs activation by hepatic isoenzyme CYP2C19 for its activity. PPI appears to reduce the efficacy of clopidogrel by inhibiting hepatic isoenzyme CYP2C19. This reduces clopidogrel’s antiplatelet activity leading to enhanced chances of coronary thrombosis and myocardial infarction. The mechanism which was initially thought to be an inhibition of hepatic isoenzyme CYP2C19 is now considered to be genetic polymorphism which causes impaired clopidogrel activity. Such polymorphism leads to reduced function of CYP2C19 allele which is common in Asian Americans (51%) and African Americans (33%) leading to fourfold increase in the risk of poor cardiac outcome. One copy is associated with 47% reduction and two copies with 65% reduction of clopidogrel activity. The third generation inopyridines like prasogrel and ticagrelor activity remain unaffected by variants in CYP2C19 genotype.

Adverse outcomes were noted in patients with high risk ischaemic heart disease independent of clopidogrel use when they were put on PPI.

Reduced therapeutic benefits were also noted when patients of acute coronary syndrome were treated with PPI and antiplatelet drugs like aspirin and ticagrelor which do not require activation by CYP2C19 like that of clopidogrel. It is thought that change in gastric pH is responsible for reduced absorption of these drugs, resulting in reduced antiplatelet activity. It is important to note that similar change in gastric pH by H2 blockers do not modify antiplatelet activity of these drugs. Unlike PPIs, H2 blockers do not enhance cardiovascular risk.

Other possible explanations for observed relation between PPI and increased cardiovascular risk are impaired cardiovascular haemodynamics or certain nutritional deficiencies like those of magnesium, vitamin B12 and hypokalemia.

In vitro studies with PPI have shown negative inotropic effects on the myocardium and thus enhancing the cardiovascular risk. Another in vitro study done by Wolfgang Schillinger on human and rabbit myocardium showed its depressed contractility. This is attributed to the inhibition of Ca++ signalling, intracellular Ca++ transients and impaired Ca++ responsiveness of myofilaments. Similarly, studies conducted on isolated failing human myocardium showed negative inotropy by different types of PPI. Results of in vitro studies could not be extrapolated in the clinical situations and the findings failed to show negative ionotropy of pantoprazole on left ventricular function when tried in healthy volunteers. This was considered as result of interplay of physiological effects in vivo like afterload, preload, heart rate and sympathetic activation. Patients with heart failure are more susceptible to the negative inotropic drugs because of blunted contractile reserve subsequent to decreased sympathetic sensitivity or negative force-frequency relationship. Hence caution needs to be exercised while administering intravenous PPI like pantoprazole in patients with failing myocardium. Patient should be switched over to the oral PPI therapy at the earliest.

Chronic PPI usage might lead to decreased absorption of vitamin B12 and its deficiency leading to hyperhomocysteinemia which is a known cardiovascular risk factor. This deficiency usually does not arise in people on normal diet with a good gastrointestinal function unless PPIs are given for prolonged duration. PPI induced hypomagnesaemia was first noted in year 2006. Since then many case reports have confirmed this association. Cause for hypomagnesaemia was its decreased gastrointestinal absorption and not its enhanced excretion. Passive paracellular gastrointestinal absorption of magnesium was intact but its active transport via transient receptor potential melastatin 6 and 7 (TRPM 6/7) channel was decreased.

Hypomagnesaemia presented with cardiac arrhythmias and electrocardiographic changes associated with weakness, cramps, tetany, seizure and ataxia. It is often accompanied by hypokalemia and hypocalcemia which again contribute for cardiac arrhythmias. PPI induced hypomagnesaemia is a class effect. Such an electrolyte imbalance was not noted with chronic use of H2 blockers. PPI related hypomagnesaemia induced cardiac effects warn against its usage in patients with compromised cardiac function with or without cardiac arrhythmias.

El Charabaty et al conducted a study to assess the association between the use of PPI, serum magnesium level and the incidence of cardiac arrhythmias in a large group of patients admitted to the intensive care unit with acute coronary syndrome. A positive correlation was observed between PPI therapy and cardiac arrhythmias. Similarly, a case control study was conducted in 80 patients with electrocardiophysiological studies. It was found that there was fourfold increase in focal arrhythmias in a group of 40 patients on PPI when compared to control group without PPI. Hypokalemia induced by PPI was noted in various studies. Hoorn E J et al found two men aged 63 and 81 years and two women with age of 62 and 73 years who developed hypokalemia after using PPI for about 1-13 years. There was associated hypomagnesaemia and hypocalcemia also. One patient had collapse possibly due to cardiac arrhythmia. Others had abnormal electrocardiographic changes such as prolonged QT interval, ST depression and presence of U wave. This electrolyte imbalance was thought to be the culprit for these changes. Similarly, Maeda Y, Kojima M et al noted hypokalemia in two women aged 59 and 80 years who were on long term omeprazole. These patients recovered from hypokalemia as soon as the drug was stopped. The cause of hypokalemia was hypomagnesaemia induced kaliuresis and not the decreased absorption of potassium. Shah NH et al after going through multiple data sources and screening over 2.9 million individuals using PPI to find out the association between the use of PPI and cardiovascular risk in general population found 1.16 fold increased association (95%-CI 1.09-1.24) with myocardial...
infarction. This group included young people and also those who were not on antiplatelet drugs. Recent physiological, cellular, molecular and in vivo data suggest the role of increased asymmetric dimethyl arginine (ADMA) levels due to PPIs as a result of inhibition of enzyme dimethyl arginine dimethylamino hydrolase (DDAH). Inhibition of DDAH and rise in ADMA by PPIs explain the cardiovascular risk induced by them. Enzyme DDAH metabolises ADMA which is an endogenous competitive inhibitor of endothelial nitric oxide synthase (eNOS) and is responsible for generation of endothelial nitric oxide (eNO). Vascular tone and vasorelaxation is regulated by eNO. It also contributes to vascular homeostasis by inhibiting platelet aggregation. Platelet also contain NO which act via NO-cGMP pathway and inhibit platelet activation which is the trigger for thrombus formation. NO prevents adhesion of monocytes and leukocytes to the endothelium and also inhibits smooth muscle cell proliferation. NO acts as an antioxidant and blocks the oxidation of low density lipoproteins resulting in prevention of foam cell formation in the vessel wall. Plaque formation is also affected by NO dependent reduction in endothelial cell permeability to lipoproteins. NO also protects against atherogenesis by inhibiting proliferation and migration of vascular smooth muscle cells. Along with inhibition of platelet aggregation NO inhibits blood coagulation by enhancing fibrinolysis via plasminogen. In addition it suppresses vascular inflammation by inhibiting expression of adhesion molecules and chemokines. Hence NO is labelled as endogenous antiatherosclerotic substance. Reduced eNOS and eNO lead to cardiovascular risk. Enhanced ADMA reduces NO production by inhibiting eNOS resulting in to endothelial dysfunction and its consequences. Plasma ADMA has been considered as an independent risk factor and risk marker for atherosclerotic cardiovascular diseases and mortality. There are two isoforms of DDAH-1 and 2. DDAH 2 is predominantly present in the tissues containing eNOS. Enhanced homocysteine also reduces the DDAH levels. ADMA levels have been shown to be increased in cardiovascular risk factors like diabetes mellitus, hypertension, obesity, hyperlipidemia, vascular inflammation and hyperhomocystenemia. Endothelial dysfunction induced by ADMA is known to promote coronary spasm and is responsible for slow coronary blood flow. Increased carotid artery intima/media thickness a known marker of cardiovascular risk is also associated with enhanced ADMA levels. Patients of unstable angina had higher ADMA levels than those with stable angina. ADMA is considered as an independent prognostic predictor of coronary cardiovascular diseases and mortality. Number of clinical studies have shown a relation between raised plasma ADMA concentration and coronary artery disease, chronic heart failure, hypertrophic cardiomyopathy, peripheral artery disease, pulmonary hypertension, cerebrovascular stroke and toxemia of pregnancy.

Experimental studies showed that PPIs increased intracellular ADMA levels in cultured human and mice endothelial cells and impaired the endothelium dependent vasodilatation of mouse aortas. PPIs also reduced generation of NO by human sephane vein segment. Study conducted by Ghebremariam Y in eNOS knockout mice suggest that ADMA may have an independent effect by upregulating angiotensin converting enzyme and angiotensin 1 dependent oxidative stress. Thus PPI inhibits DDAH, enhances levels of ADMA, inhibits eNOS, reduces generation of NO and predisposes the vasculature for atherosclerosis, increased cardiovascular diseases and mortality. Shih CJ et al conducted a propensity score (PS) matching analysis and cross over analysis by studying 126367 PPI users and 126367 matched PPI nonusers who underwent follow up for 120 days and found to have 1.58 fold greater risk of myocardial infarction in PPI users.

CONCLUSION
PPI can be an independent risk factor for myocardial infarction but the beneficial effects of PPI may outweigh the risk of cardiac adverse events. Similar to other myriad of adverse events of PPIs their cardiovascular effects among normal individuals warrant attention. High doses of parenteral PPIs predisposes for cardiac arrhythmias and cardiovascular risk. PPI by modifying NO activity enhances cardiovascular risk manifold in general population also. Hence there is a definite need to conduct cross-sectional, prospective and community based trial to uncover human applicability of the observations done by these researchers. If this is proved beyond doubt there will be a necessity for taking proper steps to enhance the pharmacovigilence of these drugs and to monitor the excess use of PPIs available as over the counter preparations. These measures need to be supplemented with appropriate practice guidelines for primary and secondary care physicians to avoid indiscriminate prescriptions of PPI. This will reduce the potentially modifiable cardiovascular risk among general population.

REFERENCES


