Six showed that, while vioxx decreased the risk

Six COXIBs were initially approved for use in US and EU. These include rofecoxib, celecoxib, valdecoxib, parecoxib (prodrug of valdecoxib), etoricoxib and lumiracoxib.

However, celecoxib is the only drug currently available in the US market. These selective COX-2 inhibitors were mainly developed based on the hypothesis that they could afford efficacy similar to traditional NSAIDs whilst having a better GI tolerability (FitzGerald and Patrano, 2001). ROFECOXIB: Drug MK0966 from Merck's methylsulphonylphenyl series was approved by the US-FDA for launch in the market under the brand name " Vioxx" in May 1999. In November 1999 however, the VIGOR study which was originally launched by Merck to test the GI safety of Vioxx compared to Naproxen showed that, while Vioxx decreased the risk of gastric ulcers and GI bleeding, it caused approximate four-fold increased risk of acute myocardial infarction (MI) in rofecoxib patients compared to naproxen patients over a 12-month study plan. This elevated risk of MI began during the second month of rofecoxib use.

In September 2004, Merck voluntarily withdrew Vioxx, following a colon-polyp prevention study (APPROVe) which showed an elevated risk of adverse thrombotic events (MI and stroke) with 18 months of rofecoxib use. Lancet later reported that, of the 20 million Americans who had used Vioxx between 1999 and 2004, 88000 had suffered from heart attacks and 38000 had died. In May 2006, a separate analysis of data sent to FDA from the Vioxx APPROVe study showed that the cardiovascular risks from Vioxx began shortly after patients started taking the drug and that these risks persisted long after the withdrawal of the drug. Further, Zhang et. al in 2006 reported

an increased risk of cardiac arrhythmias associated with the use of rofecoxib. Levesque et. al. in 2006 have shown that the risk of MI is highest following first-time use of rofecoxib, with events occurring within a median of 9 (6–13) days after therapy is started.

Repeated exposure to rofecoxib was associated with a small but statistically nonsignificant delayed risk (RR 1. 17, 95% CI 0. 98–1.

40). Treatment duration is not associated with increasing risk for either agent. The risk remained elevated for the first 7 days after rofecoxib was discontinued but appeared to return to baseline between day 8 and 30. Considering the normal timelines for the development of myocardial infarct, it is worthwhile to speculate the possibility that cardiovascular complications other than MI may be involved in the sudden cardiac deaths associated with rofecoxib use. VALDECOXIB: Valdecoxib was manufactured and marketed under the brand name Bextra by G. D. Searle & Company as an anti-inflammatory drug for use in arthritis patients.

It was approved by the United States FDA on November 20, 2001, to treat arthritis and menstrual cramps and was available by prescription in tablet form until 2005. However, Bextra was withdrawn from the US market due to FDA citation of “ potential increased risk for serious cardiovascular (CV) adverse events” and “ increased risk of serious skin reactions” and the “ fact that Bextra has not been shown to offer any unique advantages over the other available NSAIDs.” Etoricoxib and Lumiracoxib are sold worldwide but not in the USA, although lumiracoxib has already been withdrawn in Australia and several other countries.

(Frolov, 2014)CELECOXIB: Celecoxib (Celebrex; Searle-Monsanto and Pfizer) was the first selective COX-2 inhibitor approved by the US-FDA and it is currently the only COXIB available in the US market. Celecoxib is ~30 times more selective for COX-2 than COX-1. Chemically, celecoxib is a benzenesulphonamide (1, 5- diaryl substituted pyrazole) with a pKa of 11. 1. It is commonly prescribed for symptomatic treatment of pain and inflammation associated with rheumatoid arthritis and osteoarthritis.

Clinical trials of celecoxib have shown significantly reduced upper gastrointestinal tract complications for celecoxib compared to traditional NSAIDs such as naproxen, ibuprofen and diclofenac (Davies et. al. 2000). CLASS (Celecoxib long-term arthritis safety study) compared the GI safety records of celecoxib to ibuprofen and diclofenac. The osteoarthritis cohort in this study were allowed to take low-dose aspirin along with celecoxib.

Six-months data from CLASS did not show any difference in the incidence of appearance of complicated ulcers (which was the primary end-point for CLASS). However, the incidence of symptomatic ulcers was significantly decreased compared to ibuprofen, but not diclofenac. Further, one-year data from CLASS showed some benefit compared to ibuprofen but not when aspirin was co-administered.

While celecoxib does seem to have a significant GI benefit, there are discrepancies in the data generated from different clinical trials on the cardiovascular safety of celecoxib. In December 2004, a clinical trial for colon cancer prevention, “ APC,” showed that a high dose of celecoxib (400 mg and 800 mg daily) administered for a long-term (33 months) led to increased

risk of cardiovascular complications compared to placebo (Solomon et al., 2005; Bertagnolli et al., 2006).

However, PreSAP, a separate Celebrex clinical trial, did not demonstrate such an increased risk (Arber et al., 2006). On the other hand, a large Alzheimers prevention trial, called ADAPT, was terminated early after preliminary data suggested that the nonselective NSAID naproxen, but not celecoxib, was associated with increased cardiovascular risk (Group et al., 2007). After an extensive review of data, the FDA in 2005 concluded that it was likely “ that there is a ‘ class effect’ for increased CV risk for all NSAIDs.” (Jenkins, 2005). However, combined with the rofecoxib data, there is some indication that COXIBs may lead to increased risk of severe cardiovascular complications. Clinical studies demonstrate that celecoxib may cause increased risk of serious and potentially fatal adverse CV thrombotic events, MI and stroke.

The hazard ratio for the composite end-point of CV complications is 3. 1 for 400 mg celecoxib twice daily and 1. 8 for 200mg celecoxib twice daily (Solomon et. al. 2008).

Further, two meta-analyses scrutinized the cardiovascular risks of celecoxib and other NSAIDs. The first of these (Kearney et al., 2006) looked at the incidence of cardiovascular events in allprevious randomized controlled trials of COX-2 inhibitors, as well as some trials of other NSAIDs. It was concluded that a significant increased risk did exist for celecoxib, as well as some other selective and nonselective NSAIDS. However, the increased cardiovascular risk in celecoxib was only noted at daily doses of 400 mg or greater. Another meta-analysis (McGettigan & Henry, 2006), which included observational

rather than randomized studies (mostly at lower doses) did not find an increased cardiovascular risk of celecoxib vs placebo. Further, meta-analysis by Zhang et. al showed that rofecoxib significantly increased risk of arrhythmias, however, such a risk was not seen in the celecoxib cohort.

(Zhang et. al JAMA 2006). The mechanism(s) underlying these adverse effects are still debatable. Whether the adverse cardiovascular effects of celecoxib result from inhibition of COX-2, or from the off- target interaction of celecoxib with some other molecules, is the main question that needs thought (Shapiro, 2009). Celecoxib has been shown to interact with numerous molecular receptors other than cyclooxygenases. These effects on various molecular receptors are non-selective, and are reported throughout the body.

Celecoxib can directly alter the expression of various genes involved in many cellular processes, including metabolism (Cervello et. al., 2011; Schonthal, 2010), cellular growth, proliferation and death (Dogne et. al., 2007; Grosch et. al., 2006; Hasinoff et. al.

, 2007). For instance, celecoxib (as well as valdecoxib) can inhibit carbonic anhydrases with greater (nanomolar) affinity (Weber et al., 2004). Further, celecoxib can also inhibit cell cycle progression by decreasing the expression of cyclins A, B and D whilst enhancing the expression of various cell cycle inibitors.

Celecoxib (but not rofecoxib) also shows cytotoxicity towards rat cardiomyocytes via a mechanism independent of COX (Hasinoff et al., 2007). Moreover, Zhang et. al. have shown that celecoxib can inhibit L-type calcium

channels in PC12 cells at low micromolar concentrations, by a COX-independent mechanism. Celecoxib can also inhibit tetradotoxin- resistant and sensitive voltage gated sodium channels in rat dorsal root ganglia (Park et.

al. 2007). These findings suggest a possibility of a rather straightforward mechanistic explanation for at least some of these effects because ion channel dysfunctions often accompany the primary causes of heart failure and can account for death due to arrhythmias (Amin et al., 2010; Martin et al., 2013). Moreover, as voltage-activated channels are involved in numerous cellular processes apart from providing for excitability, such as cell proliferation, cell volume control, apoptosis and immune responses (Franco et. al., 2008; Jehle et al.

, 2011), these new data may be instrumental for explaining the corresponding changes in cellular functioning in the presence of celecoxib. It has been shown that celecoxib can alter voltage-activated sodium, calcium and potassium currents, inhibiting or augmenting them with strikingly similar values of IC50 in the low micromolar range (Brueggemann et al., 2009; Du et al.

, 2011; Frolov et. al., 2008, 2011; Macias et al.

, 2010; Park et al., 2007; Zhang et al., 2007). Instances of myocyte dysfunction as a result of ion channel modulation have been reported in animal models. They include arrhythmic heart beat in Drosophila and cultured rat ventricular cardiomyocytes (Frolov et al., 2008), vasodilatation of rat mesenteric arteries (Brueggemann etal.

, 2009), prolongation of action potential duration in mouse cardiomyocytes and action potential shortening in guinea pig cardiomyocytes (Macias et al., 2010). Noteworthy, although research is mainly focused on the CV adverse effects of celecoxib, modulation of ion channels in other tissues and organs and the corresponding functional changes could be also important.

Frolov et. al. showed that at low micromolar concentrations, celecoxib reduced heart rate in Drosophila and induced pronounced arrhythmia. Similarly, it reduced the rate of beating in rat heart cells in culture and made the beating arrhythmic.

The fact that Drosophila lack the cyclooxygenase enzyme is evidence that these cardiovascular effects are mediated by a mechanism separate from cyclooxygenase inhibition. Electrophysiological analyses by Frolov et. al. has shown that these effects are mediated via the inhibition of delayed rectifier potassium channels.

Failure of Aspirin to inhibit the rat Kv2. 1 channels further support the COX-independence of channel inhibition by celecoxib. Further, SC-791, a drug molecule similar to celecoxib, altered heart beat and inhibited several cardiac ion channels, particularly, the L-type Calcium channels and Kv2 channels. Frolov et. al further demonstrated that celecoxib suppresses voltage-gated sodium currents and potassium currents in rat retinal neurons at low micromolar concentrations. Further, in Drosophila muscle, celecoxib attenuates various ion channels with varying potencies. For instance, Kv2 currents are inhibited with an IC50 of 11.

4uM, L-type calcium currents with IC50 of 74uM and Kv1 currents with IC50 around 100uM. The potencies also vary with the type of preparation under study. For example, in the retina, the range celecoxib potencies range from 5-16uM. In rats, it was shown that the rate of spontaneous contraction of cardiac muscle fibers was reduced and there was a reduction in spontaneous spike firing of retinal neurons.