

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

PAIN MANAGEMENT IN THE SURGICAL PATIENT

SUMMARY

Adequate pain relief is essential to not only patient comfort, but also pulmonary toilet and wound healing. In the surgical patient, pain is best relieved using a combination of pharmacologic agents including opioid analgesics, nonopioid analgesics (such as non-steroidal anti-inflammatory drugs or NSAIDS), local anesthetics, and analgesic adjuvants.

RECOMMENDATIONS

- **Level 1**
 - **None**

- **Level 2**
 - **A patient's pain medication regimen should be constantly evaluated and adjusted as needed to achieve appropriate pain control while avoiding oversedation.**
 - **For enteral opioid therapy, a combination of a sustained-release formulation for long-acting pain control and an immediate-release formulation for breakthrough pain is preferred.**
 - **For parenteral opioid therapy, morphine, fentanyl or hydromorphone should be utilized in titrated doses as indicated.**
 - **Enteral pain medication therapy should be initiated as soon as the patient is able to tolerate such medications.**
 - **COX-2 inhibitors and non-selective NSAIDS should be avoided in patients with or at high risk for thrombotic cardiovascular events (see Appendix I).**

- **Level 3**
 - **NSAIDS and COX-2 inhibitors should not be used in patients with renal dysfunction, hypovolemia, or active gastrointestinal hemorrhage.**
 - **NSAIDS and COX-2 inhibitors should not be used in patients with acute orthopedic fractures unless the benefit outweighs the potential risk.**

INTRODUCTION

"Pain" may be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". "Analgesia" is defined as the blunting or absence of sensation of pain or noxious stimuli. Pain and physical discomfort is common in the surgical patient as a result of injury, invasive procedures, or preexisting illnesses. It may also be caused by monitoring and therapeutic devices (such as invasive catheters, drains, and tubes), routine patient care (such as airway suctioning, physical therapy, dressing changes, and patient mobilization), and prolonged immobility (1). Unrelieved pain may contribute to patient discomfort, anxiety, exhaustion, disorientation, agitation, tachycardia, increased myocardial oxygen consumption, pulmonary dysfunction,

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

immunosuppression, and persistent catabolism. Effective pain control, in addition to improving patient comfort, may also decrease the incidence of many complications (such as pulmonary dysfunction) in the postoperative patient.

The patient's perception of pain plays a major role in its control. A realistic goal for pain management in the surgical patient is to *minimize* the sensation of pain rather than *eliminate* it. Pain may be alleviated through the combined use of analgesics (addressed in this evidence-based medicine guideline) and sedatives (addressed in the guidelines on control of agitation and delirium). Patient education and patient-physician communication can play as important and effective a role in relieving pain as the actual pharmaceutical agents prescribed. No medication regimen can overcome the unrealistic expectations of the uninformed patient.

Pain can be divided into two types based upon its etiology. *Acute pain* follows injury and generally resolves when the bodily injury heals. It is commonly associated with physical signs such as tachycardia, hypertension, diaphoresis, mydriasis, and pallor. *Chronic pain* may be acute, chronic, or intermittent, is usually associated with a definable etiology, and is rarely associated with physical signs.

Pain is now considered the "fifth vital sign" by JCAHO, and should be documented during each patient assessment. A variety of tools and assessment scales have been advocated to document the degree of pain. The most reliable and valid indicator of pain has been shown to be the patient's self-report. In the comatose or unresponsive patient, however, the physician must infer the patient's level of pain based upon clinical experience and interpretation of the patient's physiologic parameters.

Pain control is a major process improvement issue in many hospitals as physicians have historically inadequately treated pain, fearing side effects and adverse events such as narcotic addiction. Multiple studies have demonstrated that these fears are largely unfounded.

Pain is prevented and/or treated using various pharmaceutical agents. These medications can be divided into four general categories:

1. **Nonopioid analgesics** (aspirin, acetaminophen, NSAIDS)
2. **Opioid analgesics** (morphine, hydromorphone, fentanyl, oxycodone, hydrocodone)
3. **Local anesthetics** (lidocaine, bupivacaine)
4. **Analgesic adjuvants** (tricyclic antidepressants, antihistamines, benzodiazepines, steroids, phenothiazines, anticonvulsants, clonidine)

Nonopioid Analgesics

Aspirin and other salicylates, acetaminophen, and NSAIDS are useful for treating both acute and chronic pain due to a variety of etiologies including surgery, trauma, arthritis, and cancer. These drugs act primarily by inhibiting the enzyme cyclooxygenase (except acetaminophen), preventing the formation of prostaglandins that tend to sensitize peripheral nerves and central sensory neurons to painful stimuli. They do not promote tolerance or physical or psychological dependence. They have the added effect of being antipyretic. Both aspirin and NSAIDS may cause gastric disturbances and hemorrhage that can limit their usefulness in certain patients, and can inhibit platelet activity, which can be detrimental in the surgical patient.

Acetaminophen has no antiplatelet activity, few anti-inflammatory effects, and does not damage the gastric mucosa. Excessive doses can cause hepatic necrosis and must be kept in mind as many of the oral opioid preparations contain acetaminophen and the cumulative acetaminophen dose is frequently under recognized.

NSAIDS inhibit platelet aggregation by reversibly inhibiting prostaglandin synthetase (unlike aspirin whose binding is irreversible). Such agents must therefore be taken "around-the-clock" as opposed to "as needed" in order to be effective. Anticoagulation, coagulopathy, and the presence of thrombocytopenia are all relative contraindications to the use of NSAIDS. NSAIDS are associated with dose-independent gastrointestinal complications such as ulceration, bleeding, and perforation. NSAID therapy is commonly accompanied by administration of either H₂-blocker or proton pump inhibitor therapy in an attempt to

avoid these complications. NSAIDs can also induce renal insufficiency, especially in the presence of dehydration.

A drug class that selectively inhibits the COX-2 isoform of cyclooxygenase (the isoenzyme associated with inflammation) is available. This class purportedly avoids inhibition of the COX-1 isoenzyme that is associated with renal and gastric side effects. Prospective, randomized controlled studies comparing the COX-2 inhibitors with standard NSAID therapy demonstrate equivalency of these medications, but with a decreased incidence of gastrointestinal side effects including perforation, bleeding, and ulceration (2,3). Despite the initial enthusiasm regarding the pharmacologic benefits of selective COX-2 inhibition, significant safety concerns have emerged resulting in the removal of two such agents from the market. COX-2 inhibitors, like standard NSAIDs, can cause renal failure (especially in patients with pre-existing dysfunction or hypovolemia) and are associated with potentially life-threatening gastrointestinal bleeding. Additionally, they are associated with an increase in the potential for thrombotic cardiovascular events by creating an imbalance between the prothrombotic properties of thromboxane A₂ and the antithrombotic properties of prostacyclin (PGI₂). Finally, the use of COX-2 inhibitors for the treatment of acute pain following traumatic musculoskeletal injury has become a controversial practice due to a growing body of literature suggesting that NSAIDs interfere with fracture healing and may be associated with an increased incidence of non-union. Although the mechanism of these adverse effects is not fully understood, it is postulated that decreased prostaglandin synthesis and inhibition of the initial inflammatory response are responsible. There may also be a direct effect on osteoblast proliferation, differentiation or maturation.

TABLE I: SELECTED NONOPIOID ANALGESICS

Medication	Average Analgesic Dose (mg)*	Dose Interval (hr)	Maximal Daily Dose (mg)	Analgesic Efficacy Compared to Standards	Half-Life (hr)	Comments
Acetaminophen (Tylenol)	500-1000	4-6	4000	Comparable to aspirin	2-3	Rectal and sustained release preparation available.
Aspirin (ASA)	500-1000	4-6	4000		0.25	Not for use in children. Rectal and sustained release preparation available.
Ibuprofen (Motrin, Advil)	200-400	4-6	2400	200 mg superior to ASA 650 mg	2-2.5	
Naproxen (Naprosyn)	500 initial, 250 subsequent	8-12	1250		12-15	
Ketorolac (Toradol)	30-60 mg IM or 30 mg IV initial, 15-30 mg IM or IV subsequent	6	150 mg first day, 120 mg subsequent	30 mg equivalent to 6-12 mg morphine	6	Limit treatment to 5 days. May precipitate renal failure in dehydrated patients.
Rofecoxib (Vioxx) Withdrawn from market	50 mg	24	50 mg	Comparable to ibuprofen	17	
Celecoxib (Celebrex)	100-200 mg	12-24	400 mg	Less effective than ibuprofen	11	Avoid in sulfa allergies. Caution in liver and renal dysfunction.
Valdecoxib (Bextra) Withdrawn from market	10-20 mg	12-24	40 mg	Comparable to naproxen	8-11	Avoid in sulfa allergies. Potential for drug interaction with coumadin.

* All doses are oral unless otherwise specified.

Opioid Analgesics (1,4)

Opioid analgesics relieve pain by interacting with a variety of central and peripheral opioid receptors. These agents are typically added to nonopioid analgesics when the patient's pain does not respond to nonopioids alone. A common mistake is substituting one class of agent for the other. Both classes work well synergistically through their differing mechanisms of action. For this reason, opioids are commonly marketed in combination with a nonopioid analgesic such as aspirin or acetaminophen.

Opioids may be administered by a variety of methods (orally, rectally, intramuscularly, intravenously, subcutaneously, transdermally). The onset of action, peak effect, and duration varies by method. For oral (PO) administration (with the exception of sustained-release formulations), peak drug effect occurs within 90-120 minutes. Patients with inadequate pain control after an initial opioid dose may safely take a second dose 2 hours after the first dose. Rectal (R) opioid formulations are useful in the patient who is unable to take PO medications. Intramuscular (IM) administration is marked by painful injection, variable absorption, delayed onset, and decreased duration of effect. Such injections should be avoided in the patient with inadequate perfusion and shock, as bolus opioid absorption may occur once perfusion is restored, potentially resulting in over sedation and respiratory depression.

Intravenous (IV) administration has the most rapid onset of effect with the time to peak effect varying according to the lipid solubility of the drug. Duration of action is shorter than for other methods, but additional doses may be given earlier as a result. Continuous opioid infusions, or "patient controlled analgesia" (PCA) provides for maintenance of steady blood drug levels and effective control of severe pain. Transdermal (TD) administration is slow in onset (12-24 hours) and long in duration making this method especially useful for control of chronic pain. This method is less effective in the patient with acute pain as rapid titration of drug to effect is not possible.

The selection and administration of an individual opioid agent is dependent upon its pharmacology, potential side effects, and indications for use. The most commonly utilized opioids are listed in Table II. Of the intravenous opioids, fentanyl has the most rapid onset and shortest duration of effect. It has minimal effects on systemic blood pressure making it particularly useful in the hemodynamically unstable patient. Repeated administration can lead to drug accumulation and prolonged side effects. Morphine, perhaps the most commonly used intravenous opioid, has a longer duration of action making intermittent dosing efficacious. Morphine, however, can cause hypotension in the hemodynamically unstable or hypovolemic patient as a result of peripheral vasodilation and an active metabolite may accumulate in patients with renal insufficiency. Hydromorphone has a similar duration of effect as morphine, but it lacks an active metabolite and is not associated with histamine-mediated vasodilatation. Meperidine's metabolite, normeperidine, is a central nervous system excitotoxin that causes anxiety, tremors, myoclonus, and generalized seizures with accumulation. As meperidine and normeperidine are renally excreted, such side effects are a concern in patients with decreased renal function. Meperidine should also be used with caution in patients receiving monoamine oxidase inhibitors as the combination of these two drugs can lead to a hyperpyrexia syndrome with delirium.

Opioid therapy may be initiated using the recommended initial doses from Table II. Therapy should be titrated to achieve control of the patient's acute pain using opioids with a relatively rapid onset of effects. Once a patient's opioid requirement for a 24-hour period has been determined, longer acting opioid analgesics can be administered on a scheduled around-the-clock basis achieving "smoother", more efficacious pain control with fewer side effects. Essential to this method is provision for a supplementary, rapid-acting opioid for "break through" pain in addition to the scheduled sustained release formulations. In general, approximately two-thirds of the patient's estimated opioid dose should be administered as a sustained-release formulation with the remaining one-third prescribed as an immediate-release formulation to be administered every 2 hours as needed. As with any drug therapy, the efficacy of the medication regimen must be constantly assessed and altered as needed to achieve the intended effect.

TABLE II: EQUIANALGESIC OPIOID DOSE CHART						
Medication	Parenteral (IM/SC/IV)	Oral (PO)	Onset (min)	Peak (min)	Duration (hr)	Half-life (hr)
Morphine (MSO ₄ , Oramorph SR, MS Contin)	10 mg	30 mg	30-60 (PO) 30-60 (CR) ² 30-60 (R) 5-10 (IV) 10-20 (SC) 10-20 (IM)	60-90 (PO) 90-180 (CR) ² 60-90 (R) 15-30 (IV) 30-60 (SC) 30-60 (IM)	3-6 (PO) 8-12 (CR) ² 4-5 (R) 3-4 (IV) ^{1,3} 3-4 (SC) 3-4 (IM)	2-4
Fentanyl (Sublimaze, Duragesic)	100 mcg/hr IV or TD = 4 mg/hr morphine IV; 1 mcg/hr TD = morphine 2 mg/24 hr PO	---	5 (OT) 1-5 (IV) 7-15 (IM) 12-16 hr (TD)	15 (OT) 3-5 (IV) 10-20 (IM) 24 hr (TD)	2-5 (OT) 0.5-4 (IV) ^{1,3} 0.5-4 (IM) 48-72 (TD)	3-4 ⁴ 13-24 (TD)
Codeine	130 mg	200 mg	30-60 (PO) 10-20 (SC) 10-20 (IM)	60-90 (PO) unknown (SC) 30-60 (IM)	3-4 (PO) 3-4 (SC) 3-4 (IM)	2-4
Hydrocodone (Vicodin, Lortab)	---	30 mg ⁵ NR	30-60 (PO)	60-90 (PO)	4-6 (PO)	4
Hydromorphone (Dilaudid)	1.5 mg ⁶	7.5 mg	15-30 (PO) 15-30 (R) 5 (IV) 10-20 (SC) 10-20 (IM)	30-90 (PO) 30-90 (R) 10-20 (IV) 30-90 (SC) 30-90 (IM)	3-4 (PO) 3-4 (R) 3-4 (IV) ^{1,3} 3-4 (SC) 3-4 (IM)	2-3
Meperidine (Demerol)	75 mg	300 mg NR	30-60 (PO) 5-10 (IV) 10-20 (SC) 10-20 (IM)	60-90 (PO) 10-15 (IV) 15-30 (SC) 15-30 (IM)	2-4 (PO) 2-4 (IV) ^{1,3} 2-4 (SC) 2-4 (IM)	2-3
Oxycodone (Percocet, Tylox, Oxycontin, OxyIR)	---	20 mg	30-60 (PO) 30-60 (CR) ⁷ 30-60 (R)	60-90 (PO) 90-180 (CR) ⁷ 30-60 (R)	3-4 (PO) 8-12 (CR) ⁷ 3-6 (R)	2-3 4.5 (CR)

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CR – oral controlled-release; IM – intramuscular; IV – intravenous; OT – oral transmucosal; PO – oral; R – rectal; SC – subcutaneous; TD – transdermal; NR – not recommended; hr – hours; min - minutes

¹ Duration of analgesia is dose dependent; the higher the dose, usually the longer the duration.

² As in, e.g., MS Contin.

³ IV boluses may be used to produce analgesia that lasts approximately as long as IM or SC doses. However, of all routes of administration, IV produces the highest peak concentration of the drug, and the peak concentration is associated with the highest level of toxicity (e.g. sedation). To decrease the peak effect and lower the level of toxicity, IV boluses may be administered more slowly (e.g., 10 mg of morphine over a 15 minute period) or smaller doses may be administered more often (e.g., 5 mg morphine every 1-1.5 hours).

⁴ At steady state, slow release of fentanyl from storage in tissues can result in a prolonged half-life of up to 12 hr.

⁵ Equianalgesic data not available.

⁶ The recommendation that 1.5 mg of parenteral hydromorphone is approximately equal to 10 mg of parenteral morphine is based on single dose studies. With repeated dosing of hydromorphone (e.g., PCA), it is more likely that 2-3 mg of parenteral hydromorphone is equal to 10 mg of parenteral morphine.

⁷ As in, e.g., OxyContin

The most common side effects encountered with the use of opioids include sedation, constipation, nausea, vomiting, itching, and respiratory depression. These potentially detrimental effects of therapy are associated with high peak serum levels that are avoided through the use of sustained-release

preparations or continuous intravenous infusions. In some patients, switching to a different opioid may also decrease the incidence of side effects. All patients on narcotics should be placed on a bowel regimen to prevent constipation. Patients with impaired renal and hepatic function are at particular risk for developing side effects as the opioids are commonly metabolized and excreted by these two organs.

“Tolerance” refers to the need for increasing doses of opioid analgesic to maintain the original effect. This is a common finding in virtually all patients on chronic opioid analgesics. The first sign of tolerance may be a decrease in the duration of effective analgesia. “Withdrawal” refers to the development of anxiety, tachycardia, sweating, and other autonomic symptoms occurring with the abrupt discontinuation of an opioid drug. Such symptoms can be avoided by slowly tapering the dose downward prior to discontinuing therapy altogether. Symptoms may also be lessened by administration of a transdermal clonidine patch delivering 0.1-0.2 mg/day.

Local Anesthetics (5)

Peripheral use of local anesthetics for prophylaxis against postoperative pain and as an adjunct to nonopioid and opioid analgesics is becoming increasingly popular. With the trend towards performing many surgical procedures on an outpatient basis, local anesthetic infiltration either during or at the conclusion of the procedure has been proposed as one method by which to improve postoperative pain control. Over 60 trials have been performed evaluating the use of local anesthetics following laparoscopic surgery alone. Unfortunately, the methodology behind these trials has been quite variable making comparisons and systematic analysis difficult. Overall, there is insufficient agreement in these trials to make clear recommendations regarding intraperitoneal, port-site, or subcutaneous infiltration using local anesthetic agents.

Analgesic Adjuvants (4)

A variety of medications can be utilized to either enhance the effects of opioid analgesics or counteract their side effects. Occasionally, these agents may actually have pain-relieving properties of their own. These medications are discussed below.

TABLE III: ANALGESIC ADJUVANTS

Medication	Therapeutic Effect	Contraindications / Side Effects
Tricyclic antidepressants (amitriptyline, imipramine, nortriptyline, desipramine)	Used to treat neuropathic pain. May potentiate opioids. No data to support use in acute pain.	Patients with coronary artery disease, conduction abnormalities. Amitriptyline can cause sedation, anticholinergic effects. Nortriptyline and desipramine can cause insomnia.
Antihistamines (hydroxyzine)	Has mild analgesic (IM), antiemetic, and sedative activity.	
Benzodiazepines (diazepam, lorazepam)	Effective for acute anxiety or muscle spasm associated with acute pain.	Can cause sedation and respiratory depression
Steroids	Can ameliorate painful nerve or spinal cord compression by reducing edema.	Can increase the risk of GI bleeding, especially when used in combination with NSAIDs. Rapid withdrawal may exacerbate pain.
Phenothiazines (chlorperazine, prochlorperazine)	Useful in treating anxiety / agitation	Prolonged use may lead to tardive dyskinesia
Anticonvulsants (gabapentin, phenytoin, carbamazepine, clonazepam)	May relieve brief lancinating pains arising from peripheral nerve syndromes such as trigeminal neuralgia, diabetic neuropathy, postherpetic neuralgia, glossopharyngeal neuralgia, and posttraumatic neuralgia.	
Clonidine	Useful as an epidural infusion for neuropathic pain	Rarely may cause hypotension and bradycardia

LITERATURE REVIEW

Prospective, randomized comparative trials or evidence-based medicine guidelines of opioid therapy in the management of postoperative pain are lacking. The existing evidence for this therapy is based upon small clinical trials, consensus statements, widespread clinical practice, and expert opinion. As a result, no Level 1 recommendations can be made at this time. Further, an attempt to review the numerous analgesic studies and clinical trials that have been performed over the years is beyond the intent of these guidelines. The following are literature reviews of two areas of current controversy in the management of acute postoperative / posttraumatic pain. The evidence-based medicine algorithm that follows addresses the various analgesic medication classes and their appropriate use in pain management for the surgical patient.

Non-selective NSAIDs and Bone Healing

Giannoudis et al. performed a retrospective study evaluating factors affecting bone union in patients with femoral shaft fractures (6). Non-union occurred in 32/377 (9%) patients. Sixty-seven patients with fracture union served as a control group. There was more NSAID use in the nonunion group (63%) compared with the union group (13%). The odds ratio for nonunion was 10.7 (95% CI 3.55-33.23). The reliability of these results has been questioned due to inaccuracy of the outcome measures used to define union and failure to include detail regarding NSAID administration. Additionally, baseline characteristics were variable between groups making it difficult to attribute non- or delayed union to NSAIDs alone (Class III).

COX-2 Inhibitors and Bone Healing

Long et al. investigated the effect of COX-2 specific inhibitors on spinal fusion in 66 New Zealand White rabbits (7). A single level posterolateral intertransverse process arthrodesis was performed bilaterally at the level of the fifth and sixth lumbar segment with bone from both iliac crests. Seventy-two rabbits were randomized to receive either celecoxib (10 mg/kg), indomethacin (10 mg/kg), or placebo daily for eight weeks. Following the 8-week treatment course, the lumbar spines were harvested and evaluated with gross palpation, radiographs, and histological analysis. All analyses were blinded. Results of gross examination revealed that fusion rates in the control and celecoxib groups were significantly better than in the indomethacin group. Radiographic assessment demonstrated a significantly lower fusion rate in the indomethacin group compared with the control group. Finally, the histologic scores were significantly better in the control group than in the indomethacin group. No significant difference was found between the control and celecoxib groups. The authors concluded that celecoxib does not significantly inhibit the rate of spinal fusion in rabbits and that impaired bone healing is likely mediated by inhibition of COX-1.

In contrast to the previous trial, the results of a smaller study demonstrate that bone growth is impaired by COX-2 inhibition (8). Goodman and colleagues examined the effects of a non-specific COX inhibitor versus a COX-2 inhibitor on bone ingrowth and tissue differentiation in eight rabbits. Subjects receiving either naproxen or rofecoxib had significantly less bone ingrowth when compared to placebo. There was no significant difference between naproxen and rofecoxib. Simon et al. conducted a study assessing the effects of COX-2 inhibition on femur fracture healing in a rat model (9). The four treatment arms included placebo, indomethacin, celecoxib, or rofecoxib. Drug administration began two days prior to fracture. Radiographic analysis demonstrated that healing was delayed with indomethacin and inhibited with celecoxib and rofecoxib. Mechanical testing data revealed that healing was delayed with both indomethacin and rofecoxib. There were no significant differences between the celecoxib and placebo treated rats. Histologic evaluation revealed that both indomethacin and the COX-2 inhibitors resulted in abnormal cartilage formation. The authors concluded that COX-2 function is essential for fracture healing.

COX-2 Inhibitors and Adverse Cardiovascular Events

Mukherjee et al. analyzed the randomized trials that have evaluated whether COX-2 inhibitors are associated with an increased risk of cardiovascular events (10). These include the Vioxx Gastrointestinal Outcomes Research Study (VIGOR), Celecoxib Arthritis Safety Study (CLASS), and two unpublished trials (Study 085 and Study 090) (2,10,11). In addition, the annualized myocardial infarction rate in the placebo group of a recent meta-analysis of four aspirin primary prevention trials was compared to that found in the VIGOR and CLASS studies. The annualized myocardial infarction rates were significantly

higher for rofecoxib in VIGOR (0.74%) and celecoxib in CLASS (0.8%) when compared to the placebo group in a meta-analysis of four aspirin primary prevention trials (0.52%) (Class II) (10).

STUDY	INTERVENTION	INDICATION	CV EXCLUSIONS	ASA USE PERMITTED	CARDIOVASCULAR EVENTS
VIGOR (2)	Rofecoxib (R) 50mg daily versus naproxen (N) 500mg BID	Long-term Treatment of RA (median=9 months; range=0.5-13 months)	Cerebrovascular event within past two years MI/CABG within past year	No; patients requiring ASA for cardiac indications were excluded	<p><u>VIGOR Data</u> Mortality: 0.5% (R) versus 0.4% (N)</p> <p>Death from CV causes: 0.2% for both groups</p> <p>Ischemic cerebrovascular events: 0.2% for both groups</p> <p>MI: 0.4% (R) versus 0.1% (N), RR=0.2 (95% CI 0.1-0.7)</p> <p>No significant difference for MI endpoint for patients without indications for ASA as secondary prophylaxis</p> <p><u>Mukherjee et al. Data</u> RR of developing a CV event in (R) group: Overall = 2.38 (95% CI 1.39-4; p<0.001)</p> <p>ASA indicated patients = 4.89 (95% CI 1.41-16.88; p=0.01)</p> <p>ASA not indicated patients = 1.89 (95% CI 1.03-3.45; p=0.04)</p>
CLASS (11)	Celecoxib 400mg BID versus ibuprofen 800mg TID versus diclofenac 75mg BID	OA 73% RA 27%	None	Yes; <325mg/d ~20% of patients in each group were taking low-dose ASA	No significant difference between groups in CVA, MI or angina
STUDY 085	Rofecoxib (R) 12.5mg daily versus nabumetone (N) 1000mg daily versus placebo (P)	OA of the knee (6 week treatment duration)		Yes; low-dose for cardioprotection	R: 0.2% N: 0.4% P: 0%
STUDY 090	Rofecoxib (R) 12.5mg daily versus nabumetone (N) 1000mg daily versus placebo (P)	OA of the knee		Yes; low-dose for cardioprotection	R: 1.5% N: 0.5% P: 0.5%

The finding of increased cardiovascular events in the rofecoxib arm of VIGOR must be interpreted in conjunction with several factors. First, the VIGOR study enrolled patients with rheumatoid arthritis, a disease known to increase the risk of myocardial infarction, while the CLASS study primarily enrolled patients with osteoarthritis. Second, four percent of the VIGOR study population met criteria for aspirin administration and did not receive it. Third, naproxen has significant antiplatelet effects (more so than ibuprofen or diclofenac). Although naproxen is not proven to influence the incidence of cardiovascular events, it may have contributed to the differences in thrombotic events observed between the rofecoxib and naproxen groups. Pharmacologic differences between the non-selective NSAIDs used for comparison in the VIGOR and CLASS studies may have influenced the differing results of these trials.

Following publication of the above studies, debate surrounding the significance of COX-2-related adverse cardiovascular events continued. Recently, additional information was published and is summarized below. Rofecoxib and valdecoxib have been removed from the market due to their association with an increased risk of serious cardiovascular events. Additionally, the FDA has asked that the labeling of celecoxib be revised to include a boxed warning highlighting the potential for an increased risk of cardiovascular events associated with its use. Further information is available at <http://www.fda.gov/cder/drug/infopage/COX2/default.htm>.

Solomon and colleagues performed an independent review of the cardiovascular safety data from a trial evaluating the efficacy of celecoxib for the prevention of adenomatous polyps in patients who had undergone endoscopic polypectomy (12). The Adenoma Prevention with Celecoxib (APC) study was a prospective, randomized, double-blind, multi-center trial comparing the efficacy and safety of celecoxib 200 mg twice daily, 400 mg twice daily and placebo in reducing the occurrence of adenomatous polyps in the colon and rectum one and three years after endoscopic polypectomy. Patients were stratified according to the use or nonuse of aspirin for cardiovascular prophylaxis. Endpoints evaluated included death from cardiovascular causes, myocardial infarction (MI), stroke, heart failure, unstable angina and the need for a cardiovascular procedure. A total of 2035 patients were included in the analysis. The hazard ratio (relative to the placebo group) for the composite endpoint of death from cardiovascular causes, non-fatal MI, stroke or heart failure was 2.3 (95% CI, 0.9-5.5) in the 200 mg group and 3.4 (95% CI, 1.4-7.8) in the 400 mg group. The hazard ratio was not significantly affected by baseline aspirin use. The cardiovascular safety committee concluded that continued exposure to celecoxib placed patients at increased risk for serious cardiovascular events.

Bresalier and colleagues evaluated potential thrombotic events in the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial (13). APPROVe was designed to evaluate the hypothesis that three years of rofecoxib therapy would reduce the risk of recurrent adenomatous polyps in patients with a history of colorectal adenomas. Patients with evidence of uncontrolled hypertension, angina or congestive heart failure, MI, coronary angioplasty, coronary-artery bypass grafting within the preceding year or stroke or transient ischemic attack within two years before screening were excluded. Patients were randomized to rofecoxib 25mg daily or placebo daily for three years. Initially, low-dose aspirin was not permitted. However, following the publication of VIGOR the protocol was modified to allow randomized patients to take low-dose aspirin for cardiovascular protection. A total of 2586 patients were included in the analysis. Although this study was terminated early, the mean duration of treatment was 2.4 years in the rofecoxib group and 2.6 years in the placebo group. The risk of confirmed thrombotic events (including cardiac, cerebrovascular and peripheral vascular events) was significantly higher in the rofecoxib group (hazard ratio, 1.92; 95% CI, 1.19 to 3.11). A post-hoc analysis revealed that the difference in thrombotic events became evident after 18 months of therapy. The use of low-dose aspirin did not influence outcome.

The CABG surgery study was a multi-center, randomized, double-blind, placebo-controlled study designed to clarify the safety of parecoxib and valdecoxib following CABG (14). Patients were randomized to one of the following groups:

- Parecoxib 40mg IV on the morning after surgery followed by 20mg IV every 12 hours for three days, followed by valdecoxib 20mg orally every 12 hours through day 10
- Placebo for three days, followed by valdecoxib 20mg orally every 12 hours through day 10
- Placebo through day 10

All patients received aspirin through day 10. The primary endpoint was the combined incidence of cardiovascular, renal, surgical wound and gastrointestinal complications. Cardiovascular events included cardiac, cerebrovascular and peripheral vascular events. Cardiac events were further defined as myocardial infarction, severe myocardial ischemia, sudden cardiac death or unexpected death without an identifiable non-cardiac cause. Patients were stratified first according to risk (high versus low) and then according to geographic location. A total of 1671 patients were randomized. Cardiovascular events were significantly more frequent in the parecoxib/valdecoxib group compared to the placebo group (2% versus 0.5%; risk ratio, 3.7; 95% CI, 1 to 13.5). There was no significant difference between the valdecoxib and placebo groups.

APPENDIX I: PATIENTS WITH OR AT HIGH RISK FOR THROMBOTIC CARDIOVASCULAR EVENTS

The following table may be used to identify patients with or at high risk for thrombotic cardiovascular events based upon whether or not they are candidates for aspirin therapy.	
Primary Prevention (15)	Secondary Prevention (16)
<p>Aspirin therapy is considered for patients >50 years of age who have at least one major risk factor for coronary artery disease</p> <ul style="list-style-type: none"> • Cigarette smoking • Hypertension • Diabetes mellitus • Hypercholesterolemia • History of parental infarction 	<p>Aspirin therapy is indicated for patients with a history of atherosclerotic cardiovascular disease (i.e., acute myocardial infarction, stroke, transient ischemic attack)</p>

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