Enhanced Recovery After Surgery (ERAS) cardiac turnkey order set for perioperative pain management in cardiac surgery: Proceedings from the American Association for Thoracic Surgery (AATS) ERAS Conclave 2023

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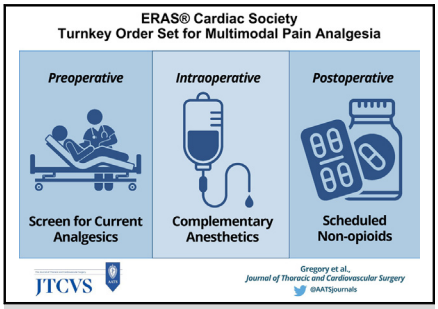
ABSTRACT

Objective: Optimal perioperative pain management is an essential component of perioperative care for the cardiac surgical patient. This turnkey order set is part of a series created by the Enhanced Recovery After Surgery Cardiac Society, first presented at the Annual Meeting of The American Association for Thoracic Surgery in 2023. Several guidelines and expert consensus documents have been published to provide guidance on pain management and opioid reduction in cardiac surgery. Our objective is to consolidate that guidance into an evidence-based order set that will assist in the implementation of a comprehensive multimodal approach to pain management.

Methods: Subject matter experts were consulted to translate existing guidelines and peer-reviewed literature into a sample turnkey order set for pain management. Orders derived from consistent Class I, IIA, or equivalent recommendations across referenced guidelines and consensus manuscripts appear in the order set in bold type. Selected orders that were inconsistently Class I or IIA, Class IIB, or supported by published evidence, were also included in italicized type.

Results: Opioid-based analgesia is associated with delayed recovery and opioid-related adverse events. Several multimodal medications have been shown to reduce reliance upon opioids. These include the scheduled use of acetaminophen, gabapentinoids, and nonsteroidal anti-inflammatory drugs. In addition, intravenous analgesics such as dexmedetomidine, ketamine, magnesium, and lidocaine have been shown to both complement the maintenance of anesthesia as well as optimize pain control postoperatively. Long-acting opioids remain a key component of pain management when provided to reduce the overall use of short-acting synthetic opioids or in direct response to break though pain after exhausting other alternatives. When applied in a bundled fashion, several studies have demonstrated a reduction in overall opioid administration and improved rates of postoperative recovery.

Conclusions: There has been increased awareness regarding the potential short- and long-term adverse effects of both inadequate analgesia and excessive opioid administration after cardiac surgery. This turnkey order set aims to facilitate implementation of a comprehensive approach toward provision of multimodal, opioid-sparing medications to optimize pain management in cardiac surgery. (JTCVS Open 2024;22:14-24)



ERAS Cardiac Society Turn Key Order Set for Multimodal Analgesia.

CENTRAL MESSAGE

Integration of guideline recommendations and consensus statements into a standardized turnkey order set facilitates practical implementation of multimodal analgesia for adult cardiac surgery patients.

PERSPECTIVE

Previous guidelines and consensus statements provide guidance for pain management following adult cardiac surgery. The Enhanced Recovery After Surgery (ERAS) Cardiac Society has translated existing recommendations into a "turnkey" order set to assist clinicians in implementing a comprehensive multimodal plan to improve analgesia, reduce opioid requirements and optimize patient recovery.

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Abbreviations and Acronyms

ANZCA = Australian and New Zealand College of Anaesthetists
ERAS = Enhanced Recovery After Surgery
NPOU = new persistent opioid use
NSAID = nonsteroidal anti-inflammatory drug
ORADE = opioid-related adverse event
TKO = "turnkey" order set

Traditionally, an opiate-based anesthetic and analgesic strategy was the mainstay of cardiac surgical care. There has been a recent shift to minimizing opioid analgesia perioperatively, in part as the result of recent international concerns with inappropriate opioid-prescribing practices, misuse, and opioid-related fatalities. New persistent opioid use (NPOU), generally defined as patients who were previously opioid-naïve who continue taking opioids several months after surgery, has an incidence of up to 13% in cardiac surgery.[1-3] In addition, there are several well-documented side effects and adverse clinical events, termed opioid-related adverse events (ORADEs), secondary to opioid use in the postoperative recovery period. This includes sedation, gastrointestinal dysfunction, nausea/vomiting, respiratory depression, increased pain sensitization, and immune system suppression. These events may occur in up to 40% of patients who undergo cardiac surgery.[4] Unfortunately, simply eliminating opioids without an analgesic replacement may contribute to suboptimal pain management. Severe pain itself has undesirable adverse effects such as anorexia, reduced mobilization, delirium, and sleep deprivation.[5] Furthermore, postsurgical pain has been consistently shown to be a risk factor for the development of chronic persistent postsurgical pain, which has a reported incidence of nearly 30% in cardiac surgery and negatively impacts quality of life.[6,7]

Pain management after cardiac surgery requires achieving acceptable analgesia while minimizing the use of opioids. Several nonopioid medications may be considered, each with its own mechanisms of action and potential side effects (Table 1). In general, a comprehensive approach to analgesia should include assessing for pain, as well as the side effects and adverse events related to administered analgesic medications. Nonopioid options should be exhausted first, reserving opioids as a last-line therapy, in accordance with a strategy endorsed by the World Health Organization.[8] When opioids are required, practitioners should begin with very low doses and titrate upward only in the event of moderate or severe pain.

Optimal postoperative analgesia after cardiac surgery can be a challenge. To succeed, a multidisciplinary approach is required, built on a foundation of nonopioid multimodal therapies, and including active patient and caregiver participation. Multiple societies have published evidence-based guidelines for the perioperative pain management in patients who undergo cardiac surgery. From a provider standpoint, however, meaningful standardized adoption and implementation of comprehensive pain management plan amidst the various available guidelines can be challenging. Therefore, we analyzed published guidelines to develop a practical pain management order set that can be widely implemented. This "turnkey" order set (TKO) is part of a series created by the Enhanced Recovery After Surgery (ERAS) Cardiac Society and was presented at The American Association for Thoracic Surgery Annual Meeting ERAS Conclave, in April 2023.

METHODS

To assist with development and implementation of cardiac ERAS programs, we have created a sample TKO. The order set has been generated by subject matter experts translating accumulated evidence, peer-reviewed literature, and current enhanced recovery practices. The subject matter experts (all listed authors) have expertise in enhanced recovery, perioperative care, and implementation science. A scoping literature search was performed to identify existing peer-reviewed society guidelines or consensus statements on postsurgical pain management. Recommendations from each document were evaluated, with those receiving Class I and IIA (or equivalent) grades identified for consideration (Table 2). A full description of the grading methodology and recommendations from each society is provided in Appendix E1. Translation of these recommendations into a TKO divided them into action categories (assessment, communication, and therapies) and displayed across phases of care (Table 3). Orders derived from Class I or IIA recommendations across all referenced guidelines and consensus manuscripts appear in the TKO **in bold type**. Selected orders that were inconsistently Class I or IIA, Class IIB, or supported by evidence published in peer-reviewed journals, were also included *in italicized type*. Notably, the intent was not to recapitulate the evidence base justifying existing recommendations, as this task was

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TABLE 1. Common nonopioid analgesic medications, including mechanism of action and side effects/adverse events

Medication	Route(s)	Analgesia mechanism of action	Potential side effects and adverse events
Acetaminophen	PO/PR	Complex and multifactorial. TRPV1 and CB1 in the brain and spinal cord. PG reduction through inhibition of COX pathway likely not the primary mechanism. May also be a 5-HT3 and opioid receptor agonist in the brain.	Liver toxicity
Celecoxib	PO	Selective COX-2 inhibition leading to reduction of PG synthesis.	Renal injury GI irritation/bleeding Bleeding Increased CV events
Dexamethasone	PO/IV	Anti-inflammatory through inhibition of phospholipase, which reduces COX and LOX pathway activity.	Hyperglycemia Immune suppression Sleep disturbance
Dexmedetomidine	IV	Selective inhibition of α2-adrenergic receptors, inhibiting HCN channels in the dorsal root ganglion.	Bradycardia Hypotension (including orthostatic) Hypertension (usually with rapid loading) Sedation Confusion/agitation Nausea
Gabapentin	PO	Reduced neurotransmitter release in the brain and spinal cord by blocking synaptic alpha-2 delta calcium channels. May have secondary analgesic effects through NMDA, neurexin, and thrombospondin activity.	Sedation Unsteadiness/dizziness Confusion/agitation Sleep disturbance Altered mood Nausea Vision changes Dry mouth
Ketamine	IV/TD	NMDA receptor antagonist, reducing pain signal amplification/sensitization. May have secondary analgesic effects through 5-HT3, sodium-channel, MAO, and Ach receptor activity.	Hallucinations Confusion/agitation Unsteadiness/dizziness Sleep disturbance Nausea Amnesia
Ketorolac	PO/TD	Nonselective COX-1 and COX-2 inhibition leading to reduction of PG synthesis.	Renal injury GI irritation/bleeding Bleeding Increased CV events
Lidocaine	IV/TD	Sodium-channel blockade in the CNS. May have secondary analgesic effects through other central voltage/ligand-gated channels or GPCRs involved in pain pathways.	Local anesthetic toxicity Unsteadiness/dizziness Vision changes Nausea Headache
Magnesium	IV	NMDA receptor antagonist, reducing pain signal amplification/sensitization.	Muscle weakness Hypotension Confusion Unsteadiness/dizziness Flushing Sedation
Naproxen	PO	Non-selective COX-1 and COX-2 inhibition leading to reduction of PG synthesis.	Renal injury GI irritation/bleeding Bleeding Increased CV events

(Continued)

TABLE 1. Continued

Medication	Route(s)	Analgesia mechanism of action	Potential side effects and adverse events
Paracetamol	PO/IV	Complex and multifactorial. TRPV1 and CB1 in the brain and spinal cord. PG reduction through inhibition of COX pathway likely not the primary mechanism. May also be a 5-HT3 and opioid receptor agonist in the brain.	Liver toxicity
Pregabalin	PO	Reduced neurotransmitter release in the brain and spinal cord by blocking synaptic alpha-2 delta calcium channels. May have secondary analgesic effects through NMDA, neurexin, and thrombospondin activity.	Sedation Unsteadiness/dizziness Confusion/agitation Sleep disturbance Altered mood Nausea Vision changes Dry mouth
Tramadol	PO	In addition to its opioid receptor agonism, it also functions as a reuptake inhibitor of both norepinephrine and 5-HT3.	Sedation Unsteadiness/dizziness Constipation Nausea Headache Dry mouth

PO, Oral; *PR*, rectal; *TRPV1*, transient receptor potential vanilloid 1; *CB1*, cannabinoid receptor type 1; *PG*, prostaglandin; *COX*, cyclooxygenase 1; *5-HT3*, serotonin; *COX-2*, cyclooxygenase 2; *GI*, gastrointestinal; *CV*, cardiovascular; *IV*, intravenous; *LOX*, lipoxygenase; *HCN*, hyperpolarization-activated cyclic nucleotide-gated; *NMDA*, *N*-methyl-D-aspartate; *MAO*, monoamine oxidase; *Ach*, acetylcholine; *TD*, transdermal; *CNS*, central nervous system; *GPCR*, G-protein–coupled receptor.

performed as part of the original guidelines and consensus statements efforts. Decisions regarding order inclusion were made on the basis of estimated benefit, risk, cost, implementation complexity, and generalizability. Each of these orders should be considered on the basis of local institutional priorities, resources, practices, and expertise. Although it is a growing component of multimodal pain management, regional anesthesia was not included within the scope of this TKO.

Published Guidelines and Consensus Documents

Although publications consistently report use of a multimodal analgesia bundle within an ERAS program, there are limited data in the cardiac surgical literature to guide which agents should be used (Table 2). The PeriOperative Quality Initiative and the ERAS Cardiac Society have recently published a consensus report on pain management and opioid stewardship.[9] Similarly, the Society of Cardiovascular Anesthesiologists Quality, Safety, and Leadership Committee has also published a Practice Advisory on pain management following cardiac surgery.[10] Given the limited evidence from which to base recommendations from the cardiac surgery literature, the fifth edition update of the Australian and New Zealand College of Anaesthetists (ANZCA) acute pain management scientific evidence review, which focuses on the noncardiac surgery patient population, was also included.[11,12] The ANZCA evidence review is one of the largest, most comprehensive sources of assessing evidence for postoperative analgesia interventions across all surgical specialties. Given the variety of analgesic agents with limited evidence already being considered or currently used in cardiac ERAS programs, we felt its inclusion would allow for a preliminary appraisal of their efficacy. Any TKO orders that were included on the basis solely of the grading of the ANZCA document were kept as italicized to avoid an erroneous assumption that results from noncardiac patients are generalizable to cardiac surgery.

Preoperative

A comprehensive plan for perioperative multimodal analgesia should be initiated before surgery by first screening patients for a history of pain and current or recent use of analgesics, including both prescribed and over-the-counter agents. Ideally, a full appraisal of the patient's daily analgesic requirements would be performed at the time of the surgical and/or anesthesia consultation, as far in advance of the surgery as possible.

TABLE 2. Summary of multimodal analgesic and respective orders that received Class I/IIA, or equivalent, from ANZCA, ERASC/POQI, and SCA

Multimodal analgesia intervention	ANZCA	ERAS/POQI	SCA
Medications			
Acetaminophen	✓	✓	✓
Celecoxib	✓		✓
Dexamethasone	✓		
Dexmedetomidine	✓	✓	
Gabapentin	✓		
Ketamine	✓	✓	
Ketorolac	✓		✓
Lidocaine	✓		
Magnesium	✓		
Methadone	✓	✓	✓
Naproxen	✓		✓
Paracetamol	✓	✓	✓
Pregabalin	✓		✓
Tramadol	✓		
General principles and health care system measures			
Avoid high doses of opioids	✓	✓	
Pain and quality of analgesia should be regularly assessed	✓		
Preoperative patient education	✓	✓	✓

(Continued)

TABLE 2. Continued

Multimodal analgesia intervention	ANZCA	ERAS/POQI	SCA
Staff education to improve assessment, analgesia, and prescribing practices.		✓	
Opioid-related adverse events impede recovery and are associated with poor outcomes			
Pain specialist consultation may improve pain relief and reduce adverse effects			
Use of multimodal nonopioid analgesics	✓	✓	
Perioperative opioid stewardship		✓	
Short-term opioid therapy may lead to long-term use/misuse			
Multidisciplinary pathways tailored to each cardiovascular surgery program		✓	
Preoperative screening to identify patients at risk for persistent opioid use			
Preoperative screening to identify patients at risk for chronic pain or opioid tolerance			
Preoperative cognitive, behavioral, or psychosocial interventions to reduce pain	✓		

Complete listing of referenced grades provided in Appendix E1. *ANZCA*, Australian and New Zealand College of Anaesthetists; *ERASC/POQI*, Enhanced Recovery After Surgery Cardiac Society PeriOperative Quality Initiative; *SCA*, Society of Cardiovascular Anesthesiologists.

Particular attention should be given to daily opioid use and the potential of opioid tolerance. The US Food and Drug Administration defines opioid tolerance as requiring the equivalent of 60 milligrams of oral morphine per day for 1 week or longer[13] and opioid conversion charts can guide practitioners. In the event a patient utilizes opioids regularly, they should be advised to take their standard opioid medications on the day of surgery or provide the oral equivalent in the preoperative holding area to optimize analgesia and prevent potential withdrawal symptoms. As outlined in Table 3, preoperative analgesic medications should be identified and communicated to the prescribing provider to ensure appropriate dosing (and withholding where necessary) of preoperative analgesic medications. For more complex pain patients, or those with opioid dependance, it is ideal to consult a Pain Specialist before surgery to collaboratively develop an individualized pain management plan and coordinate any necessary postoperative follow-up.

A single preoperative dose of acetaminophen is encouraged in the absence of severe pre-existing liver disease, and although there remains a debate regarding the ideal formulation, the relative efficacy versus cost favors oral administration in the preoperative period.[14-16] Gabapentinoids, including gabapentin and pregabalin, have been the subject of multiple randomized trials in cardiac surgery and found to provide efficacy in improving pain while reducing subsequent opioid exposure.[17-20] Both agents require dose modification in older patients (age >75 years) or reduced baseline creatinine clearance (glomerular filtration rate <30), and only 1 of the 2 agents should be administered.

Intraoperative

The intraoperative phase of the comprehensive plan for perioperative multimodal analgesia should be characterized by the provision of several agents shown to both complement the maintenance of anesthesia and reduce the reliance on opioid-based analgesia, both during surgery and afterwards. Dexmedetomidine has been extensively studied in the cardiac surgical setting, with reported benefits including earlier extubation, reduced delirium, and prevention of arrhythmia.[21,22] It has also been shown to significantly improve patient-reported pain scores and reduce opioid requirements after surgery.[23,24] The dosing range provided represents an appropriate balance to maximize analgesic benefits and reduce side effects such as bradycardia and hypotension. Although results have at times been conflicting, *N*-methyl-D-aspartate receptor antagonists such as ketamine have yielded a modest reduction in opioid requirements and pain scores. "Subanesthetic dosing" (0.1-0.3 mg/kg/h) provides the necessary balance of analgesia while avoiding side effects such as hallucination or tachycardia.[25,26] Magnesium, a potent antiarrhythmic *N*-methyl-D-aspartate antagonist, has a wide therapeutic window, allowing for routine bolus and infusion to promote analgesia. Other agents, such as intravenous lidocaine, are well studied in noncardiac surgery, and its dosing in cardiac procedures should be tailored to avoid the potential for local anesthetic toxicity,[27] particularly if providers anticipate the use of additional lidocaine upon separation from cardiopulmonary bypass or in concert with regional analgesia.

Importantly, the use of weight-based dosing of short-acting synthetic opioids has increasingly fallen out of favor, both to minimize delayed emergence from anesthesia and lessen the potential for ORADEs. Low-dose regimens are favored over the historical high-dose approaches previously used in cardiac surgery (defined as: fentanyl >20 μg/kg, sufentanil >2 μg/kg, remifentanil >1.7 mg, morphine >2 mg/kg). Lower dose regimens are associated with shorter time to extubation with no major differences in postoperative complications.[28,29] The pre-emptive use of longer-acting alternatives, such as methadone or hydromorphone, may reduce the risk of rapidly developing opioid tolerance and obviate the need for excessive short-acting opioid use. A recent randomized controlled trial and systematic review suggested that 0.1 to 0.3 mg/kg methadone, given before incision, significantly reduces postoperative opioid exposure compared to morphine or fentanyl.[30,31] The decision to use methadone should be considering in the context of existing institutional opioid requirements, both intra- and postoperatively and rate of ORADEs.

Postoperative

In the postoperative setting, patients benefit most from the administration of several nonopioid medications as first-line therapy to optimize pain management. These most notably include acetaminophen, gabapentinoids and nonsteroidal anti-inflammatory drugs (NSAIDs). The use of oral versus intravenous acetaminophen is best dictated by the ability of the patient to tolerate oral intake. If gabapentinoids are administered, daily surveillance of renal function and monitoring for sedation is important to best titrate dosing. Similar to the preoperative phase, gabapentinoid dosing should be adjusted (or withheld) in the setting of advanced age or reduced renal function. The primary barriers to more widespread use of NSAIDs, despite the fact that small prospective trials are supportive of their use after cardiac surgery,[32,33] are both the potential for kidney injury and an existing Food and Drug Administration warning regarding their use in the setting of

TABLE 3. Multimodal turnkey order set

Order	Route	Dose	Administration instructions
A. Preoperative			
Communication			**Please review and record any analgesic medications that the patient has taken in the past 24 h.**
Communication			**Please inform provider if the patient has taken any analgesic medications in the past 24 h.**
Acetaminophen	**PO**	**1000 mg once**	**Confirm with provider prior to administration with history of liver disease.**
Communication			*Please complete screening for chronic opioid use or "Opioid Tolerance".*
Communication			*Contact provider and consider Pain Specialist consultation for patients with history chronic opioids use or opioid tolerance.*
Choose one			
Gabapentin	*PO*	*300 mg once*	*Withhold if age >75 y or GFR <30.*
Pregabalin	*PO*	*150 mg once*	*Withhold if age >75 y or GFR <30.*
Opioid (ie, oxycodone, morphine, methadone)	*PO*	*Daily equivalent*	*If evidence of opioid tolerance and patient has not taken daily dose.*
B. Intraoperative			
Dexmedetomidine	**IV – infusion**	**0.2-0.7 mcg/kg/h**	**Initiate postinduction, continue on transfer to ICU, discontinue following extubation. Consider continuing postextubation for inadequate analgesia.**
Ketamine	**IV – bolus**	**0.5 mg/kg**	**Consider administering pre-incision, followed by infusion.**
Ketamine	**IV – infusion**	**0.1-0.3 mg/kg/h**	**Initiate following Ketamine bolus. Discontinue at time of chest closure.**
Lidocaine	**IV – bolus**	**1.5 mg/kg**	**Administer pre-incision, followed by infusion.**
Lidocaine	**IV – infusion**	**1.0 mg/kg/h**	**Initiate following Lidocaine bolus. Discontinue at time of chest closure.**
Dexamethasone	*IV – bolus*	*0.2 mg/kg*	*Administer pre-incision.*
Magnesium	*IV – bolus*	*30 mg/kg*	*Administer during procedure, followed by infusion.*
Magnesium	*IV – infusion*	*10 mg/kg/h*	*Initiate following Magnesium bolus. Discontinue on chest closure.*
Methadone	*IV – bolus*	*0.1-0.3 mg/kg*	*Administer pre-incision.*
C. Postoperative			
Hydromorphone	**IV Q2-4H PRN**	**0.2-0.4 mg**	**If age >75 y or weight <60 kg. Administer for pain >3/10 and no other analgesic options available. Confirm with provider prior to administration with history of liver disease. Re-evaluate daily.**
Hydromorphone	**IV Q2-4H PRN**	**0.4-0.8 mg**	**If age <75 y and weight >60 kg. Administer for pain >3/10 and no other analgesic options available. Confirm with provider prior to administration with history of liver disease. Re-evaluate daily.**
Hydromorphone	**PO Q4H PRN**	**0.5-1 mg**	**If age >75 y or weight <60 kg. Administer for pain >3/10 and no other analgesic options available. Confirm with provider prior to administration with history of liver disease. Re-evaluate daily**
Hydromorphone	**PO Q4H PRN**	**1-2 mg**	**If age <75 y and weight >60 kg. Administer for pain >3/10 and no other analgesic options available. Confirm with provider prior to administration with history of liver disease. Re-evaluate daily**
Communication			*Contact provider and consider Pain Specialist consultation for refractory postoperative pain greater than 6/10.*
Communication			*Contact provider and consider Transition Pain Service consult for patients requiring opioid analgesia prior to discharge.*
Choose one			
Gabapentin	*PO*	*100 mg TID*	*Withhold if age >75 y or GFR <30. Titrate dose if analgesia is ineffective and there are no side effects. Stop and re-evaluate after 5 d, or prior to discharge.*
Pregabalin	*PO*	*25 mg BID*	*Withhold if age >75 y or GFR <30. Titrate dose if analgesia is ineffective and there are no side effects. Stop and re-evaluate after 5 d, or prior to discharge.*

(Continued)

TABLE 3. Continued

Order	Route	Dose	Administration instructions
Choose one			
Ketorolac	*IV*	*15 mg Q8H PRN*	*Withhold if patient has history of chronic kidney disease or if current GFR <60. Stop after 3 doses.*
Celecoxib	*PO*	*200 mg BID*	*Withhold if patient has history of chronic kidney disease or if current GFR <60. Stop and re-evaluate after 3 d.*
Naproxen	*PO*	*500 mg BID*	*Withhold if patient has history of chronic kidney disease or if current GFR <60. Stop and re-evaluate after 3 d.*
Tramadol	*PO*	*25-50 mg Q4H PRN*	*Confirm with MRP prior to administration with history of liver disease. Stop and re-evaluate after 3 d.*

A: preoperative phase; B: intraoperative phase; C: postoperative phase. **Bold**; Class I/IIA (or equivalent) recommendations across all referenced guidelines and consensus manuscripts. *Italicized*; Inconsistently Class I/IIA (or equivalent), Class IIB, or supported by evidence published in peer-reviewed journals. *PO*, Oral; *GFR*, glomerular filtration rate; *IV*, intravenous; *ICU*, intensive care unit; *PRN*, as needed; *TID*, three times day; *BID*, twice a day.

coronary revascularization.[34-36] Dosing strategies are provided for several types of NSAIDs and, if deemed appropriate, clinicians should select a single agent from this class. Ultimately, patients benefit most from the scheduled (rather than as needed) utilization of nonopioid medications.

The scheduled use of nonopioids represents one foundational aspect of multimodal analgesia. Another, as introduced by one of the consensus statements used for this order set, is the concept of individual opioid stewardship.[9] As it states, "Opioid stewardship means to judiciously use opioids, balancing the benefits of optimal analgesia against side effects and risks of opioid use. The desire to seek opioid-free perioperative care, though note-worthy, does not usually account for current gaps in understanding regarding the appropriateness of such a strategy in the surgical setting or the potential associated risks. It is more advisable to consider opioid-sparing perioperative care, optimizing the delivery of opioids to their greatest potential." Therefore, after exhausting the use of appropriate schedule non-opioids, the use of as needed breakthrough opioid medications maximizes their efficacy to address untreated pain while minimizing the risk of ORADEs.[9] Subsequent opioid use should be provided in the lowest effective dose for the shortest duration possible using the representative orders as outlined. The final aspect of opioid stewardship is conscientious and standardized discharge planning. Although there are existing guidelines recommending an approach to opioid prescribing for nonsurgical and noncardiac surgical pain, there is limited guidance in the cardiac surgical population.[37,38] The Michigan Opioid Prescribing Engagement Network (ie, Michigan OPEN) has published an opioid-prescribing approach guided by inpatient opioid use on the day before discharge, which may a framework for future guidelines for cardiac surgery patients.[39]

Putting the Guidelines Together: A TKO

The TKO set provides an evidence-based framework to assist clinicians in the bedside implementation of a comprehensive multimodal pain management plan. Certain orders and recommendations were considered fundamental. These essential recommendations have been depicted in Table 3 as assessments, therapy, and clinical communications organized by phase of care and written as orders reflecting fairly common practice patterns. Some agents are best used if provided in a scheduled fashion throughout the patient journey (eg, gabapentinoids), whereas others are typically ordered as needed (pro re nata, or PRN). Other recommendations, such as the use of specific anesthetic agents, are generally isolated to a single phase of care. There are potential omissions in our order set, which is not intended to be all-encompassing. Rather, our aim is to provide programs with a sample of essential guideline-recommended interventions to optimize pain management while minimizing both opioid exposure and ORADEs. It is therefore recommended that the provided order set (including route, dose and scheduled vs PRN) be modified according to local clinical needs, medication formularies, provider constraints, and institutional policies. Finally, although beyond the scope of this manuscript, it is important to acknowledge the potential barriers to implementing enhanced recovery program elements or other quality improvement initiatives. There has been a growing appreciation for the importance of team-building, implementation science, and audit-all important considerations when applying this TKO to patient care.[40,41]

FUTURE STUDY

Despite the growing body of published research related to pain management in cardiac surgery, there are opportunities to improve the evidence base. There is ongoing investigation into how setting expectations before surgery may lead to greater patient empowerment, shared decision-making regarding postoperative analgesia, and improved outcomes.[42] Although this TKO has provided several non-opioid analgesic options, their impact on pain, adverse effects, and opioid requirements have been relatively underrepresented in the existing literature compared to the non-cardiac surgical population. As such, large studies that examine the collective application of numerous agents in concert are necessary to establish clear rates of efficacy and identify potential side effects. There are only limited examples of programs that have published their experiences with the bundled application of these agents.[43-45] However, those studies confirmed both a significant reduction in intra- and postoperative opioid use as well as opioid-related side effects, including gastrointestinal complications and delayed recovery. Regional analgesia has shown to be a promising alternative to the use of analgesic medications and additional study is warranted to establish the ideal technical approach, dosing strategy and timing of various techniques in relation to the surgical procedure.[9] There are numerous nonpharmacologic interventions that may reduce pain and improve the patient experience.[46] Although this approach has demonstrated potential benefit in cardiac surgery patients, it is an area of limited evidence that requires greater study before widespread adoption can be recommended.[47] Many of the proposed analgesic interventions are likely to reduce reliance upon perioperative opioids, which is anticipated to mitigate the potential for NPOU. However, additional study is necessary to establish the role of

dashboard tracking of opioid use or formal guidance regarding discharge planning and prescription practice in systematically reducing the incidence of NPOU after cardiac surgery.[3,48] Finally, although this order set introduces the concept of screening for chronic opioid use and ensuring adequate replacement of daily equivalents, the literature is generally devoid of comprehensive strategies to ideally manage patients with chronic opioid tolerance in the setting of cardiac surgery.

CONCLUSIONS

The benefit of a comprehensive multimodal pain management plan in cardiac surgery is increasingly well established, reflected in several recent published guidelines and consensus statements, including part of the recently published Joint Consensus Statement by the ERAS Cardiac Society, ERAS International Society, and The Society of Thoracic Surgeons.[49] However, implementation remains highly variable. Although existing guidelines establish the basic evidence and rationale for care, translating that guidance into concrete interventions remains a challenge. Here, we provide a TKO set to facilitate the integration of the foundational principles of multimodal analgesia into daily cardiac surgical practice to optimize pain management.

Conflict of Interest Statement

A.J.G. reports speaker and advisory activities for Edwards Lifesciences. R.C.A. reports honoraria from Edwards Lifesciences and HLS Therapeutics. In addition, he functions on an Advisory Board for Renibus Therapeutics Inc. S.C. served on advisory boards for Edwards Lifesciences, La Jolla Pharmaceutical Company, Baxter Healthcare, and Eagle Pharmaceuticals. V.M.B. and A.R. report speaker's bureau, Edwards Lifesciences. R.S. reports consulting/advisory relationships with Zimmer Biomet, AtriCure, La Jolla, Terumo, Encare, and Edwards Lifesciences. D.T.E. reports Device Safety Monitoring Board: Edwards Lifesciences Transcatheter Valves, Trial Steering Committees: Renibus, Alexion, Cardiorenal Systems, Genentech; Medical Advisory Boards: Astellas, Medela, Arthrex, AtriCure. K.W.L reports consultant for Abiomed, Alexion, Medela, Medtronic, and Renibus. G.M. reports consultant for Edwards Lifesciences. S.R. reports advisor and speaker for 3M. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: pain, analgesia, multimodal analgesia, opioid, opioid-sparing, comfort, enhanced recovery, perioperative care

APPENDIX E1. COMPLETE LISTING OF RECOMMENDATIONS AND GRADES REFERENCED FOR PRODUCTION OF THE MULTIMODAL TURNKEY ORDER SET

Grading Methodology

Australian and New Zealand College of Anaesthetists (ANZCA). Level I: Evidence obtained from a systematic review of all relevant randomized controlled trials (RCTs)[E1,E2]

Level III-2: Evidence obtained from well-designed pseudo-RCTs (alternate allocation or some other method)

Level III-3: Evidence obtained from comparative studies with historical control, 2 or more single-arm studies, or interrupted time series without a parallel control group

Level IV: Evidence obtained from case series, either post-test or pretest and post-test

Peri-Operative Quality Initiative (POQI) and the Enhanced Recovery After Cardiac Surgery Society (ERAS Cardiac).

Medications. **Recommend vs May Consider**. No formal methodology described. Suggestions were based on expert consensus regarding the expected effectiveness and possible harm based on existing literature.[E3]

General Principles & Health care System Measures.

Grade:

Strong; Authors are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.

Level of evidence:

A, Strong Evidence; B, Moderate Evidence; C, Weak Evidence; D, Conflicting Evidence

Society of Cardiovascular Anesthesiologists (SCA).

Category. **A** Supportive literature (RCTs)[E4]

Level 2 Studies insufficient in number to conduct meta-analysis

B Suggestive literature (observational studies)

Level 2 Noncomparative studies with associative or descriptive statistics

C Inconclusive or conflicting literature

D Insufficient evidence from literature

Grade

B Beneficial

E Equivocal

E-References

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Medications	ANZCA	ERAS/POQI	SCA		
	Evidence	Recommendation	Category	Level	Grade
Acetaminophen	Level I	Recommended	A	2	B
Celecoxib	Level I	May consider	A	2	B
Dexamethasone	Level I	N/G	D	–	–
Dexmedetomidine	Level I	Recommended	C	–	–
Gabapentin	Level I	May consider	C	–	–
Ketamine	Level I	Recommended	C	–	–
Ketorolac	Level I	May consider	A	2	B
Lidocaine	Level I	May consider	D	–	–
Magnesium	Level I	N/G	C	–	–
Methadone	Level I	Recommended	A	2	B
Naproxen	Level I	May consider	A	2	B
Paracetamol	Level I	Recommended	A	2	B
Pre-gabalin	Level I	May consider	A	2	B
Tramadol	Level I	N/G		N/G	

General principles & health care system measures	ANZCA	ERAS/POQI		SCA		
	Evidence	Grade	LOE	Category	Level	Grade
Avoid high doses of opioids	Level I	Strong	B		N/G	
Pain and quality of analgesia should be regularly assessed	Level I	N/G			N/G	
Preoperative patient education	Level I	Strong	C	A	2	B
Staff education to improve assessment, analgesia, and prescribing practices.	Level III-3	Strong	C		N/G	
Opioid-related adverse events impede recovery and are associated with poor outcomes	Level III-2	N/G			N/G	
Pain specialist consultation may improve pain relief and reduce adverse effects	Level III-3	N/G			N/G	
Use of multimodal nonopioid analgesics	Level I	Strong	C	B	2	B
Perioperative opioid stewardship	N/G	Strong	B		N/G	
Short-term opioid therapy may lead to long-term use/misuse	Level III-2	N/G			N/G	
Multidisciplinary pathways tailored to each CV surgery program	N/G	Strong	C		N/G	
Preoperative screening to identify patients at risk for persistent opioid use	N/G	N/G		B	2	B
Preoperative screening to identify patients at risk for chronic pain	Level III-2 & Level IV	N/G		B	2	B
Preoperative cognitive, behavioral, or psychosocial interventions to reduce pain	Level I	N/G		B	2	B

ANZCA, Australian and New Zealand College of Anaesthetists; *ERASC/POQI*, Enhanced Recovery After Surgery Cardiac Society PeriOperative Quality Initiative; *SCA*, Society of Cardiovascular Anesthesiologists; *N/G*, not graded; *LOE*, level of evidence; *CV*, cardiovascular.