NSAIDS
THEORY & REALITY

R2 NATTACHAI HEMTANON
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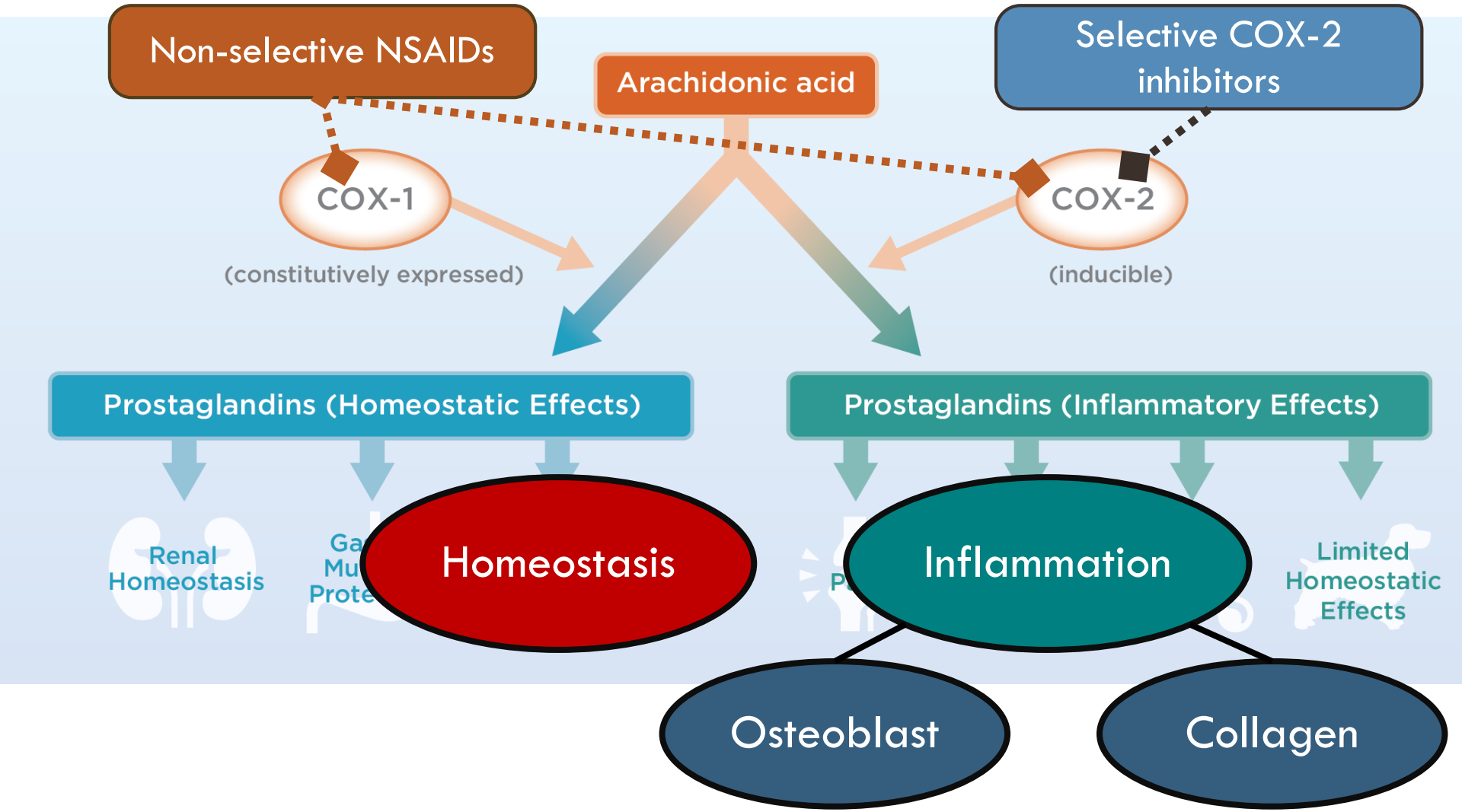
NSAIDs

- Nonsteroidal anti-inflammatory drugs

- Mechanism of action
  - Inhibit cyclooxygenase (COX) enzyme
  - Inhibit transformation of arachidonic acid to prostaglandins, prostacyclin and thromboxanes
    - COX-1 : Housekeeping enzyme
    - COX-2 : Inflammatory process

Mechanism of action



Role of NSAIDs

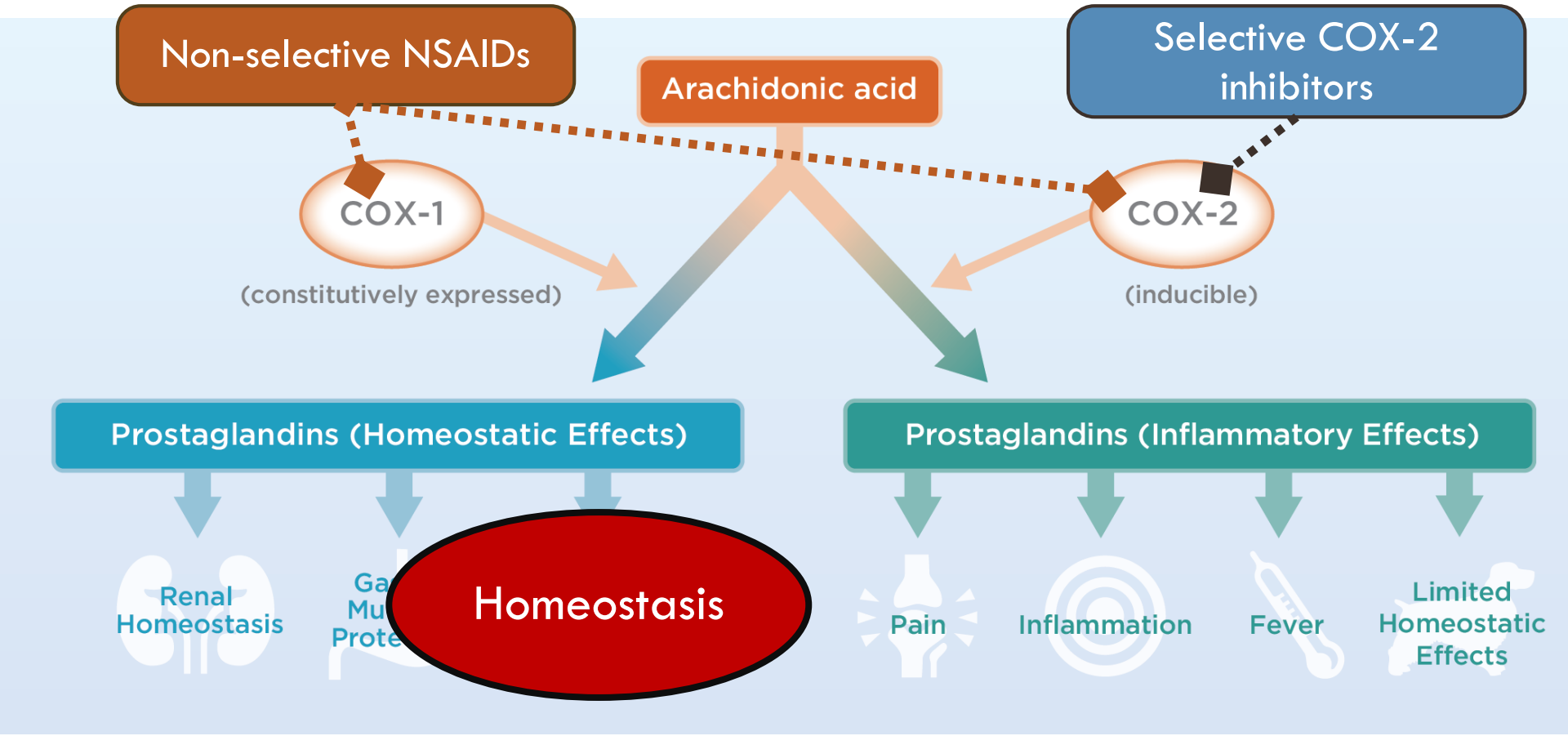
- Treatment for mild-to-moderate pain
- Component of multimodal analgesia
  - Decrease opioids consumption
  - Reduce risk of opioid-related side effects
- Anti-inflammatory and anti-pyretic effect

Concern of perioperative NSAIDs

- Bleeding ?
  - After tonsillectomy?
- Delayed union and nonunion ?
- Anastomosis leakage ?

Post-tonsillectomy bleeding

Bleeding


Non-selective NSAIDs
Arachidonic acid
Selective COX-2 inhibitors
COX-1
(constitutively expressed)
COX-2
(inducible)
Prostaglandins (Homeostatic Effects)
Prostaglandins (Inflammatory Effects)
Renal Homeostasis
Homeostasis
Pain
Inflammation
Fever
Limited Homeostatic Effects

Post-tonsillectomy bleeding ?

Cons

Anesthesiology 2003; 98:1497–502

Effects of Postoperative, Nonsteroidal, Antiinflammatory Drugs on Bleeding Risk after Tonsillectomy

Meta-analysis of Randomized, Controlled Trials

Emmanuel Marret, M.D., Antoine Flahault, M.D., Ph.D.,† Charles-Marc Samama, M.D., Ph.D.,‡ Francis Bonnet, M.D.§*

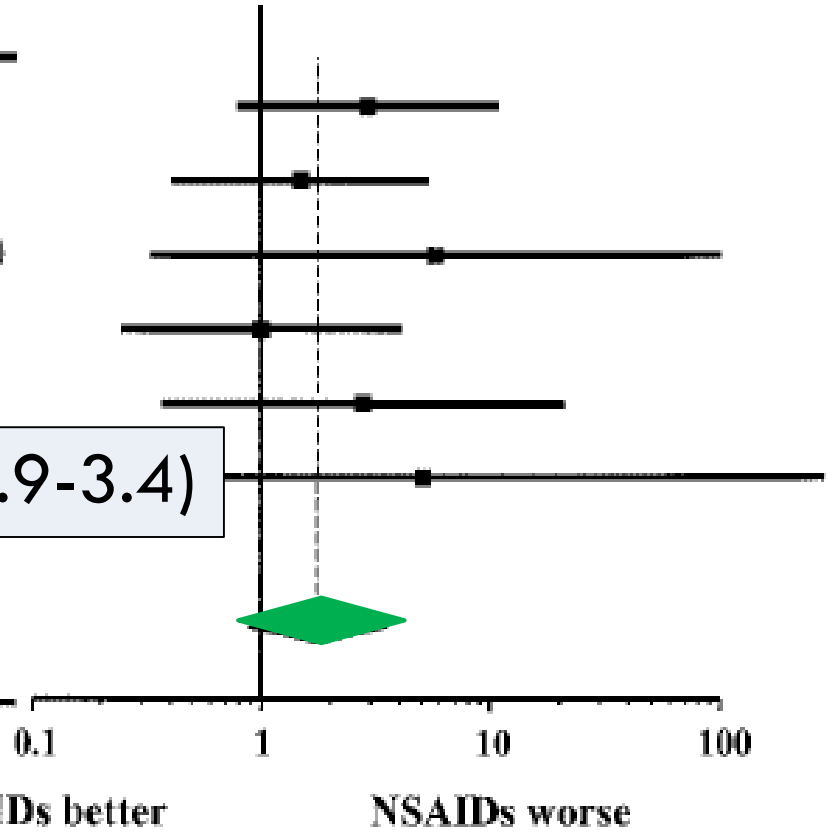
- Systematic review; 2003
- 7 RCTs studies (n = 505)
- NSAIDs use after operation finished
  - Ketorolac 1 mg/kg/dose IV/IM in first 24 h or
  - Ibuprofen 5 mg/kg/dose PO in first 2 wk

Anesthesiology, V 98, No 6, Jun 2003

Effects of postoperative administration of NSAIDs after tonsillectomy on the relative risk for **severe postoperative bleeding**

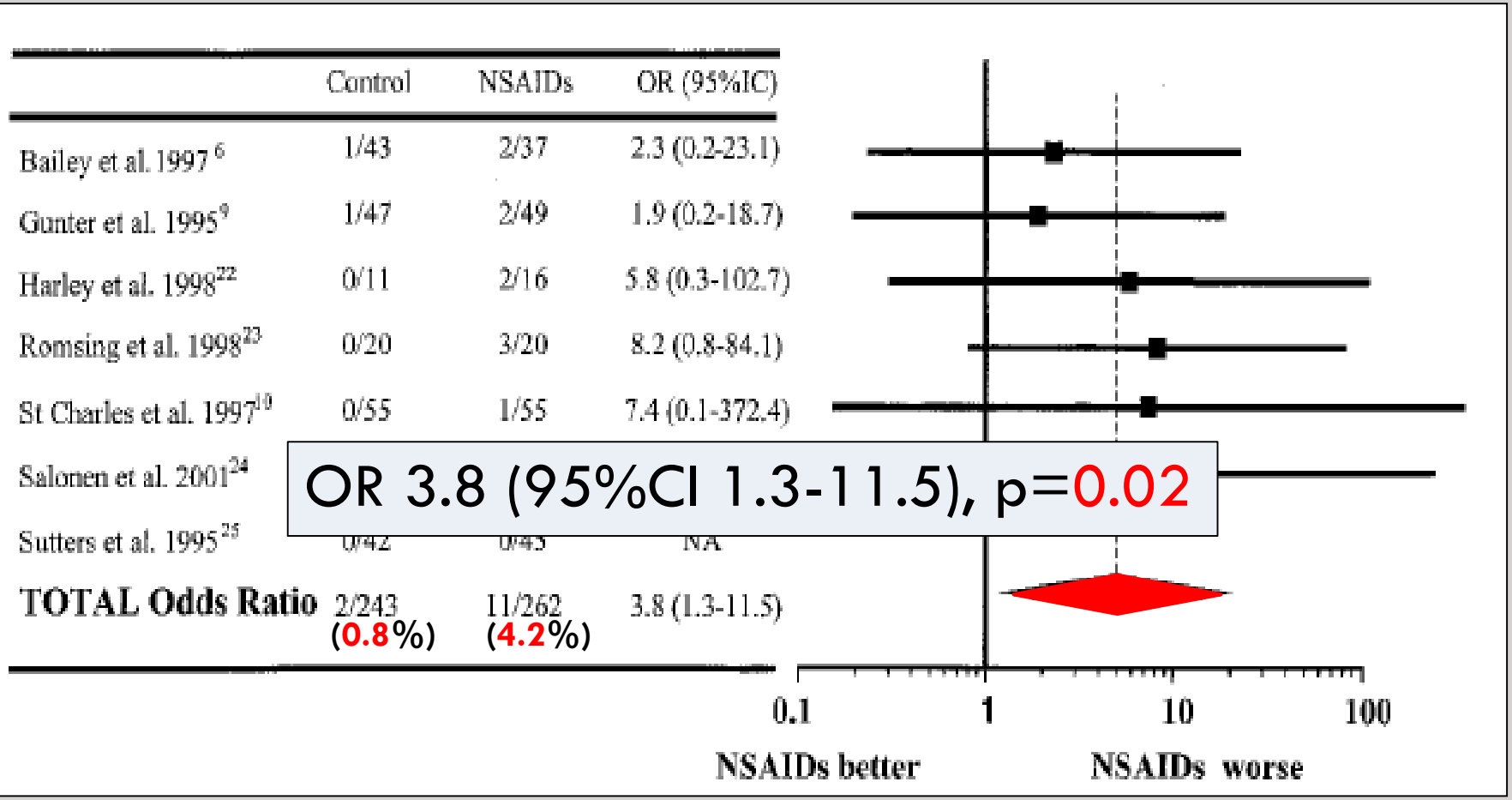
	Control	NSAIDs	OR (95%CI)
Bailey et al. 1997 [6]	3/43	7/37	2.9 (0.8-11.0)
Gunter et al. 1995 [9]	4/47	6/49	1.5 (0.4-5.5)
Harley et al. 1998 [22]	0/11	2/16	5.8 (0.3-102.7)
Romsing et al. 1998 [23]	5/20	5/20	1.0 (0.2-4.1)
St Charles et al. 1997 [10]	1/55	3/55	2.8 (0.4-20.4)
Salonen et al. 2001 [24]			
Sutters et al. 1995 [25]	0/42	0/45	NA
Total Odds Ratio	13/243 (**5.3**%)	24/262 (**9.2**%)	1.8 (0.9-3.4)

OR 1.8 (95%CI 0.9-3.4)



Anesthesiology, V 98, No 6, Jun 2003

Effects of postoperative administration of NSAIDs after tonsillectomy on the relative risk for **reoperation**



Anesthesiology, V 98, No 6, Jun 2003

Post-tonsillectomy bleeding ?

Pros

Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy

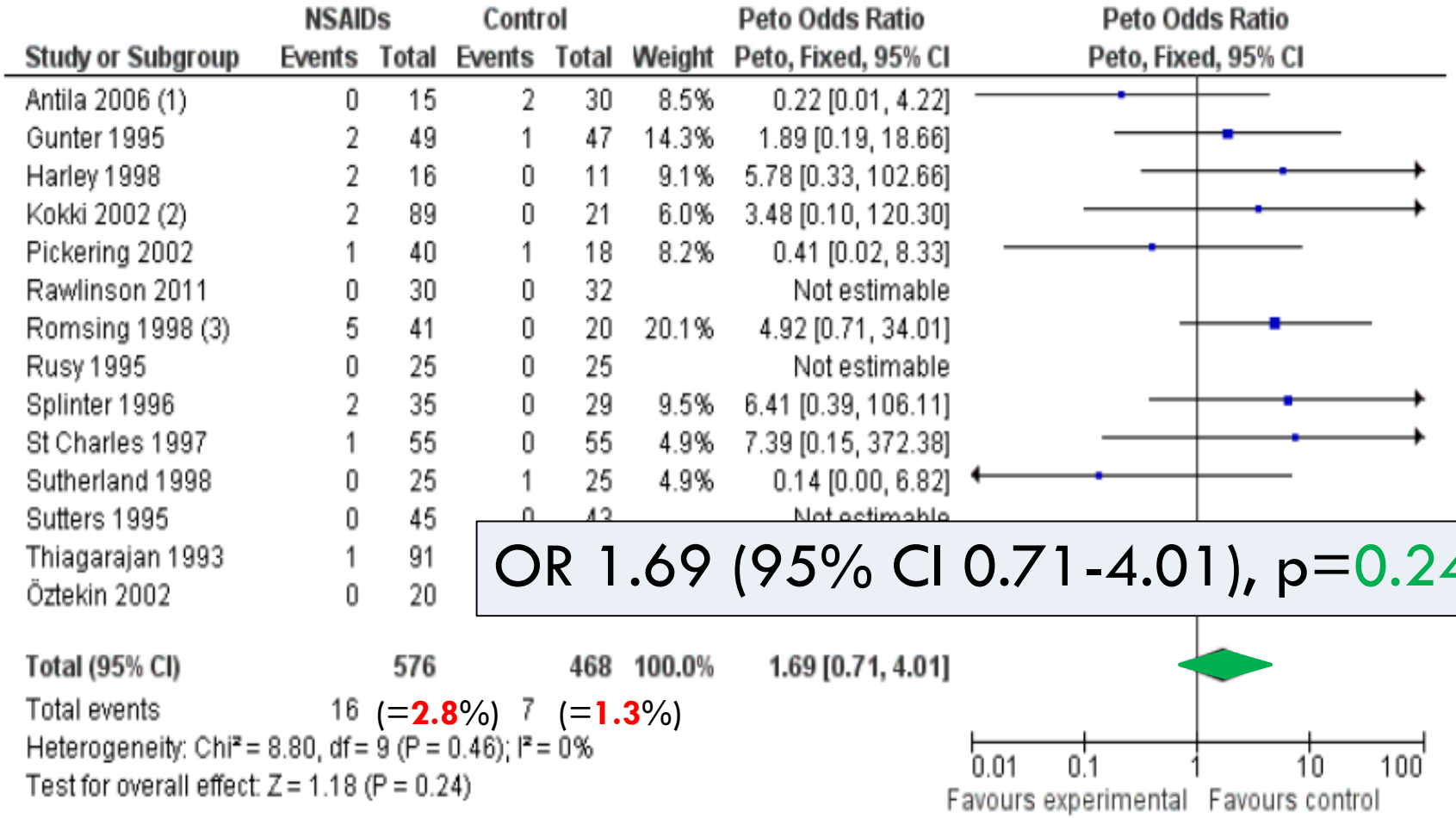
Sharon R Lewis[1], Amanda Nicholson[2], Mary E Cardwell[3], Gretchen Siviter[4], Andrew F Smith[4]

[1]Patient Safety Research, Royal Lancaster Infirmary, Lancaster, UK. [2]Faculty of Health and Medicine, Furness Building, Lancaster University, Lancaster, UK. [3]Department of Anaesthetics, North Manchester General Hospital, Manchester, UK. [4]Department of Anaesthetics, Royal Lancaster Infirmary, Lancaster, UK

- Systematic review; 2013
- 15 RCTs (n = 1,101)
- Perioperative NSAIDs use >> Ketorolac (6), Ibuprofen (3), Diclofenac (3), Ketoprofen (2) or Tenoxicam (1)

Cochrane Database of Systematic Reviews 2013, Issue 7.

Figure 4. Forest plot of comparison: 1 Nonsteroidal versus control (analgesics or placebo), outcome: 1.1 Perioperative bleeding requiring surgical intervention.



Cochrane Database of Systematic Reviews 2013, Issue 7.

Post-tonsillectomy bleeding ?

Pros

A 2013 updated systematic review & meta-analysis of 36 randomized controlled trials; no apparent effects of non steroidal anti-inflammatory agents on the risk of bleeding after tonsillectomy

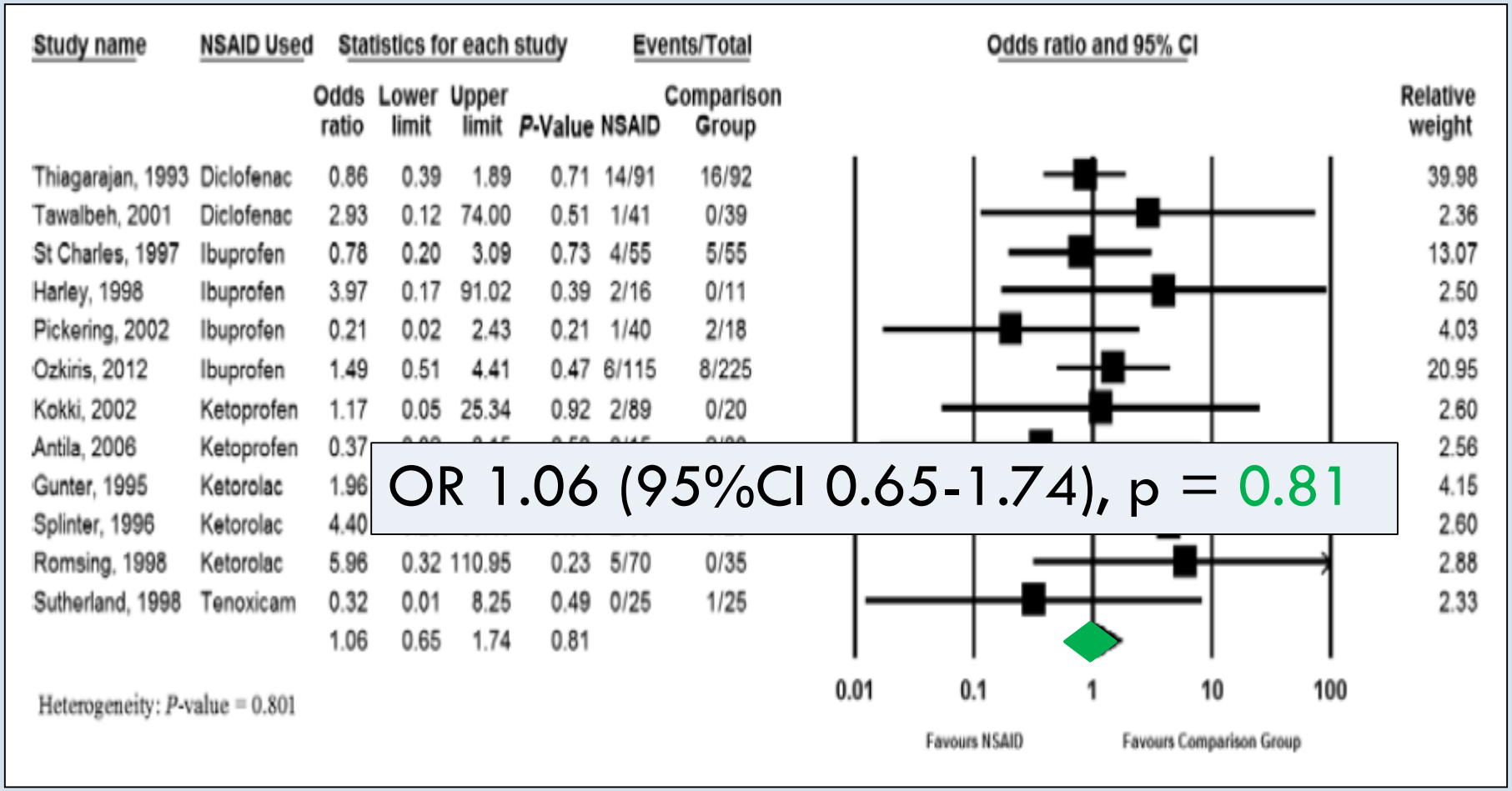
Riggin, L.,[1] Ramakrishna, J.,[2] Sommer, D.D[2] & Koren, G.[1]

[1]*Ivey Chair in Molecular Toxicology & Hospital for Sick Children, Western University Schulich School of Medicine & Dentistry & Hospital for Sick Children, London & Toronto, and* [2]*Division of Otolaryngology – Head & Neck Surgery, Department of Surgery, McMaster University, Hamilton, ON, Canada*

- Systematic review; 2013
- 36 RCTs (n = 4,878)
- Perioperative NSAIDs use >> Diclofenac (13), Ketorolac (8), Ibuprofen (6), Ketoprofen (4), Aspirin (3) or other (2)

Clinical Otolaryngology 2013, 38, 115–129

A complication of all of the post-operative hemorrhages reported in **studies on children**.



OR 1.06 (95%CI 0.65-1.74), p = 0.81

Clinical Otolaryngology 2013, 38, 115–129

Post-tonsillectomy bleeding ?

Pros

Perioperative Ketorolac Increases Post-Tonsillectomy Hemorrhage in Adults But Not Children

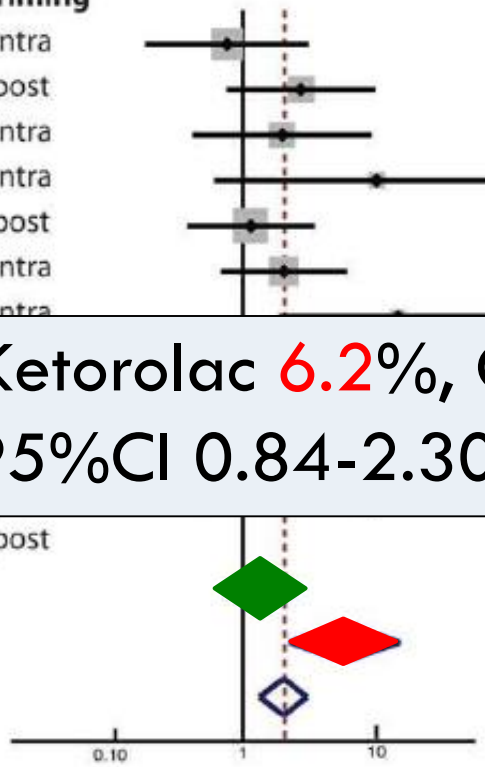
Dylan K. Chan, MD, PhD; Sanjay R. Parikh, MD

- Systematic reviews; 2014
- 10 studies >> 7 Prospective RCTs and 3 Retrospective case-control studies (n=1,357)
- Perioperative Ketorolac use in pediatric (<18) and adult (>18) tonsillectomy

Laryngoscope 124: August 2014

Relative risk of post-tonsillectomy hemorrhage in subjects receiving perioperative ketorolac compared to controls.

Study (ref)	Year	age	Design	Technique	Follow-up	Timing	RR	95% CI
Agrawal (10)	1999	≤ 18	R	C	NR	intra	0.76	0.19-3.11
Bailey (1)	1997	> 18	P	E	NR	post	2.71	0.76-9.74
Gallagher (8)	1995	< 13	R	NR	NR	intra	1.96	0.42-9.15
Gallagher (8)	1995	≥ 13	R	NR	NR	intra	10	0.61-165.03
Gunter (11)	1995	< 13	P	E	14	post	1.14	0.38-3.44
Judkins (4)	1996	≤ 18	R	NR	NR	intra	2.02	0.68-6.00
Judkins (4)	1996	> 18	R	NR	NR	intra	14.46	1.85-113.16
Keidan (12)	2004	< 11	P					
Romsing (13)	1998	< 16	P					
Rusy (14)	1995	< 16	P					
Splinter (9)	1996	< 13	P					
Sutter (15)	1995	pediatric	P	NR	1	post	N/A	N/A
All children							**1.39**	**0.84-2.30**
All adults							**5.64**	**2.08-15.27**
All studies							**2.04**	**1.32-3.15**



Children: Ketorolac 6.2%, Control 4.8%
RR 1.39 [95%CI 0.84-2.30], p=0.2

Adult: Ketorolac 19%, Control 3.2%
RR 5.64 [95%CI 2.08-15.27], p <0.001

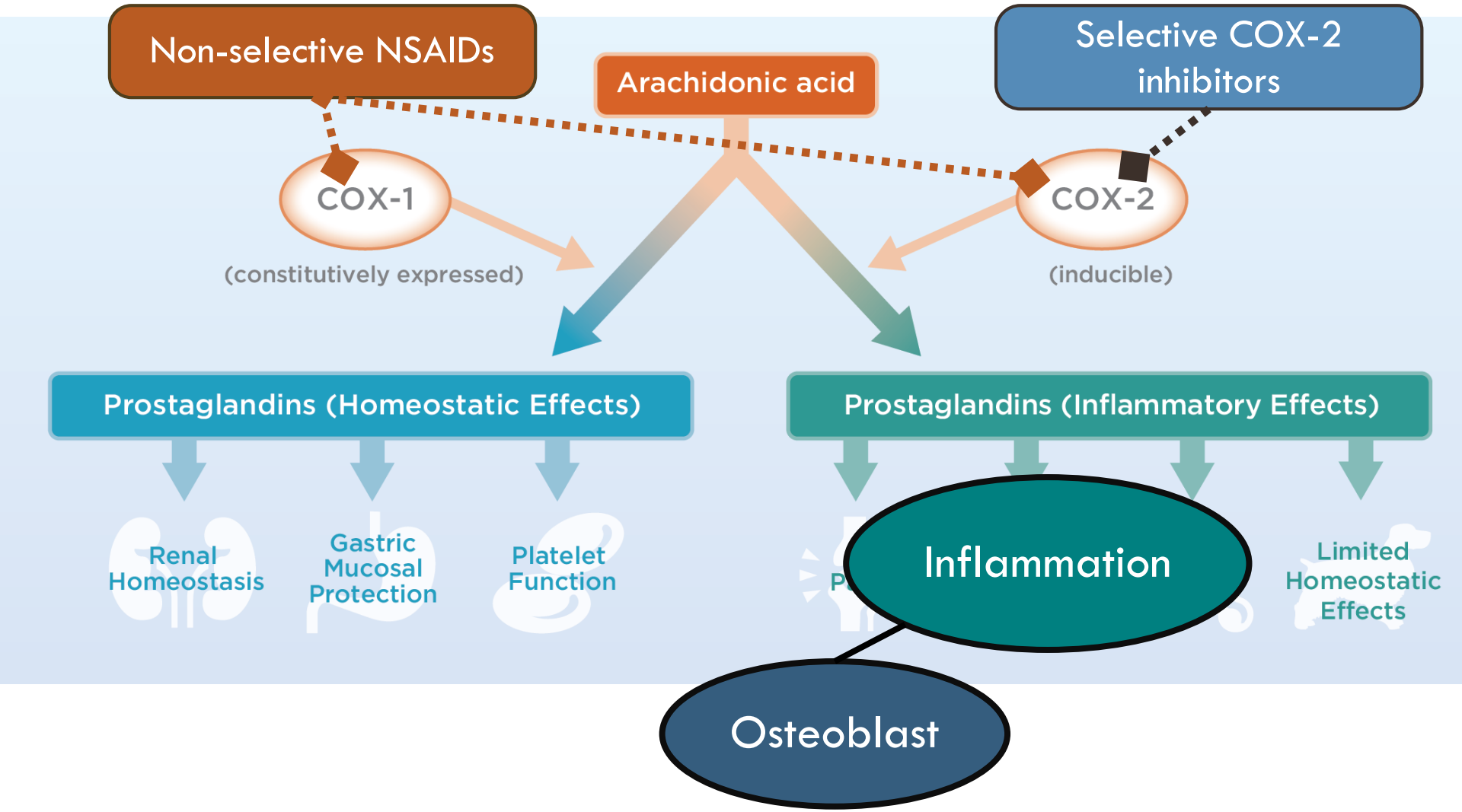
st 2014

Post-tonsillectomy bleeding

- Summary
  - NSAIDs is possibly one method of analgesia in children undergoing tonsillectomy
  - The perianesthesia team should weigh carefully between the risk of bleeding and benefit of the NSAIDs use especially nonselective group

Bone healing

Mechanism of action



Delayed bone healing ?

Cons

Selective and Nonselective Cyclooxygenase-2 Inhibitors and Experimental Fracture-Healing

Reversibility of Effects After Short-Term Treatment

By L.C. Gerstenfeld, PhD, M. Al-Ghawas, MSD, DDS, Y.M. Alkhiary, BDS, MSD, DScD, D.M. Cullinane, PhD, E.A. Krall, PhD, J.L. Fitch, BS, E.G. Webb, MS, M.A. Thiede, PhD, and T.A. Einhorn, MD

Investigation performed at Orthopaedic Research Laboratory, Department of Orthopaedic Surgery, Boston University Medical Center, Boston, Massachusetts

- Animal reseach (rats); 2007
- 3 groups; Control, Ketorolac (4mg/kg/day), Valdecoxib (5 mg/kg/day) duration 7 or 21 days (start within 24 h)

The Journal Of Bone & Joint Surgery Vol.89-A · No 1 · Jan. 2007

TABLE I Nonunion Rate

Group	Day Tested	Number of Nonunions	Number of Bones Tested	Percentage of Nonunions
Short-course (7-day) treatment				
Ketorolac	21	4	25	16
Valdecoxib	21	5	23	21.7
Control	21	2	24	8.3
Ketorolac	35	1	22	4.5
Valdecoxib	35	0	18	0
Control	35	2	22	
Total		14	134	
Long-course (21-day) treatment				
Ketorolac	21	3	23	13
Valdecoxib	21	9	25	36*†
Control	21	1	25	4
Ketorolac	35	0	22	0
Valdecoxib	35	0	20	0
Control	35	1	22	4.5
Total		14	137	10.2

P = 0.05

*The difference between the valdecoxib group and the control group was significant (p = 0.05, Fisher exact test). †The difference between the valdecoxib group and the ketorolac group was significant (p = 0.05, Fisher exact test).

The Journal Of Bone & Joint Surgery Vol.89-A · No 1 · Jan. 2007

Cons

Delayed bone healing ?

High dose nonsteroidal anti-inflammatory drugs compromise spinal fusion

[De fortes doses d'anti-inflammatoires non stéroïdiens compromettent l'arthrodèse vertébrale]

Scott S. Reuben MD,* David Ablett FRCP,† Rachel Kaye‡

- Retrospective review; 2005
- n = 434 >> elective decompressive posterior lumbar laminectomy with instrumented spinal fusion
- Perioperative NSAIDs use >> Ketorolac / Rofecoxib / Celecoxib in 5 days compared with non-NSAIDs

Canadian Journal Of Anesthesia, 2005

TABLE III Multivariate odds ratio, 95% confidence intervals for non-union

Group comp		
Rofecoxib		
Celecoxib		
Ketorolac *vs* no NSAID	3.3 (1.0–10.3)	< 0.001
Ketorolac (≤ 110 mg·day^{-1}) *vs* no NSAID	1.2 (0.2–6.1)	NS
Ketorolac (120–240 mg·day^{-1}) *vs* no NSAID	8.8 (2.8–28.0)	< 0.0001
Smokers *vs* no smokers	14.7 (5.3–40.9)	< 0.0001
Nonsmokers	1.3 (0.3–6.2)	
Smokers	20.1 (6.4–63.1)	

NS – not significant. NSAID – nonsteroidal anti-inflammatory drugs. Odds ratio were computed from a multivariate logistic regression model including NSAID treatment, smoking status, levels of fusion, and the interaction between smoking status and levels of fusion.

Nonunion: Ketorolac (All) 19.2%, No NSAIDs 8.4%
OR 3.3 [95%CI 1.0-10.3, P <0.001

Nonunion: Ketorolac (>120 mg/d) 28.6%, No NSAIDs 8.4%
OR 8.8 [95%CI 2.8-28, P <0.001

Canadian Journal Of Anesthesia, 2005

Delayed bone healing ?

Ketorolac and Spinal Fusion

Does the Perioperative Use of Ketorolac Really Inhibit Spinal Fusion?

Ben B. Pradhan, MD, MSE,* Robert L. Tatsumi, MD,† Jason Gallina, MD,‡ Craig A. Kuhns, MD,§ Jeffrey C. Wang, MD,¶ and Edgar G. Dawson, MD||

- Retrospective review; 2008
- n = 405 >> primary lumbar post.lat. intertransverse process fusion with pedicle screw instrumentation
- Ketorolac 30 mg IV q 6 h for 48 h compared with non-Ketorolac

SPINE Volume 33, Number 19,2008

Table 2. Nonunion Results

	Toradol Group	Non-Toradol Group	*P*
Nonunions	12/228 (5.3%)	11/177 (6.2%)	>0.05
Nonunions in 1-level fusions	5/126 (4.0%)	5/80 (6.3%)	>0.05
Nonunions in 2-level fusions	5/77 (6.5%)	3/71 (4.2%)	>0.05
Nonunions in 3-level fusions	2/25 (8.0%)	3/26 (11.5%)	>0.05
Nonunions with iliac crest bone graft	10/25 (8.0%)	10/153 (6.5%)	>0.05
Nonunions with local bone ± allograft	2/103 (1.9%)	1/24 (4.2%)	>0.05
Nonunions in patients of surgeon 1	12/228 (5.3%)	7/85 (8.2%)	>0.05
Nonunions in patients of surgeon 2		4/92 (4.3%)	

SPINE Volume 33, Number 19,2008

Pros

Delayed bone healing ?

Perioperative Ketorolac Use in Children Undergoing Lower Extremity Osteotomies

Robert Michael Kay, MD,† Michael Leathers, BS,† Michael P. Directo, BS,† Karen Myung, MD, PhD,*† and David L. Skaggs, MD*†*

- Retrospective review; 2011
- n = 327 >> Lower extremity osteotomy
- Ketorolac 0.5 mg/kg q 6 h compared with non-Ketorolac use

SPINE Volume 33, Number 19,2008

The result of delayed union rate and estimated blood loss in ketorolac used group compared with control group

	Ketorolac group (n=625)	Non-Ketorolac group(n=57)	P-value
Delayed union rate % (n)	0.6% (4)	1.8% (1)	0.893
EBL mL	89 +/- 130	115 +/- 282	0.584

SPINE Volume 33, Number 19,2008

Pros

Delayed bone healing ?

Ketorolac Administered in the Recovery Room for Acute Pain Management Does Not Affect Healing Rates of Femoral and Tibial Fractures

David Donohue, MD, Drew Sanders, MD,† Rafa Serrano-Riera, MD,†‡ Charles Jordan, MD,§ Roger Gaskins, MD,* Roy Sanders, MD,*† and H. Claude Sagi, MD‖*

- Retrospective study; 2016
- n = 328 fractures
- Ketorolac use 15-30 mg q 6 h in the PACU or on the ward within the first 24 hours compared with those who did not

J Orthop Trauma Volume 30, Number 9, September 2016

The result of nonunion rate of Femur and Tibial fracture in ketorolac used group compared with control group

TABLE 2. Comparison Between Study and Control Groups

	Femur			Tibia		
	Ketorolac (n = 33)	No Ketorolac (n = 104)	*P**	Ketorolac (n = 52)	No Ketorolac (n = 139)	*P**
Time to union in days (range)	147 (85–304)	159 (44–406)	0.81	175 (58–456)	175 (45–387)	0.57
Nonunion, n (%)	3 (9.1)	11 (10.6)	1.00	3 (5.8)	17 (12.2)	0.29

**P* value calculated using Mann–Whitney *U* test for time to union. *P* value calculated using Fisher Exact test for percent nonunion.

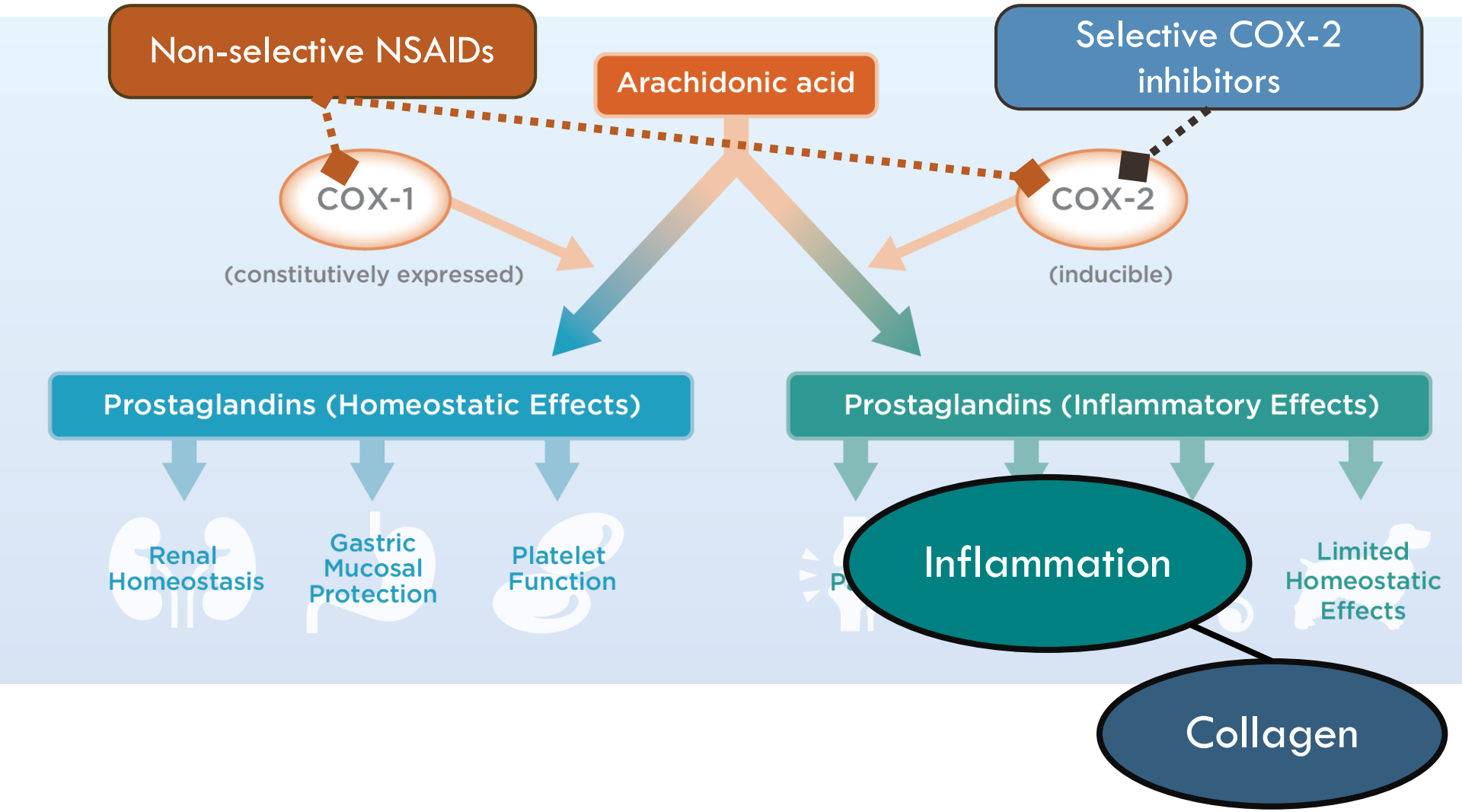
J Orthop Trauma Volume 30, Number 9, September 2016

Bone healing

- Summary
  - Selective COX-2 inhibitor inhibit fracture healing more than nonselective NSAIDs in animal study
  - The low dose and short course of NSAIDs use in orthopedic surgery has no significant effect on bone healing

Anastomotic failure

Mechanism of action



Anastomotic failure ?

Cons

Nonsteroidal Anti-inflammatory Drugs and the Risk for Anastomotic Failure:

A Report From Washington State's Surgical Care and Outcomes Assessment Program (SCOAP)

Timo W. Hakkarainen, MD, MS, Scott R. Steele, MD, Amir Bastaworous, MD, MBA, E. Patchen Dellinger, MD, Ellen Farrokhi, MD, MPH, Farhood Farjah, MD, MPH, Michael Florence, MD, Scott Helton, MD, Marc Horton, MD, Michael Pietro, MD, Thomas K. Varghese, MD, and David R. Flum, MD, MPH

- Retrospective cohort study; 2015
- n = 13,082 patients >> bariatric or colorectal surgery at 47 hospitals
- Do not specify which NSAID was administered

JAMA Surguery. 2015 March 1

The result of Anastomotic complication and mortality in NSAIDs used group compared with control group

	NSAIDs group (n=3,158)	Control group (n=9,924)	P-value
Anastomotic complication ,n (%)	151 (4.8%)	417 (4.2%)	0.16
90-days mortality, n (%)	41 (1.3%)	278 (2.8%)	< 0.001

JAMA Surguery. 2015 March 1

The result of Anastomotic complication after controlling for covariates in NSAIDs used group compared with control

Patients who received NSAIDs
- Younger
- Less co-morbidities
- Lower cardiac risk index
- Underwent elective procedures

Table 2. Risk for Anastomotic Leak Among All Patients

Variable	OR (95% CI) Unadjusted	Adjusted
Age	1.00 (1.00-1.01)	0.99 (0.99-1.00)
Male sex	1.56 (1.27-1.93)	1.50 (1.27-1.75)
BMI ≥30	0.74 (0.57-0.96)	1.04 (0.71-1.41)
Albumin level <3 g/dL	2.73 (2.01-3.70)	2.20 (1.63-2.96)
Procedure type		
Bariatric	1 [Reference]	1 [Reference]
Anastomosis tested	0.76 (0.59-0.97)	1.10 (0.90-1.35)
Postoperative NSAID administration	1.15 (0.92-1.42)	1.24 (1.01-1.56)
Epidural	1.07 (0.70-1.63)	1.05 (0.74-1.50)
Patient-controlled analgesia	0.94 (0.60-1.46)	0.95 (0.60-1.50)

Postop. NSAIDs = OR 1.24 [95% CI, 1.01-1.56]; $P = 0.04$

JAMA Surguery. 2015 March 1

Association between NSAIDs administration and anastomotic leakage

Procedure	Odd Ratio	95% CI	P-value
All surgery	1.24	1.01-1.56	0.04
Non-elective	1.70	1.11-2.68	0.01
Elective			
- Colorectal	1.13	0.87-1.49	0.36
- Bariatric	1.04	0.53-2.06	0.89

JAMA Surguery. 2015 March 1

Anastomotic failure ?

Cons

Nonsteroidal anti-inflammatory drugs and anastomotic dehiscence after colorectal surgery: a meta-analysis

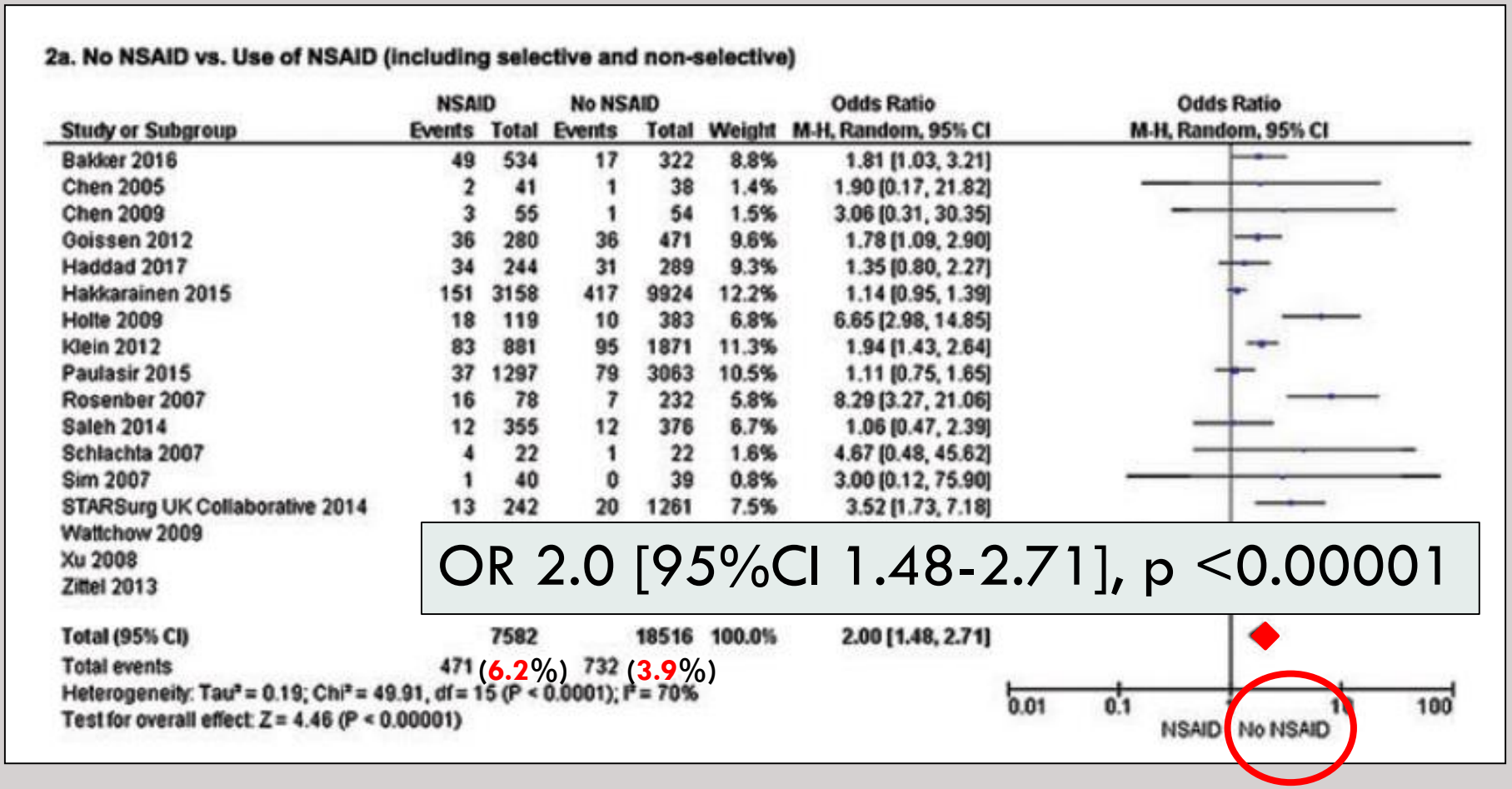
Yeqian Huang, Stephen R. Tang and Christopher J. Young

Department of Colorectal Surgery, Discipline of Surgery, The University of Sydney, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia

- Meta-analysis; 2017
- 6 RCTs, 10 cohort and 1 case–control studies
- n = 26,098
- 12 studies use non-selective NSAIDs, 5 studies use selective COX-2 inhibitor

ANZ Journal of Surgery, 2017

Association between NSAIDs administration and anastomotic dehiscence



ANZ Journal of Surgery, 2017

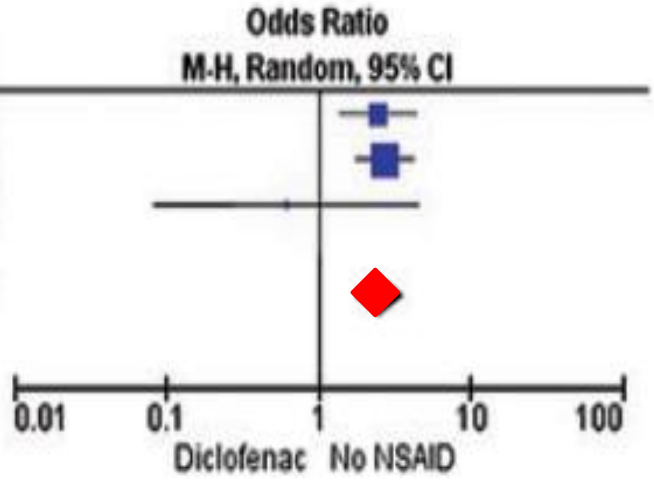
Association between Diclofenac administration and anastomotic dehiscence

2f. No NSAID vs. Use of Diclofenac

Study or Subgroup	Diclofenac Events	Diclofenac Total	No NSAID Events	No NSAID Total	Weight	Odds Ratio M-H, Random, 95% CI
Bakker 2016	45	372	17	322	36.1%	2.47 [1.38, 4.41]
Klein 2012	29	226	95	1871	60.7%	2.75 [1.77, 4.28]
Wattchow 2009	2	79	2	50	3.2%	0.62 [0.08, 4.57]
Total (95% CI)		677		2243	100.0%	2.52 [1.77, 3.60]
Total events	76 (11.2%)		114 (5.1%)			

Heterogeneity: Tau² = 0.00; Chi² = 2.06, df = 2 (P = 0.36); I² = 3%

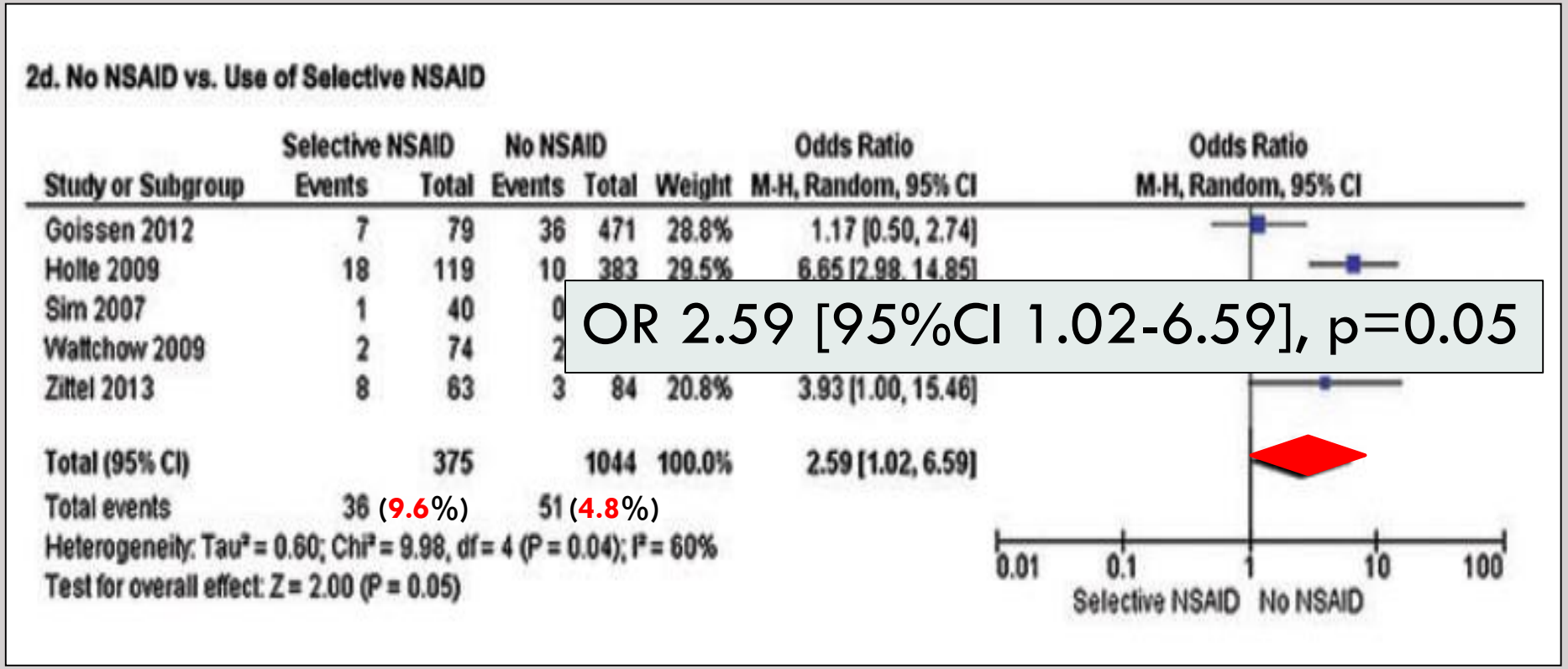
Test for overall effect: Z = 5.11 (P < 0.00001)



OR 2.52 [95%CI 1.77-3.6], p=0.05

ANZ Journal of Surgery, 2017

Association between Selective COX-2 inhibitor administration and anastomotic dehiscence



ANZ Journal of Surgery, 2017

Association between Ketorolac administration and anastomotic dehiscence

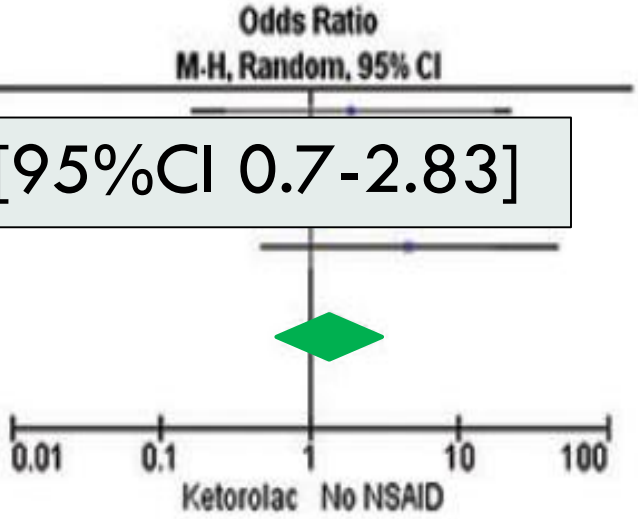
2g. No NSAID vs. Use of Ketorolac

Study or Subgroup	Ketorolac Events	Ketorolac Total	No NSAID Events	No NSAID Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen 2005	2	41	1	38	8.1%	
Chen 2009	3	55	1	54	9.2%	
Saleh 2014	12	355	12	376	73.3%	
Schlachta 2007	4	22	1	22	9.3%	4.67 [0.48, 45.62]
Total (95% CI)		473		490	100.0%	1.41 [0.70, 2.83]
Total events	21 (4.4%)		15 (3.1%)			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.03$, $df = 3$ ($P = 0.57$); $I^2 = 0\%$

Test for overall effect: $Z = 0.96$ ($P = 0.34$)

OR 1.41 [95%CI 0.7-2.83]



ANZ Journal of Surgery, 2017

Anastomotic failure ?

Pros

Perioperative use of nonsteroidal anti-inflammatory drugs and the risk of anastomotic failure in emergency general surgery

Nadeem N. Haddad, MD, Brandon R. Bruns, MD, Toby M. Enniss, MD, David Turay, MD, Joseph V. Sakran, MD, MPH, MPA, Alisan Fathalizadeh, MD, Kristen Arnold, MD, Jason S. Murry, MD, Matthew M. Carrick, MD, Matthew C. Hernandez, MD, Margaret H. Lauerman, MD, Asad J. Choudhry, MBBS, David S. Morris, MD, Jose J. Diaz, MD, Herb A. Phelan, MD, Martin D. Zielinski, MD, *and* **NSAIDs SHAPES Workgroup**, *Rochester, Minnesota*

- Post hoc analysis; 2017
- n = 533 >> urgent/emergent bowel resection and anastomosis
- NSAIDs = Aspirin, Ibuprofen, Naproxen, Ketorolac, others

J Trauma Acute Care Surgery Volume 83, Number 4

TABLE 3. Multivariable Model for Features Associated With AF (n = 533)

Variables	OR	95% CI
Perioperative NSAIDS	1.48	0.80–2.75
Contamination	1.83	0.93–3.58
Perioperative corticosteroids	2.22	1.02–4.70
Male sex	1.21	0.66–2.25
Damage control	0.56	0.20–1.51
Age (per year)	1.01	0.99–1.03
Albumin	0.69	0.45–1.04
Colocolonic or colorectal anastomosis	2.58	1.00–6.27

*$p = 0.049$.
CI, confidence interval; OR, odds ratio.

Anastomotic failure: NSAIDs 13.9%, no NSAIDs 10.7%
OR 1.48 (95% CI 0.8-2.75), p=0.26

Pros

Anastomotic failure ?

Nonsteroidal anti-inflammatory drugs and the risk of anastomotic leakage after anterior resection for rectal cancer☆

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- Retrospective multi-centre cohort; 2017
- n =1,495 >> anterior resection for rectal cancer
- Any NSAIDs for at least two days in the first postoperative week

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	No NSAID (N = 1084)	NSAID (N = 411)	P-value[a]
Age (years: median/range)	68 (23—93)	66 (32—86)	< 0.001
	N (%)	*N (%)*	
Sex			0.195
Male	650 (60.0)	231 (56.2)	
Female	434 (40.0)	180 (43.8)	
ASA classification			0.003
I	252 (23.2)	129 (31.4)	
II	643 (59.3)	237 (57.7)	
III	154 (14.2)	41 (10.0)	
Missing	35 (3.2)	4 (1.0)	
Intraoperative blood loss			< 0.001
≤400 ml	543 (50.1)	253 (61.6)	
>400 ml	480 (44.3)	143 (34.8)	
Missing	61 (5.6)	15 (3.6)	
Anastomotic leakage			0.151
No	928 (85.6)	364 (88.6)	
Yes	156 (14.4)	47 (11.4)	
Reoperation for leakage			0.440
No	1042 (96.1)	399 (97.1)	
Yes	42 (3.9)	12 (2.9)	
Mortality within 90 days			0.005
No	1060 (97.8)	410 (99.8)	
Yes	24 (2.2)	1 (0.2)	

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Anastomotic failure

- Summary
  - From recent studies, the association between NSAIDs and the risk of anastomotic failure is still controversy, the further studies may be needed

Take home message

- The use of perioperative NSAIDs is still controversy in some issues.
- A short course and effective dose as low as possible of NSAIDs use may be recommended
- The risk and benefit should be weigh and discuss to healthcare team

- Thank you