Summary of the Evidence

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/studies, cohort definition, etc.)	Outcome(s) Studied	Key Findings	Limitations and Biases
Lim C, et al. (2022)	Level IV – Retrospective Cohort Study	Retrospective cohort study of 12,798 older adults (≥65 years) receiving prescriptions between March 2015–December 2017 within Singapore's largest public healthcare cluster (SingHealth), including Singapore General Hospital and seven polyclinics. Patients with severe kidney dysfunction (eGFR <15 mL/min/1.73 m^2) or missing creatinine/potassium data were excluded. Half were female (50.9%). The multi-ethnic cohort were mostly Chinese (n = 10,369, 81.0%), followed by Malay (7.5%), Indian (6.3%), and other ethnicities (5.2%). Comorbid conditions such as diabetes (36.2%) and CKD (36.4%) were frequent, as was use of RAAS blockers (36.5%) and diuretics (25.1%).	30-day incidence of acute kidney injury (AKI) and/or hyperkalemia after NSAID prescription _____ NSAIDs were prescribed in 7210 individuals (56.3%). Systemic NSAIDs were prescribed in 3640 individuals (28.4%), of whom 305 (2.4%) had systemic NSAID prescriptions for >14 days and 3335 (26.1%) received short-course systemic NSAID prescriptions for 1–14 days	• Incidence: 16.7% developed AKI and/or hyperkalemia within 30 days. • NSAID risk: Compared with no NSAID, risk increased with route/duration: – Topical NSAIDs: aOR 1.29 (95% CI 1.15–1.45) – Systemic NSAIDs 1–14 days: aOR 1.43 (95% CI 1.27–1.62) – Systemic NSAIDs > 14 days: aOR 1.84 (95% CI 1.37–2.49). • Other independent risk factors: diabetes, cardiovascular disease, lower eGFR, and diuretic use. While prolonged systemic NSAIDs use is associated with AKI, there was little data on the nephrotoxicity of short-term NSAIDs or topical NSAIDs. The findings from this study further showed that there were incremental	NSAID prescriptions may not equate to NSAID use and data on over-the-counter NSAID use was not available • Selection bias: only included those with both baseline and follow-up labs. • Possible confounding by indication (e.g., patients with comorbidities needing NSAIDs). • Observational design—cannot infer causality.

				odds of an acute adverse renal outcome with longer NSAID duration and systemic route, compared with topical. This is consistent with the greater nephrotoxicity expected with greater cumulative exposure, since topical NSAIDs have lower bioavailability and plasma concentrations compared with oral NSAIDs. While age, diabetes, and diuretic use were similar between the groups, our cohort of older adults who received systemic NSAIDs > 14 days were more likely to have had CVD-related hospitalization within 6 months	
Osani M. C. et al. (2020)	Level I- Systematic review & meta-analysis	Systematic review + meta-analysis of randomized controlled trials involving non-steroidal anti-inflammatory drugs (NSAIDs) in human subjects with knee osteoarthritis (OA) 72 RCTs were included; 26,424 participants; sample size in the included RCTs ranged from 47 to 844; the follow-up duration ranged from 1 week to 2 years, but 96% of the trials had a duration of 13 weeks	<u>Efficacy outcomes</u> • Changes in pain intensity and functional outcomes <u>Safety outcomes</u> • Incidence of Treatment-Related AEs. • Incidence of Serious Adverse Events (SAEs): Defined by FDA criteria (e.g., potentially life-threatening, requiring	NSAIDs showed statistically significant, clinically important effects on pain as early as two weeks from baseline, with a SMD of −0.43 (95% CI −0.48, −0.38) This treatment effect remained statistically significant up to 26 weeks (SMD −0.21 [95% CI −0.39, −0.03]), though	**Attrition Bias:** There was potential for attrition bias because a larger share of patients withdrew from the placebo group due to lack of efficacy (while more withdrew from the treatment group due to adverse events). This imbalance means the results may have ultimately understated the overall treatment effects of NSAIDs

		or less; mean age of included participants ranged from 53 to 69 years , and the mean body mass index of patients ranged from 27 kg/m2 to 34 kg/m2. The percentage of females ranged from 49% to 85% Compared traditional NSAIDs (e.g., Diclofenac, Ibuprofen, Indomethacin, Naproxen, and Piroxicam), selective COX-2 inhibitor (Celecoxib), and intermediate COX inhibitors (e.g., Etodolac, Meloxicam, and Nabumetone)	hospitalization, leading to disability or death). • Gastrointestinal (GI) AEs: the most commonly observed GI AEs were transient and mild, including upper abdominal pain, diarrhea, dyspepsia, and nausea. • Cardiovascular (CV) AEs: the most commonly reported CV AEs were mild in severity and duration, specifically edema and hypertension.	the effects attenuated progressively over time and lost clinical significance With respect to functional improvement, NSAIDs again showed consistent statistically significant benefits compared with placebo, from 2 weeks (SMD −0.45 [−0.52, −0.38]) to 26 weeks (SMD −0.19 [−0.32, −0.07]) Patients receiving oral NSAIDs experienced higher incidence of treatment-related AEs, cardiovascular (CV) AEs, and gastrointestinal (GI) AEs during the study follow-up period A significant risk of minor GI AEs was evident as early as 4 weeks after treatment initiation Traditional NSAIDs (**Naproxen**) had the highest risk of GI AEs & 92% greater likelihood of reporting CV AEs overall over a median follow-up of 6 weeks Traditional NSAIDs (including Naproxen)	**Lack of Long-term Data**: The median follow-up time for safety outcomes was short - 6 weeks, and 96% of included trials lasted 13 weeks or less. This prevents generalization beyond 12 weeks and means the study results may not apply to chronic NSAID use **Inability to Evaluate Serious Events:** Due to the short duration of the included studies, the review was unable to evaluate the risks for major vascular events (such as myocardial infarction, stroke, or coronary death) or serious GI complications (e.g., GI bleed, perforation, or obstruction) because very few of these events were observed during the study period **Restricted Study Population:** The knee OA population included in the RCTs was more restricted and less representative of the general OA population. Patients with previous GI or cardiovascular issues were most likely excluded from enrollment, suggesting the risk estimates may be smaller than those observed in clinical practice,

				demonstrated the largest effects with regard to efficacy outcomes, but also the least favorable safety profile of all the classes	who are typically older and often have more comorbidities
Weng, Q. et al. (2023)	Level I - Systemic review & meta-analysis	Systemic review + meta analysis of 152 randomized controlled trials including 17,431 participants with knee or hip osteoarthritis, assessed at short term (4 weeks), medium term (8 weeks), and long term (24 weeks) intervals 83.6% of the trials involved participants with only knee OA, 7.9% involved only hip OA, 8.6% involved a mix population of knee and hip OA Average age ranged from 53.0 to 65.9 years. The majority were female (62.5% to 85.1%). Exercise therapy includes aerobic, muscle strengthening, flexibility/neuromotor skills training or mind-body exercise (tai chi, yoga). Any form of exercise therapy was eligible, regardless of duration, frequency or intensity.	<u>Pain relief</u> - Scores were extracted or calculated as "change from baseline" pain score - If multiple pain scores were reported, the one with the highest sensitivity to change was used <u>Physical Function</u> - The function subscale of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) was the primary measure used - If unavailable, the Lesquesne Index or another functional measurement scale was used instead	There was **no statistical difference** between the effects of exercise and those of oral NSAIDs and paracetamol in providing short-term, medium-term, or long-term pain relief and functional improvement <u>Pain relief</u> - 4 weeks: SMD=-0.12 (95% CrI -1.74 to 1.50) - 8 weeks: SMD=0.22 (95% CrI -0.05 to 0.49) - 24 weeks: SMD=0.17 (95% CrI -0.77 to 1.12) <u>Physical Function</u> - 4 weeks: SMD=0.09 (95% CrI -1.69 to 1.85) - 8 weeks: SMD=0.06 (95% CrI -0.20 to 0.33) - 24 weeks: SMD=0.05 (95% CrI -1.15 to 1.24)	**Limited generalizability to other joints**: Included trials were restricted to those with knee or hip OA. Therefore, the study's conclusion may not be generalisable to OA at other joints. **Heterogeneity of interventions:** Exercise therapy varied widely across trials in terms of type, frequency, intensity and duration, making it difficult to pinpoint which specific exercise protocols are most effective. **Variability in outcome measures**: Different trials used different different pain and function scales, which may introduce inconsistency **Generalizability**: Most participants were older adults and predominantly female, which may limit applicability to younger population or men.

da Costa BR et al. (2021)	Level I (Systematic Review & a Network Meta-Analysis of Randomized Controlled Trials)	A total of 192 RCTs were conducted, encompassing 102,829 participants from an average age range of 48 to 72 years old. The majority of the trials lasted for a short period, approximately 4 to 12 weeks. There was no single setting involved; it was on an international scale and looked at studies up to 2021. Treatment regimens were conducted with >100 participants per trial, which consisted of NSAIDs, opioids, and paracetamol, which were administered to adult patients with osteoarthritis of the hip or knee, through 90 active regimens.	<u>Pain Relief:</u> Pain was measured as a "change from baseline" pain score in all trials, assessing pain prior to and after initiating medications. Researchers selected the best scale with the highest sensitivity to evaluate change from multiple pain measures. <u>Physical Function:</u> Two scales were used: WOMAC and the Lequesne Index as an alternative. <u>Safety:</u> Included any adverse events and any treatment discontinuation (drop-outs) as a result.	<u>Pain Relief:</u> There were only four Oral NSAIDs that demonstrated ≥99% probability of producing significant pain reduction, which included diclofenac, etoricoxib, and rofecoxib (25 mg & 50 mg). Topical diclofenac demonstrated ≥92% probability of pain relief. Opioids were the least beneficial in providing pain relief for participants in comparison to the NSAIDs. <u>Physical Function:</u> Similar to pain relief, NSAIDs had greater physical functionality outcomes versus opioids. <u>Treatment Discontinuation:</u> Drop-outs: Opioids demonstrated the highest rates of participants dropping out of studies due to adverse	**Heterogeneity variability**: Demonstrated amongst trials, including the specific drug types (names), the dosages, and the duration of treatment required. **Research:** Only considered studies conducted in English, leaving out other studies published in other languages. Demonstrating a publication bias given that this encompassed studies on an international level, and not just one single setting. **Studies:** Only studies with greater than a hundred participants were considered, so studies with smaller numbers of participants were counted out, potentially leaving out information that can be significant. Given the duration of these studies, they were very short, therefore did not account for any side effects seen long term.

				drug reactions, with a high percentage of 83.3%. Oral NSAIDs had a small percentage of 18.5% and topical NSAIDs were significant because there was no increased risk in dropouts and even in comparison to placebos. <u>Adverse Risk Events</u>: Opioids were associated with the highest chance of developing an adverse reaction of 89.5%, Oral NSAIDs at 29.8%, and Topical NSAIDs at 0%. Similar to the dropout rates, this reflected around the same percentages. <u>Overall findings:</u> Topical NSAIDs were safe in the management of osteoarthritis with no adverse events or dropouts noted. Oral NSAIDs proved to be the most effective in pain relief and restoring physical functions. Opioids were not very effective for	This was a network meta-analysis, meaning this compiled many studies, making comparisons that were not direct, and can skew the evidence.

				Osteoarthritis patients and instead brought on harmful events/ risks.	
[Trelle S. et al., 2017]	Level I: Systemic Review and Meta-Analysis	The study drew individual patient data from 446,763 adults from healthcare databases in Canada, Finland, and the United Kingdom followed by on stage bayesian individual patient date meta analysis. The sample population represented middle aged and older adults. The study cohort included current, recent, and past users of commonly prescribed oral NSAIDs and compared them to nonusers. The database included adults who recieved outpatient medical care, prescription records, and hospitalization data which helped researches identify NSAID use and confirmed cases of AMI. Among the 446, 763 adults, 61, 460 experienced an AMI.	<u>Risk of experiencing an Acute Myocardial Infraction:</u> Researchers looked at individuals who had confirmed AMI events. Compared the odds of AMI in current, recent, past, and non-users of each NSAID. Used the Bayesian one stage individual patient data analysis to estimate odds ratio for AMI for each NSAID, dose, and duration. <u>Doses and Duration:</u> Researches obtained prescription date from healthcare databases and converted the NSAID prescription into a standardized daily dose using the World Health Organization's Defined Daily Dose system. This allowed the researchers to categorize the NSAID into low dose vs high dose based on how	All NSAIDs increased the risk of acute myocardial infraction The risk increased quickly within **days 1-7 day** of NSAID use **Higher doses** of NSAIDS increased the risk of AMI **Refecoxib** has the highest risk. NSAID use for **more than 30 days** did not further increase the risk significantly	<u>Selection Bias:</u> 4 potential eligible studies were excluded due to the lack of permission to access patient data. <u>Cofounding Variables:</u> Important risk factors such as smoking, obesity, socioeconomic status, and lifestyle was not measured. These can underestimate or overestimate the risk of acute myocardial infraction. <u>Observational Data:</u> The study used medical database, which records prescriptions and drug dispensing, but did not record whether patients actually took the medications.

			much the patient was prescribed per day. <u>NSAIDs Used:</u> Researchers selected the most commonly used oral NSAIDs that appeared consistently across all databases. The NSAIDs used in the study were ibuprofen, naproxen, diclofenac, celecoxib, and rofecoxib.		

<u>Conclusions</u>

1. ↑ Systemic NSAID use (>14 days) is associated with a higher risk of AKI and hyperkalemia in older adults
    - Topical < Short-Term Systemic < Long-Term Systemic
2. Oral NSAIDs provide rapid symptom relief with peak benefit at 2 weeks, but effects wane by 8 weeks as GI and CV adverse events emerge early and persist, making chronic use less effective and more risky, especially for frail elderly with comorbidities
3. Exercise therapy was shown to be a clinically effective treatment for reducing pain and improving physical function in patients with knee or hip OA. The study recommends prioritizing exercise as a first-line treatment.
4. Oral NSAIDs gave the strongest pain relief. Topical NSAIDs were recognized as the safest option, and opioids had little to no clinical benefits in management, with the highest risk of side effects.
5. The risk for AMI occurs quickly, within the first 1-7 days of NSAID use, and is greater at higher doses. However, after 30 days, the risk of AMI does not increase significantly compared to the risk in the first 30 days.

<u>Clinical Bottom Line</u>

Chronic systemic NSAIDs increase the risk of AKI, hyperkalemia, GI bleeding, and CV events (e.g., MI), especially in older adult,s as these adverse effects can become life-threatening.

Use the lowest effective dose for the shortest time, monitor kidney function, and consider safer alternatives (PT, warm compresses, exercise, topical NSAIDs).

However, quality of life becomes the primary focus in geriatric care. As patients age, goals shift away from aggressive long-term disease prevention and toward maintaining comfort, independence, and functional ability. Clinicians must balance nonmaleficence (avoiding harm) with respect for patient autonomy by aligning care with the patient's personal values. In very elderly patients—such as a 95-year-old—the goal is not eliminating all risk but finding the right balance between safety and meaningful benefits, such as adequate pain relief. Shared decision-making is essential to ensure that treatment plans reflect what matters most to the patient