

# NSAIDs: Reducing the risk



## Key messages

- NSAIDs increase CVD and GI bleeding.
- Avoid NSAIDs at older ages and in those at high CVD risk or GI bleeding risk.
- Paracetamol, opioid analgesics or topical NSAIDs may improve short term symptoms.
- If NSAID is unavoidable use naproxen or ibuprofen plus PPI if indicated. Use for the shortest time at the lowest effective dose.
- Avoid NSAIDs with SSRIs or spironolactone.

## Aim of the guideline

**This guideline aims to improve patient safety by reducing use of NSAIDs in people at higher risk of CVD and bleeding.**

This guidance does not apply to the management of rheumatoid arthritis or other complex inflammatory conditions.

## More deaths from NSAIDs than from road traffic accidents

Look both ways before prescribing



## Avoid NSAIDs in people with... Age 65 years and older

or.....

GI bleeding risks

Chronic kidney disease

Hypertension

Increased CVD risk

Diabetes

SSRI / spironolactone use

**\*Ischaemic heart disease**

**\*Heart failure**

**\*Peripheral arterial disease**

**\*Stroke**

**\*Coxibs and diclofenac are contraindicated**

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This guidance does not apply to the management of rheumatoid arthritis or other complex inflammatory conditions.

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## Resources

### **NICE Guidance on NSAIDs.**

[http://cks.nice.org.uk/  
nsaids-prescribing-issues#!scenario](http://cks.nice.org.uk/nsaids-prescribing-issues#!scenario)

[http://cks.nice.org.uk/antiplatelet-  
treatment#!scenario:1](http://cks.nice.org.uk/antiplatelet-treatment#!scenario:1)

[http://www.nice.org.uk/guidance/cg177/  
resources/guidance-osteoarthritis-pdf](http://www.nice.org.uk/guidance/cg177/resources/guidance-osteoarthritis-pdf)

[https://www.nice.org.uk/advice/ktt13/  
resources/nonsteroidal-antiinflammatory-  
drugs-58757951055301](https://www.nice.org.uk/advice/ktt13/resources/nonsteroidal-antiinflammatory-drugs-58757951055301)

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## Authors and approval

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This guidance has been approved by the Barts Health  
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## NSAID Actions

All NSAIDs reduce prostaglandin synthesis by inhibition of two prostaglandin synthase enzymes, COX-1 and COX-2.

They have analgesic, anti-inflammatory and antipyretic effects and interfere with platelet function.

The first NSAIDs were non-selective inhibitors of both COX-1 and COX-2. Subsequently more selective COX-2 inhibitors (coxibs) were developed which reduce adverse GI effects, but at the cost of increased CVD events. There are variable types of binding of these enzymes that account for differences in adverse effects.

Both selective COX-2 inhibitors (referred to as COX-2 throughout the document) and non-selective NSAIDs cause increased bleeding and CVD events but vary in the extent to which they cause these. Their analgesic and anti-inflammatory effects are schematically represented in FIG 1

These adverse effects prompted warnings from both the American FDA and UK MHRA regulators, that all users of NSAIDs were at increased risk of cardiovascular events and to use the lowest effective dose for the shortest time.

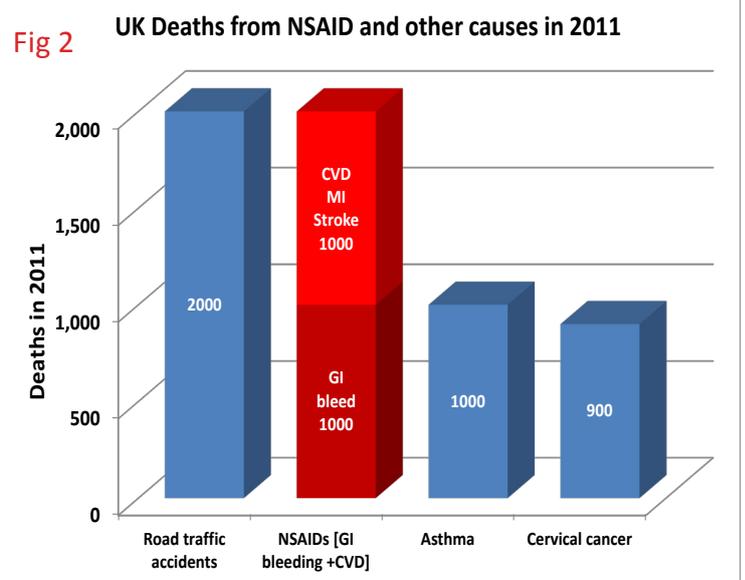
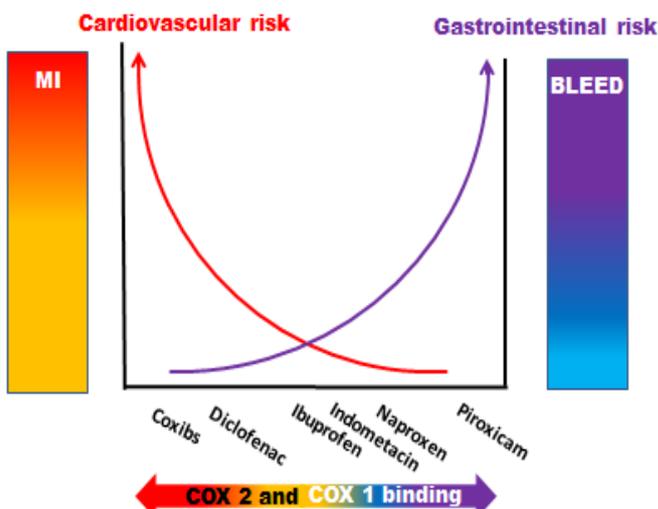
**It is estimated that in 2011, there were as many deaths caused by NSAIDs due to GI bleeding, MI and stroke as deaths from road traffic accidents in the UK. This is twice as many deaths as from asthma or cervical cancer.** FIG 2

[Ref 1 and Note in bibliography]

## Balance of harm and benefit Fig 1.

**Relative risks of adverse events with different NSAIDs**

**Note all NSAIDs increase bleeding and CVD risks**



Derived from Basic & Clinical Pharmacology & Toxicology, 2014, 115, 179–184; BMC Gastroenterology 2009;9:41, RTA and mortality stats 2011 see Note 1 at end.

## NSAID Risks

All NSAIDs increase bleeds and CVD events. Both short term and long term use are associated with these risks which are higher at higher doses.

**Increased risk of bleeding and CVD events starts immediately, on the first day of use.** The longer the time on NSAID the greater the number of bleeding or CVD events. **The risks of both bleeding and CVD events are very much higher in older people.**

- **Being over 75 years old carries the same risk of bleeding as a peptic ulcer.**

CVD events are more likely in people already at high CVD risk – which includes people with hypertension and diabetes as well as those with established CVD.

**All NSAIDs cause increased GI bleeding, heart attacks and stroke.**

**Diclofenac is contraindicated in patients with ischaemic heart disease, cerebrovascular disease, peripheral arterial disease and heart failure.**

**COX-2 inhibitors (celecoxib, etoricoxib, parecoxib) are also contraindicated in CVD.**

## Current NSAID use

Over the last ten years, overall NSAID use has shown only small reductions in people aged over 65 years.

Although COX-2 and diclofenac use has decreased substantially, these drugs are still used in some people with CVD in whom they are contraindicated. This use should be reviewed.

Of more concern are the much larger numbers of people - up to 10% - with or at high risk of CVD, hypertension or diabetes who are prescribed NSAIDs. The extent of self-medication is also high, which substantially increases these numbers.

**Avoid NSAIDs in people aged 65 years and older.**

**Review NSAID use (including OTC) in people with CVD or at high CVD risk due to hypertension, diabetes, multiple risk factors or other conditions.**

**NICE recommends co-prescription of PPIs when used for osetoarthritis, in people over age 45 years with low back pain or when there are other factors which increase bleeding risk (NICE references on back cover).**

## NSAID CVD Risks

NSAIDs of all types, are associated with increased risk of gastrointestinal (GI) bleeding, heart attacks, stroke, heart failure and renal injury[2].

There are multiple pathways through which NSAIDs act and they typically double CVD events (though in some groups post-MI, CVD risk is increased 5-fold)[3].

Fig 3 shows CVD and bleeding risks for different NSAIDs.

NSAIDs increase blood pressure by around 5mmHg and increase the likelihood of hypertension at older ages by 40-70%[4]. They interfere with thrombogenesis and reduce aspirin and clopidogrel benefit in CVD[3,5].

The renal actions of NSAIDs increase water retention and inhibit the effects of diuretics and ACE inhibitors. NSAIDs reduce renal function.

- NSAIDs worsen heart failure and are contraindicated.

Fig 3 shows the absolute additional annual adverse CVD and major GI events per 1000, caused by different NSAIDs in people at higher and lower risk of an event.

## Adverse events caused by NSAID at higher and lower baseline risk (events PA/1000)

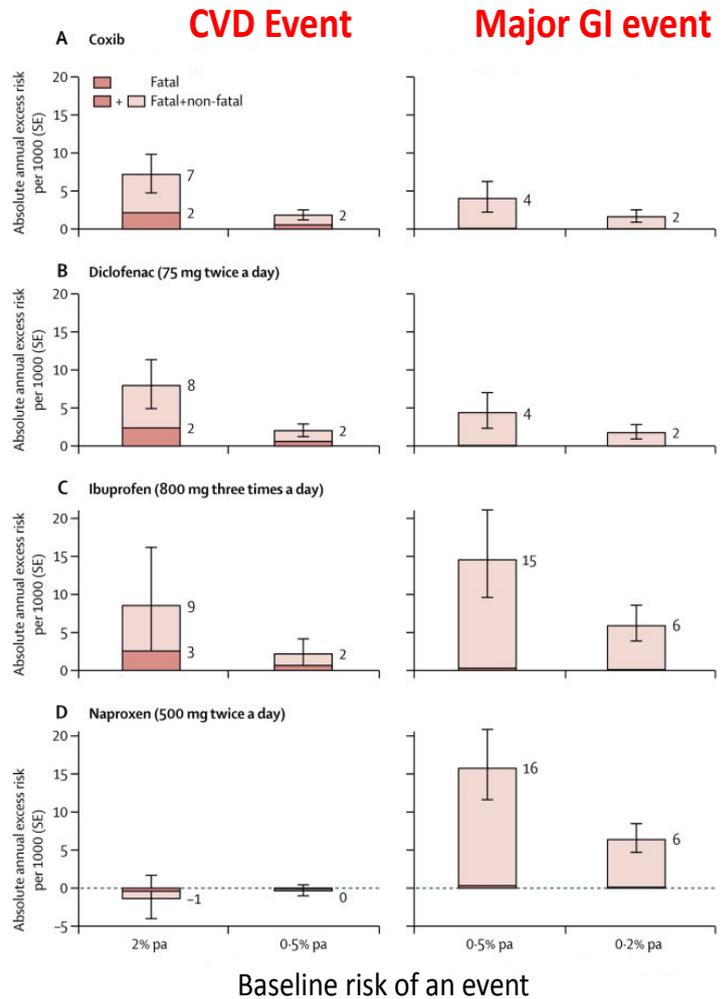


Fig3

CNT Collaboration. Lancet 2013; 382: 769–79

Fig 3 shows adverse events are higher in people at higher risk. It also shows that people at lower risk also have increased risks. In other words as baseline risk increases so will adverse events with NSAIDs. As many more people at lower risk take NSAIDs, they contribute most to the overall population burden of adverse events. Diclofenac, coxibs and high dose ibuprofen have the worst risk of CVD and naproxen the lowest. **CVD events are more often fatal than GI bleeds.**

NSAIDs also increase the risk of upper gastrointestinal complications by 2–4 times during both short and longer term treatment. Coxibs have lower risks of GI bleeds but have the highest rate of CVD events[11]. Naproxen has higher bleeding risks. This can be reduced by a PPI.

**All NSAIDs increase bleeding and CVD adverse events.**

**Naproxen did not increase CVD events in these trials but had the highest rate of GI events.**

## NSAID Risks contd.

**Adverse renal events** occur in 1 to 5 percent of all patients using NSAIDs[6]. The global extent of this problem makes even small percentages a large public health issue. Estimates of more than 70 million prescriptions and 30 billion over-the-counter doses annually in the USA alone, translate into more than 2.5 million patients experiencing a nephrotoxic event annually[7]. In the UK in 2014 there were 2 million prescriptions for diclofenac alone.

**Acute kidney injury** can occur with any class of NSAID. In a case-control study of 121,722 older patients, who did and did not use NSAIDs, risk of acute renal failure within 30 days of initiation was increased by 2.3 for rofecoxib, 2.4 naproxen, 2.3 nonselective NSAIDs and 1.5 celecoxib 1.5[8]. Renal injury is more likely in patients on diuretics and/or ACE inhibitors/ARB.

**In type 2 diabetes** NSAIDs are associated with raised HbA1c. Hospital admissions are increased by 30% with NSAID use in diabetes[9,10]. Most older people with diabetes have either impaired renal function, high blood pressure or established CVD and all are at increased CVD risk – conditions in which NSAIDs are to be avoided.

## Interactions with NSAIDs

**Warn against OTC use of NSAIDs with drugs below:**  
**Anticoagulants - NSAID contraindicated**

**Low-dose aspirin or clopidogrel +NSAID**  
Reduces antiplatelet effectiveness in people with CVD [5]  
Bleeding is also increased.

**Diuretics and ACE/ARB+ NSAID**  
Reduced renal function and may cause acute kidney injury.

**Lithium + NSAIDs** Increased lithium levels.

**SSRI + NSAID** **FOUR-FOLD bleeding risk.**

**Spironolactone+NSAID** **FOUR-FOLD bleeding risk.**

**Corticosteroid +NSAID** **FOUR-FOLD bleeding risk.**

**Biphosphonate +NSAID** **double upper GI risk.**

**Pregnancy - Paracetamol** is analgesic of choice. **NSAIDs must not be used from 30 weeks of pregnancy** without specialist advice due to premature closure of the ductus arteriosus.

See Ref 15, 16 and BNF for full list of interactions:

**Fig 4**  
**Relative risk of CVD events: NSAIDs versus non-use.**

	Observational studies	RandomisedStudies
	McGettigan and Henry, 2011[13] (CV Events)	Trelle et al., 2011 [14](APTC Composite)
<b>Etoricoxib</b>	<b>2.05</b> (1.45–2.88)	<b>1.53</b> (0.74–3.17)
<b>Etodolac</b>	<b>1.55</b> (1.28–1.87)	nr
<b>Rofecoxib</b>	<b>1.45</b> (1.33–1.59)	<b>1.44</b> (1.00–1.99)
<b>Diclofenac</b>	<b>1.40</b> (1.27–1.55)	<b>1.60</b> (0.85–2.99)
<b>Indometacin</b>	<b>1.30</b> (1.19–1.41)	nr
<b>Meloxicam</b>	<b>1.20</b> (1.07–1.33)	nr
<b>Ibuprofen</b>	<b>1.18</b> (1.11–1.25)	<b>2.26</b> (1.11–4.89)
<b>Celecoxib</b>	<b>1.17</b> (1.08–1.27)	<b>1.43</b> (0.94–2.16)
<b>Naproxen</b>	<b>1.09</b> (1.02–1.16)	<b>1.22</b> (0.78–1.93)
<b>Piroxicam</b>	<b>1.08</b> (0.91–1.30)	nr

APTC, Anti-Platelet Trialists Collaboration; CV, cardiovascular; nr, not reported.  
Adapted from McGettigan P and Henry D. PLoS Med 2013; 10(2)

## NSAIDs and bleeding

GI bleeding and ulceration caused by NSAIDs is a major issue, contributing to 20% of all upper GI bleeding.

Older age is the single most important factor increasing bleeding risk.

**People aged 75 years or more, have a risk of GI bleeding similar to the risk that is associated with a peptic ulcer.**

Over 90% of people with osteoarthritis (OA) are at increased bleeding risk, due to their age >65 years or history of CVD or GI morbidity. At least half of these people are not treated according to NICE guidance.

Both selective COX-2 and non-selective NSAIDs increase risks of adverse GI events. In large observational studies, non-selective NSAIDs (in comparison to no use) increased GI bleeding four-fold. COX-2 or low dose aspirin increased bleeding three-fold. The differences in CVD risk and bleeding risk between different NSAIDs are less clear cut than previously thought[12,13].

Though bleeding risk with COX-2 may be slightly lower than other NSAIDs, higher CVD risks make the overall adverse event rate no better and in older people it may be worse.

## Avoiding NSAIDs

Avoidance of NSAIDs is the simplest way to reduce risk particularly in people at high risk of CVD and in older people over age 65 years who are at high risk of both CVD and GI bleeds.

**Proton pump inhibitors (PPI) reduce the risk of bleeding and should be used with NSAIDs,**

There is extensive self-medication with NSAIDs, which requires patient education of the risks.

These GI bleeding risks are increased in combination with other common drugs. Drug combinations are important as about 20% of people over 75 yrs are on one or more of the drugs below[14].

NSAID GI bleeding risk is increased four-fold with SSRIs, spironolactone or corticosteroids. NSAID bleeding increases 2-3 times with aspirin/antiplatelet agents, anticoagulants and biphosphonates.

**Do not use NSAIDs with SSRIs/spironolactone and avoid with biphosphonates and antiplatelet agents[15].**

**NSAIDs should be avoided in people aged over 65 years. If NSAIDs are used, NICE recommends co-prescription of PPI for osteoarthritis or for low back pain in those age over 45 years.**

Non-pharmacological measures should accompany medication for musculo-skeletal pain (MS) and OA.

Fig 5 shows a national trend of reduced use of diclofenac (red) and to a lesser extent COX-2 and an increase in naproxen (blue). Inner East London London CCGs are among the better performing CCGs but this may be partly explained by younger population.

## Alternatives to oral NSAIDs

- NICE recommends...**
- **Paracetamol at the lowest effective dose**
  - **Topical NSAIDs or capsaicin**
  - **Opioid analgesics (may require laxatives)**
  - **Where oral NSAIDs cannot be avoided, naproxen or ibuprofen with a PPI are recommended\***  
(up to naproxen 1000mg daily or ibuprofen 1200mg daily)

There is only limited evidence of superiority of NSAIDs over paracetamol for pain relief with high rates of discontinuation in longer term use. Up to half of patients report *neither* of these drugs gives adequate pain relief.

Despite being recommended by NICE for low back pain, paracetamol has been shown *not* to be effective in low back pain and NSAIDs have only a weak effect. There is no evidence for long term benefit of either[16].

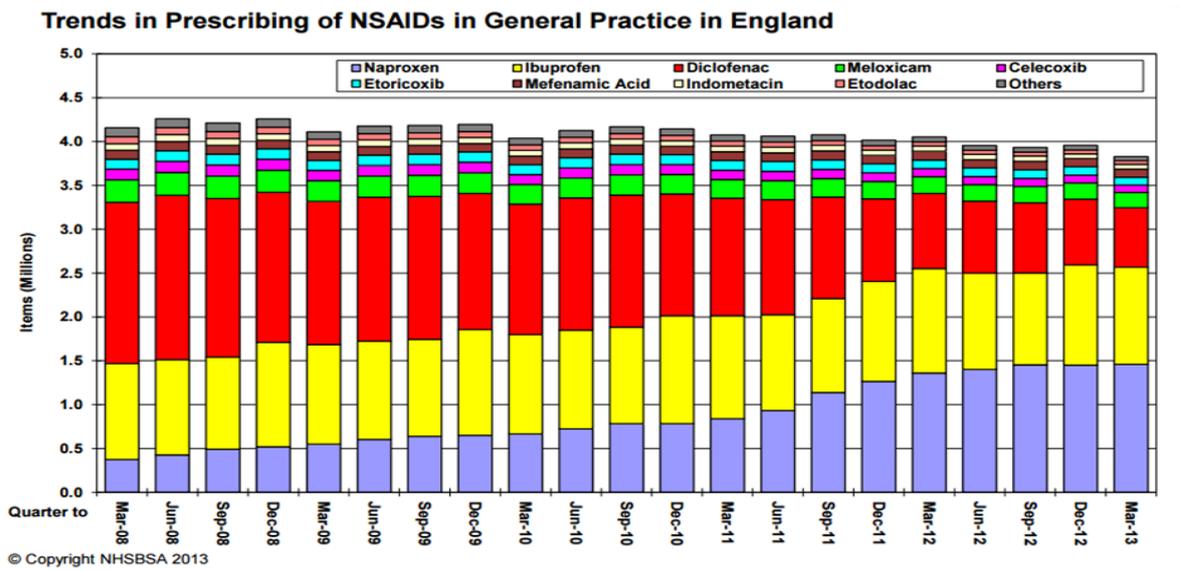
Both paracetamol and NSAIDs reduce pain in hip and knee osteoarthritis (OA), but evidence of long term benefit is lacking. **Paracetamol or weak opioids are treatment of choice for OA in older people. Strengthening exercises for OA have a much greater benefit than either paracetamol or NSAID [16].**

There are no risk free NSAIDs. Oral naproxen <1000mg dly has fewer adverse CVD events than other NSAIDs but higher bleeding risk. Ibuprofen <1200mg dly is an alternative however at higher doses, the CVD risks of ibuprofen are similar to diclofenac[12]. There are no differences between NSAIDs in pain relief.

**Naproxen (<1000mg dly) together with a PPI, is the most cost-effective NSAID strategy with the lowest GI and CVD risks\*. However, paracetamol or weak opioids are preferable.**

\*In people at high CVD risk, aspirin with PPI may be a less harmful option than NSAIDs.

FIG 5



## Topical NSAIDs

Most topical NSAID trials were industry funded, based on small numbers for short (<14 days) duration. They show benefit over placebo. Over 20 years, in these trials for acute pain, only 2000 patients were actively treated, averaging 50 patients per trial[17]. Only 4 trials tested chronic pain relief up to 12 weeks, with little benefit after 4 weeks[18]. Trials of topical salicylate rubefaciants showed no benefit and are not recommended by NICE. Evidence for topical capsaicin is weak but it is recommended by NICE for hand and knee OA.

## References

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- Note1.** Fig 2 p 3 *The CVD mortality estimate is based on 3 million people in the UK with pre-existing stroke or CHD of whom 5% are prescribed NSAID each year (150,000) and they have a 3% per annum baseline risk of a CVD event.*
- NSAIDs increase this risk at least 2 fold and one fifth of these events are fatal. This estimate is a substantial underestimate of total CVD mortality. It takes no account of events in people with diabetes, CKD, hypertension or general population risks nor does it include OTC use.*
- NICE References to NSAIDs on back cover*



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## NICE guidelines on NSAIDs

### NSAID- prescribing issues

<http://cks.nice.org.uk/nsaids-prescribing-issues>

### Osteoarthritis – care and management in adults

<https://www.nice.org.uk/guidance/cg177>

### Low back pain: Early management of persistent non-specific low back pain

<https://www.nice.org.uk/guidance/cg88/chapter/guidance>

### Key therapeutic topics: Non-steroidal anti-inflammatory drugs

<http://www.nice.org.uk/advice/ktt13/resources/nonsteroidal-antiinflammatory-drugs-58757951055301>

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