

headedness (40% versus 37%), and muscle aches (43% versus 39%). Compared to the “morning” group, more patients in the “evening” group reported excessive frequency of micturition (40% versus 36%) (2).

Certain features of this trial weaken the results, including: the lack of blinding, exclusion of patients taking blood pressure-lowering drugs several times a day, exclusion of those working at night, and the significant proportion of patients who did not adhere to their assigned dosing time (approximately 30%) (2). It cannot be ruled out that the results may have been partly influenced by these features, and that the differences from the previous trial were due to slight differences in the protocols.

**IN PRACTICE** This trial, whose level of evidence was no stronger than the previous one, did not confirm the benefit of taking blood pressure-lowering drugs in the evening as opposed to the morning in reducing mortality or the incidence of cardiovascular events. The incidence of adverse effects seemed to differ depending on the dosing time. Given the evaluation data available as of mid-2023, a reasonable option would be to let each patient choose the time of day which best suits them for taking their drugs.

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Selected references from *Prescrire's* literature search

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## Diclofenac: also harmful for the environment

● *Diclofenac*, a drug with widespread presence in the environment, has well-demonstrated environmental toxicity. Another reason not to choose *diclofenac*.

**D** *iclofenac* carries a greater risk of adverse effects than other nonsteroidal anti-inflammatory drugs (NSAIDs), in particular an increase in cardiovascular deaths, without any greater efficacy; hence its use should be avoided (1). It also has more harmful effects on the environment than other NSAIDs (2).

Drugs and their metabolites are found in the environment when they are not sufficiently removed by sewage treatment after their urinary excretion, or when they have been discarded directly into waste water (3-5).

*Diclofenac* was detected in 29% of more than 30 000 samples of surface water collected in France between 2007 and 2018. Its concentration is generally reduced by only 20% to 50% by the sewage treatment process (5).

*Diclofenac* has been detected in various plant and animal species, and in fresh and coastal waters in many countries. Its toxicity, particularly renal, has been demonstrated in trout, to the extent

that it has been blamed for their depletion in Swiss rivers (6).

*Diclofenac* is also toxic to scavenging birds (6). In the Indian subcontinent, where bovine carcasses are left for vultures, one vulture species almost disappeared in the first decade of the 21st century, before recognition of the role of *diclofenac* led to banning its use in animals in 2006 (2,6,7).

Use of *diclofenac* in veterinary medicine is prohibited in many European countries (5). It has been authorised in Spain since 2013, and led to the death of a vulture in the Pyrenees in 2021 (7).

According to the French Agency for Food, Environmental and Occupational Health and Safety (ANSES), the available data are not sufficient to establish a risk to human health in France at the levels found in water destined for human consumption (5).

The Stockholm region publishes a list of drugs recommended for its population. *Diclofenac* is excluded because of its adverse effects, both for humans and the

environment (2). Anti-inflammatory drugs such as *ibuprofen* and *naproxen* do not carry the same risk of human or environmental harms. This is also the case for *paracetamol* (2,8).

For many drugs, their impact on the environment has not yet been documented, but it could become a criterion in the choice between drugs. In the meantime, protection of the environment is another reason for not using *diclofenac*.

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