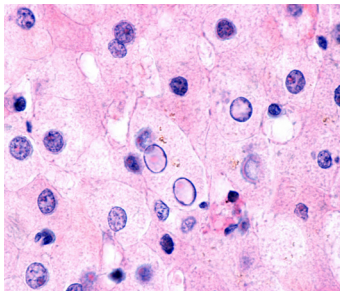
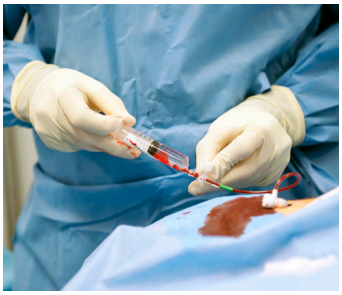
# research



Dapaglifozin for steatohepatitis p 301



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# Dapagliflozin and metabolic dysfunction associated steatohepatitis

**ORIGINAL RESEARCH** Multicentre, double blind, randomised, placebo controlled trial

## Effect of dapagliflozin on metabolic dysfunction associated steatohepatitis

Lin J, Huang Y, Xu B, et al

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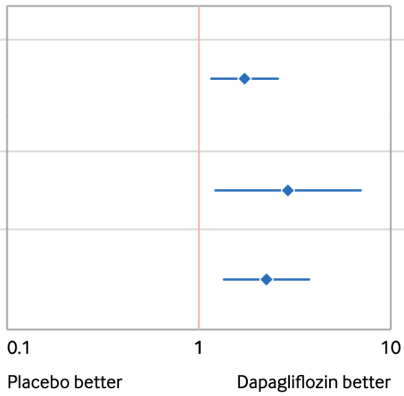
**Study question** Is dapagliflozin a treatment option for metabolic dysfunction associated steatohepatitis (MASH)?

**Methods** This multicentre, double blind, randomised, placebo controlled trial enrolled 154 patients with MASH diagnosed by biopsy from six centres in China from November 2018 to March 2023. Participants were assigned (1:1) to dapagliflozin 10 mg/day or to placebo. The primary endpoint was MASH improvement (defined as a decrease of at least 2 points in the non-alcoholic fatty liver disease activity score (NAS) or a NAS of ≤3 points) without worsening of liver fibrosis (defined as without increase of fibrosis stage) at 48 weeks.

**Study answer and limitations** Incidence of MASH improvement without worsening of liver fibrosis was higher in the dapagliflozin group (41/78; 53%) than in the placebo group (23/76; 30%) (risk ratio 1.73 (95% confidence interval 1.16 to 2.58), P=0.006) over 48 weeks, meeting the predefined primary endpoint. Incidence of MASH resolution without worsening of liver fibrosis (hepatocellular ballooning score of 0, and lobular inflammation score of 0 or 1), and fibrosis improvement without worsening of MASH (defined as without an increase in steatosis, ballooning, or inflammation score) were also significantly higher in the dapagliflozin group than in the placebo group at week 48. No significant differences were noted between the two groups in the occurrence of adverse events. Female patients and patients older than 60 years were under-represented in the current study and the findings cannot be generalised to populations of other ethnic groups.

**What this study adds** Treatment with dapagliflozin for 48 weeks is an effective and safe alternative for patients with MASH and fibrosis.

| Endpoint | Responses in placebo group (%) | Responses in dapagliflozin group (%) | Risk ratio | Risk ratio (95% CI ) | P value |
|---|---|---|---|---|---|
| **Primary endpoint** | | | | | |
| MASH improvement without worsening of fibrosis | 23 (30) | 41 (53) | | 1.73 (1.16 to 2.58) | 0.006 |
| **Comfirmatory secondary endpoints** | | | | | |
| MASH resolution without worsening of fibrosis | 6 (8) | 18 (23) | | 2.91 (1.22 to 6.97) | 0.01 |
| Fibrosis improvement without worsening of MASH | 15 (20) | 35 (45) | | 2.25 (1.35 to 3.75) | 0.001 |




Primary and confirmatory secondary endpoints at week 48. An interactive version of this graphic is available at https://public.flourish.studio/visualisation/23047808

## COMMENTARY Dapagliflozin improves fibrosis and steatohepatitis

Metabolic dysfunction associated steatotic liver disease (MASLD) encompasses a broad clinical spectrum, ranging from simple steatosis to metabolic dysfunction associated steatohepatitis (MASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma. MASLD is currently the leading cause of chronic liver disease[1 2] and one of the leading causes of cirrhosis and liver cancer,[3-5] with an estimated prevalence of 30% worldwide.[6] Prevalence has increased substantially in recent decades, primarily driven by the worldwide rise of obesity and type 2 diabetes mellitus.[6-8]

Current therapeutic pipelines primarily focus on the treatment of MASH. In this context, clinical trials typically assess two primary histological endpoints (using liver biopsy) considered key for regulatory approval: resolution of steatohepatitis without worsening of fibrosis and improvement in fibrosis without worsening of steatohepatitis.[9]

In their trial in China, Lin and colleagues evaluated the efficacy and safety of dapagliflozin in individuals with MASH, both with and without type 2 diabetes mellitus.[10] A total of 154 patients with no cirrhosis were randomly assigned in this 48 week trial to receive either 10 mg of dapagliflozin or placebo once daily, with 125 patients (81%) completing an end of study biopsy. The primary endpoint—improvement in MASH without worsening of fibrosis—was met in 53% of patients in the treatment group compared with 30% in the placebo group. Among the secondary outcomes, resolution of steatohepatitis without worsening of fibrosis occurred in 23% of patients in the dapagliflozin group versus 8% in the placebo group. Additionally, improvement in fibrosis without worsening of steatohepatitis was observed in 45% versus 20% of patients, respectively. Notably, the safety profile of dapagliflozin was favourable and consistent with previous studies. Adverse events were less frequent with dapagliflozin use (56% *v* 64%), and no serious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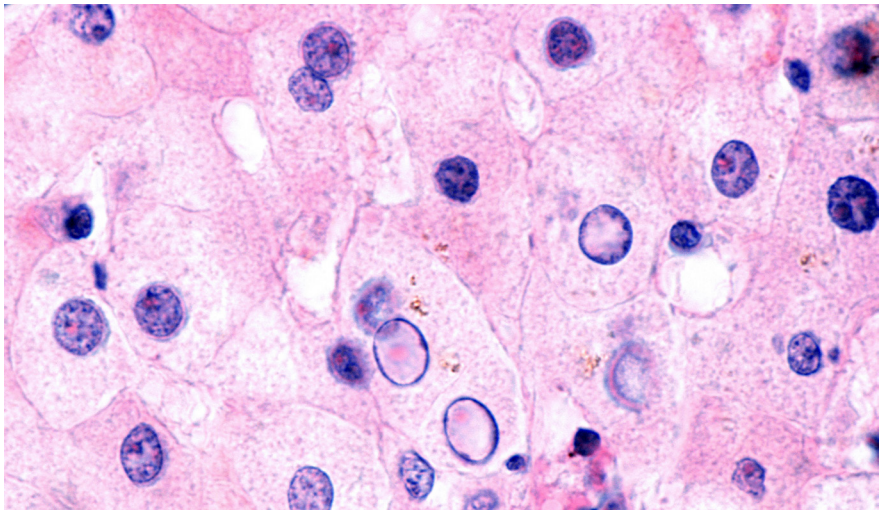

JOSE CALVO/SPL

**Funding, competing interests, and data sharing** This study was funded by the Noncommunicable Chronic Diseases-National Science and Technology Major Project, National Science Fund for Distinguished Young Scholars, Joint Funds of the National Natural Science Foundation, Key-Area Clinical Research Program of Southern Medical University, and the National Key Research and Development Project of China. No competing interests declared. Data are available at https://github.com/Yurence/DEAN_trial.git.

**Study registration** ClinicalTrials.gov NCT03723252.

events were reported in the dapagliflozin group. Insomnia, gout, and bone fractures were slightly more common in the dapagliflozin group. Emerging evidence from other studies indicates that this drug is well tolerated even in patients with cirrhosis.[11]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have grown in importance for the treatment of type 2 diabetes mellitus, showing proved efficacy in heart failure and chronic kidney disease.[12-14] In addition to glycaemic control, SGLT-2 inhibitors have improved lipid profiles and blood pressure, induced modest weight loss, and offered cardiorenal protection—even in patients without diabetes.[15]

## A promising future

Before this trial, evidence supporting the use of SGLT-2 inhibitors in people with MASLD and MASH was limited and mostly exploratory, constrained by small sample sizes, limitations in study design, or non-histological endpoints.[16]

After years without effective treatment options, two drugs from different classes have recently shown benefits and favourable safety profiles in people with MASH. Resmetirom, a thyroid hormone receptor β (THRβ) agonist, is the first drug approved in the US for this population.[17] Meanwhile, semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has shown improvements in liver histology in a phase 3 trial.[18]

**As more drugs become available, treatment decisions will likely become increasingly tailored to individual patient profiles**

As is often the case at this stage of clinical research, head-to-head comparisons are not feasible; however, all three drugs have shown encouraging treatment effects.


For the outcome of MASH resolution without worsening fibrosis, the absolute differences in response rates versus placebo were 15% for dapagliflozin, 29% for semaglutide, and 20% for resmetirom.[10 18 19] For fibrosis improvement without worsening of steatohepatitis, the corresponding differences were 25% for dapagliflozin, 14% for semaglutide, and 12% for resmetirom.[10 18 19] Of note, the dapagliflozin trial included younger patients who were predominantly male and of Asian descent, with a lower body mass index, a lower prevalence of type 2 diabetes, and less fibrosis than participants in the resmetirom and semaglutide trials.

To reach the full therapeutic potential of drugs, treatment must be accompanied by structured dietary interventions and sustained lifestyle modifications, ideally supported by motivational strategies. This principle is reinforced by consistent histological improvements observed in placebo groups across multiple MASH trials, with nearly one in five patients assigned to placebo having meaningful histological benefit.[10 18 19] These outcomes likely reflect, in part, the structured lifestyle counselling and close clinical monitoring typically provided to participants in clinical trials. Such public health and social measures remain a cornerstone of MASLD management and are strongly recommended by major clinical practice guidelines.[4 5]

The coming years are expected to be particularly exciting in the area of pharmacological treatment for MASH. As more drugs become available, treatment decisions will likely become increasingly tailored to individual patient profiles. Given the shared pathophysiological mechanisms linking MASLD, type 2 diabetes, and obesity, particularly insulin resistance and lipotoxicity, identifying drugs capable of improving overall metabolic control while also targeting liver disease remains a key goal.[16] Ideally, such treatments should provide cardiovascular benefit, have an established safety profile, and be accessible to broad and diverse patient populations.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.r1101

# Antiplatelet monotherapy after PCI

**ORIGINAL RESEARCH** Individual patient data meta-analysis of randomised clinical trials

## $P2Y_{12}$ inhibitor or aspirin after percutaneous coronary intervention

Giacoppo D, Gragnano F, Watanabe H, et al

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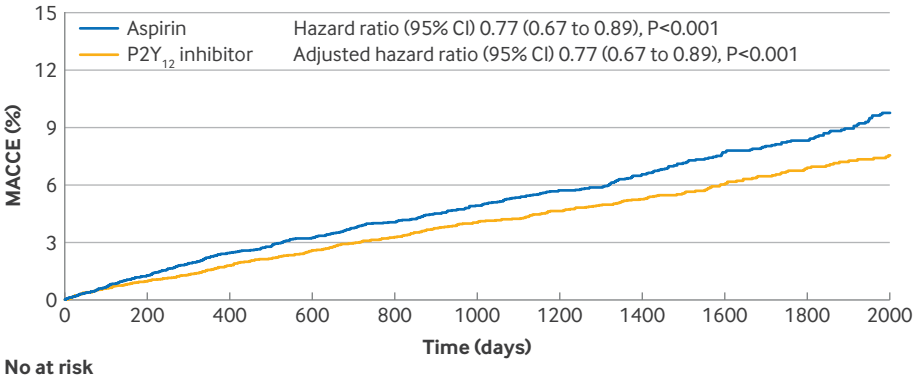
**Study question** Is traditional aspirin monotherapy more effective and safer than $P2Y_{12}$ inhibitor monotherapy for long term secondary prevention of major ischaemic events in patients who have undergone percutaneous coronary intervention (PCI)?

**Methods** This individual patient data meta-analysis involved patients who had undergone PCI and had completed post-procedural dual antiplatelet therapy (DAPT). Patients were assigned to antiplatelet monotherapy with a $P2Y_{12}$ inhibitor or aspirin. The primary and co-primary outcomes were a composite of major adverse cardiac and cerebrovascular events (MACCE), including cardiovascular death, myocardial infarction, or stroke, and major bleeding, respectively. The secondary outcomes were a net composite of adverse cardiac and cerebrovascular events (NACCE), including the primary and co-primary outcomes, and individual ischaemic and bleeding events. Data were primarily combined by mixed effects models (one stage analysis) and complemented with multivariable mixed effects models and two stage analyses based on random effects models.

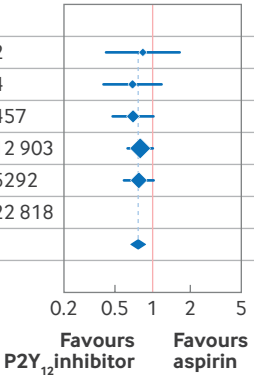
**Study answer and limitations** 16 117 patients assigned to $P2Y_{12}$ inhibitor or aspirin monotherapy after PCI and completion of the recommended DAPT regimen (median duration 12 months) in five randomised trials were included. At a median follow-up of 1351 days (interquartile range 373-1791 days), $P2Y_{12}$ inhibitor monotherapy was associated with a lower risk of MACCE compared with aspirin monotherapy (one stage analysis: hazard ratio 0.77 (95% confidence interval (CI) 0.67 to 0.89), P<0.001; multivariable one stage analysis: adjusted hazard ratio 0.77 (0.67 to 0.89), P<0.001; two stage analysis: hazard ratio 0.77 (0.67 to 0.89), P<0.001), yielding a number needed to treat to benefit of 45.5 (95% CI 31.4 to 93.6). No significant difference in major bleeding was observed. NACCE, myocardial infarction, and stroke were lower in patients assigned to a $P2Y_{12}$ inhibitor compared with patients assigned to aspirin. Changes were needed to the original design of some trials to create uniform data, one trial was conducted before the advent of contemporary advances in PCI, and certain characteristics of individual trial populations potentially reduce the generalisability of findings.




**No at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Aspirin | 7731 | 7609 | 4585 | 4193 | 4020 | 3874 | 3730 | 3623 | 1978 | 1780 | 1321 |
| $P2Y_{12}$ inhibitor | 7763 | 7644 | 4483 | 4183 | 4002 | 3867 | 3743 | 3623 | 1973 | 1755 | 1340 |

| Trial | Events/patients/person years: $P2Y_{12}$ inhibitor | Events/patients/person years: Aspirin | Hazard ratio (95% CI) | Hazard ratio (95% CI) | Weight (%) |
|---|---|---|---|---|---|
| ASCET | 16/312/624 | 19/311/622 | | 0.84 (0.43 to 1.62) | 4.5 |
| CAPRIE | 25/301/558 | 35/296/544 | | 0.69 (0.42 to 1.16) | 7.6 |
| GLASSY | 49/3347/3449 | 69/3310/3457 | | 0.70 (0.49 to 1.01) | 14.9 |
| HOST-EXAM | 158/2674/12 859 | 199/2690/12 903 | | 0.80 (0.65 to 0.98) | 45.8 |
| STOPDAPT-2 | 93/1441/5325 | 119/1435/5292 | | 0.78 (0.59 to 1.02) | 27.2 |
| Total | 341/8075/22 815 | 441/8042/22 818 | | | |
| Random effects model | | | | 0.77 (0.67 to 0.89) | P<0.001 |
| Test for heterogeneity: $^2$=0, P=0.97, $I^2$=0% | | | | | |




**Primary outcome of MACCE. Incidences were calculated using Kaplan-Meier method and compared with log rank test. (Top panel) One stage analysis accounting for differences in baseline hazard and treatment effects across trials. Mixed effects models were used to calculate hazard ratios and 95% CIs and multivariable mixed effects models to calculate adjusted hazard ratios and 95% CIs (sensitivity analysis). The corresponding P values were derived from Wald type testing. (Bottom panel) Two stage analysis by random effects models with inverse variance weighting. CI=confidence interval; ASCET=ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; CAPRIE=Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; HOST-EXAM=Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; MACCE=major adverse cardiac and cerebrovascular events (composite of cardiovascular death, myocardial infarction, or stroke); STOPDAPT-2=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study**

**What this study adds** This individual patient data meta-analysis supports the superior clinical effectiveness and comparable safety of $P2Y_{12}$ inhibitor monotherapy over aspirin monotherapy for secondary prevention of major ischaemic events in patients after PCI and discontinuation of DAPT.

Funding, competing interests, and data sharing
This study was sponsored by the Cardiocentro Ticino Institute and the Department of Cardiology at Bern University Hospital, Switzerland. See full paper on bmj.com for competing interests. Data supporting study findings are available from the corresponding author upon reasonable request.

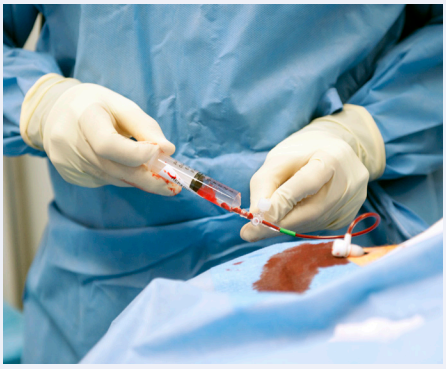
Study registration PROSPERO CRD42024517983.

Patients with coronary artery disease are often offered percutaneous coronary intervention (PCI) with drug eluting stents. International guidelines recommend dual antiplatelet therapy (DAPT) combining aspirin and $P2Y_{12}$ inhibitors after PCI followed by lifelong aspirin monotherapy for secondary prevention of cardiovascular events.[1 2] These recommendations are based on pooled data from foundational randomised controlled trials that no longer represent contemporary practice.[3]

In their study, Giacoppo and colleagues update the evidence base with their individual participant data meta-analysis of five randomised controlled trials: ASCET (ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial), CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events), GLASSY (GLOBAL LEADERS Adjudication Sub-Study), HOST-EXAM (Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy), and STOPDAPT-2 (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 study).[4] Overall, 16 117 participants were included in this study comparing $P2Y_{12}$ inhibitor monotherapy with aspirin after PCI and completion of DAPT. Compared with aspirin, $P2Y_{12}$ inhibitor monotherapy reduced the composite primary efficacy endpoint of major adverse cardiac and cerebrovascular events (MACCE) by 23% at median follow-up of 3.7 years. This finding was driven by 31% and 33% reductions in myocardial infarction and stroke, respectively; no signal emerged for cardiovascular and all cause mortality. At first glance the primary safety endpoint of major bleeding appears similar, regardless of randomised allocation.

### What do the findings mean?

This meta-analysis reports novel and important findings.[4] More than 90% of included participants had undergone PCI in the past decade, making the results highly relevant to contemporary practice. Previously, the only study designed to directly compare the efficacy and safety of $P2Y_{12}$ inhibitor monotherapy with aspirin post-PCI was HOST-EXAM.[5] By leveraging individual participant data, Giacoppo and colleagues[4] facilitated the inclusion of relevant data from additional trials that were not originally intended to answer these questions.[6-9] The reductions in myocardial infarction and stroke hold importance for patients and healthcare systems. In addition to increased risk of recurrent events[10 11] and mortality,[12 13] myocardial infarction and stroke are associated with psychological comorbidity and reduced functional status.[14 15] Consequently, these conditions are responsible for substantial healthcare expenditure and lost productivity.[16] Given the global burden of ischaemic heart disease,[13] reductions in myocardial infarction and stroke may translate to large population benefits.



P. MARAZZI/SPL

**The study supports preferential prescription of $P2Y_{12}$ inhibitor monotherapy over aspirin**

Giacoppo and colleagues' result for major bleeding is challenging to interpret.[4] Reduced bleeding with $P2Y_{12}$ inhibition in HOST-EXAM[5] is an outlier compared with the other included trials, which report effect estimates largely consistent with increased risk. The two studies contributing the largest weight to the meta-analysis, HOST-EXAM[5] and STOPDAPT-2,[6] demonstrate similar ischaemic reduction but non-overlapping bleeding risks with clopidogrel: 33% lower in HOST-EXAM but 46% higher in STOPDAPT-2. Fortunately, SMART-CHOICE-3,[17] a recent Korean randomised controlled trial specifically designed to test clopidogrel versus aspirin monotherapy in participants (n=5506) at high risk for recurrent ischaemia post-PCI recently reported data consistent with Giacoppo and colleagues' meta-analysis[4]: reductions in MACCE with equivalent bleeding.[17]

### Clinical implications

So, should these data influence clinicians and patients to switch from lifelong aspirin to $P2Y_{12}$ inhibitor monotherapy after completion of DAPT post-PCI? Although now off-label, clopidogrel remains more expensive than aspirin, and comprehensive health economic evaluation is required to better understand cost effectiveness. Whether these findings apply equally to all $P2Y_{12}$ inhibitors is also uncertain. While evidence supporting clopidogrel continues to accumulate, no trials have tested prasugrel, and only GLASSY[9] studied ticagrelor, although it did contribute ~42% of the randomised participants in Giacoppo and colleagues' study.[4] Future trials are required to replicate the GLASSY results and improve reliability, while prasugrel trials are needed to understand its role in secondary prevention monotherapy. These additional studies would help guide clinicians on using these more potent $P2Y_{12}$ inhibitors, which have stronger antiplatelet effects than clopidogrel. In acute coronary syndromes they have superior efficacy on ischaemic endpoints but increase bleeding,[19] limiting their prescription in patients at higher bleeding risk. A putative benefit with potent $P2Y_{12}$ inhibitors is reduced variability in platelet response between individuals compared with clopidogrel,[20] although whether this translates to benefit on hard outcomes in this setting is untested.

Overall, Giacoppo and colleagues' study[4] supports preferential prescription of $P2Y_{12}$ inhibitor monotherapy over aspirin owing to reductions in MACCE without increasing major bleeding in the medium term, further validated by results from the recent SMART-CHOICE-3 trial.[15] However, medium term efficacy does not necessarily extend lifelong, which is the duration we advise patients to continue these drugs. Whether the beneficial ischaemic and bleeding trade-off with antiplatelets remains durable over time is contentious, particularly in older adults, and randomised data are lacking beyond ~4 years.[21-23] In the current body of evidence, the appropriateness of existing recommendations for lifelong antiplatelet monotherapy remains an unanswered question. A large scale globally representative trial directly comparing different monotherapy strategies (including discontinuation) with extended follow-up would benefit our understanding of the long term effect of $P2Y_{12}$ inhibitor monotherapy across the treatment class for secondary prevention after PCI.

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# Oral contraceptives with progestogens desogestrel or levonorgestrel and risk of intracranial meningioma

Roland N, Kolla E, Baricault B, et al

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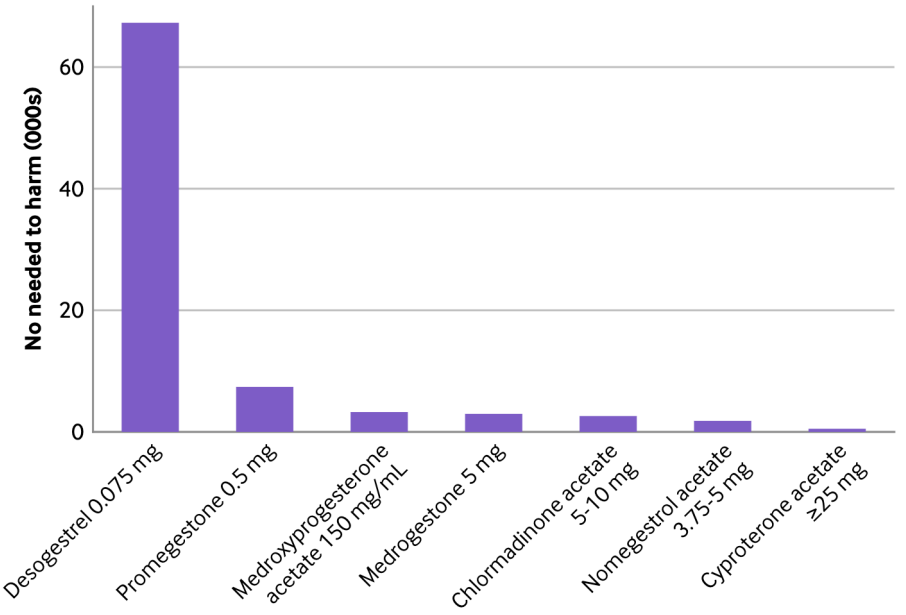


**Numbers needed to harm for one intracranial meningioma requiring surgery, by progestogen use. An interactive version of this graphic is available at https://public.flourish.studio/visualisation/23176824/**

**Study question** Is the risk of intracranial meningioma increased with use of oral contraceptives containing desogestrel, levonorgestrel, or levonorgestrel combined with oestrogen?

**Methods** This nationwide case-control study used data from the French national health data system SNDS (Système National des Données de Santé) on all women resident in France, regardless of age. After exclusions, each woman requiring surgery for intracranial meningioma (cases) was matched with 10 women without meningioma (controls) for year of birth and French geographical area (département) of residence (n=101). For each case, the start date of the corresponding hospital admission was considered the index date. The year 2020 was chosen as the start date to ensure that at least five years of data were collected for desogestrel, as this drug has been reimbursed only since 2014. The authors assessed short term (<1 year) and prolonged (≥1 year, up to ≥7 years) use of desogestrel 75 µg, levonorgestrel 30 µg, or levonorgestrel (50-150 µg) combined with oestrogen. Conditional logistic regression was used to calculate the risk of meningioma.

**Study answer and limitations** Mean age of participants was 59.7 (standard deviation 12.9) years. Among the 8391 women who had undergone surgery for intracranial meningioma, 287 (3.4%) used desogestrel 75 µg (*v* 2769/83 910 (3.3%) controls), 17 (0.2%) used levonorgestrel 30 µg (*v* 140 (0.2%)), and 157 (1.9%) used levonorgestrel combined with oestrogen (*v* 1933 (2.3%)). Women who had used desogestrel 75 µg for more than five continuous years had a slightly higher risk of an intracranial meningioma that required surgery: odds ratio 1.51 (95% confidence interval 1.17 to 1.94) for five to seven years and 2.09 (1.51 to 2.90) for ≥7 years, particularly if meningiomas were in the anterior or middle base of the skull or in multiple locations. The estimated number needed to harm with desogestrel was 67 300 women for one intracranial meningioma requiring surgery and represents a much lower risk compared with progestogens of associated increased risk, such as quarterly injectable contraceptive medroxyprogesterone acetate 150 mg/mL. Risk was no longer observed one year after discontinuation of desogestrel. Results showed no excess risk of intracranial meningioma for levonorgestrel (alone or combined with oestrogen), regardless of duration of use. This was an observational study and therefore cannot prove causal effects. However, the characteristics of the meningiomas observed in this study in women who used desogestrel 75 µg support a possible causal link.

**What this study adds** The results showed a small increased risk of intracranial meningioma in women who had used desogestrel 75 µg for more than five continuous years, but no risk in users of levonorgestrel (alone or combined with oestrogen). Discontinuing desogestrel when a meningioma is diagnosed appears to reduce the risk of further development and could potentially avoid surgery.

Funding, competing interests, and data sharing
Funded by the French National Health Insurance Fund (CNAM) and the French National Agency for Medicines and Health Products Safety (ANSM) through the Health Product Epidemiology Scientific Interest Group EPI-PHARE . No competing interests declared. Data are available from SNDS on approval.