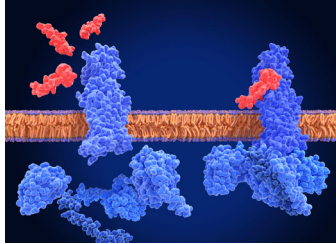


research



Multigene signature tailored breast cancer treatment p 101



GLP-1 agonists and risk of pulmonary aspiration p 102



Day of the week and suicide risk p 14

ORIGINAL RESEARCH Randomised, multicentre, phase 3 trial

Intensive v standard chemotherapy among patients with high risk, operable, triple negative breast cancer based on integrated mRNA-lncRNA signature

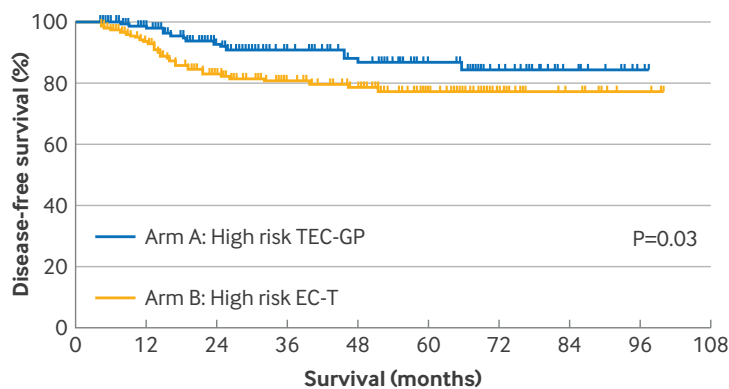
He M, Jiang Y, Gong Y, et al

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Study question Can a specific multigene signature using three mRNAs and two lncRNAs (long non-coding RNAs) be used to tailor individualised adjuvant therapy for patients with operable triple negative breast cancer?

Methods This randomised, multicentre, open label, phase 3 clinical trial conducted at seven cancer centres in China included female patients aged 18-70 years with early triple negative breast cancer after definitive surgery. After risk stratification using the multigene signature, patients at high risk were randomised to receive intensive adjuvant treatment comprising four cycles of docetaxel, epirubicin, and cyclophosphamide followed by four cycles of gemcitabine and cisplatin (arm A; n=166) or standard treatment of four cycles of epirubicin and cyclophosphamide followed by four



No at risk

Kaplan-Meier plot of disease-free survival among patients with high risk score. TEC-GP=docetaxel, epirubicin, and cyclophosphamide followed by gemcitabine and cisplatin; EC-T=epirubicin and cyclophosphamide followed by docetaxel

cycles of docetaxel (arm B; n=170). Patients at low risk received the same therapy as arm B (arm C; n=168). The primary endpoint was disease-free survival in the intention-to-treat analysis for arm A versus arm B.

Study answer and limitations The three year disease-free survival was 90.9% for patients in arm A and 80.6% for patients in arm B (hazard ratio 0.51, 95% confidence interval 0.28 to 0.95; P=0.03). The multigene signature showed potential for tailoring adjuvant chemotherapy for patients with operable triple negative breast cancer. Intensive regimens significantly improved disease-free survival with manageable toxicity in patients at high risk. Limitations include the open label design and

involvement of only centres in China.

What this study adds This study used a multigene signature to tailor individualised adjuvant therapy for patients with operable triple negative breast cancer. An intensive chemotherapy regimen significantly improved disease-free survival versus standard chemotherapy in patients identified as being at high risk by the multigene signature.

Funding, competing interests, and data sharing See full paper on [bmj.com](https://www.bmj.com) for funders. No competing interests declared. Data will be shared, with investigator support, after approval of a proposal, with a signed data access agreement.

Study registration [ClinicalTrials.gov](https://www.clinicaltrials.gov) NCT02641847.

● EDITORIAL, p 95

Glucagon-like peptide-1 receptor agonists and aspiration risk

ORIGINAL RESEARCH Cohort study

Glucagon-like peptide-1 receptor agonists before upper gastrointestinal endoscopy and risk of pulmonary aspiration or discontinuation of procedure

Alkabbani W, Suissa K, Gu KD, et al
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Study question Is use of glucagon-like peptide-1 (GLP-1) receptor agonists before upper gastrointestinal endoscopy associated with an increased risk of pulmonary aspiration or discontinuation of

the procedure compared with use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors?

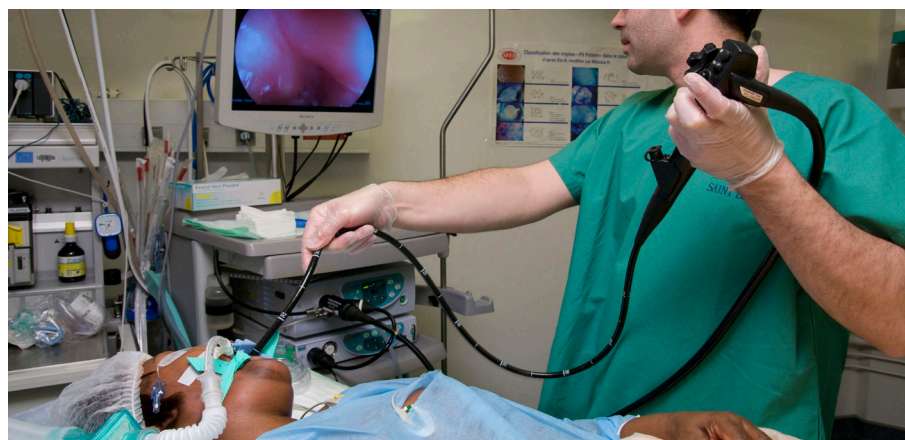
Methods Data were obtained from two deidentified US commercial healthcare databases (MarketScan Commercial Claims and Encounters, and Optum's Clinformatics Data Mart) on adults with type 2 diabetes who underwent endoscopy and were prescribed either a GLP-1 receptor agonist or an SGLT-2 inhibitor within 30 days before the procedure. The primary outcome was pulmonary aspiration during or the day after endoscopy, and the secondary outcome was discontinuation of the procedure. Risk ratios along with 95% confidence intervals

(CIs) were estimated after fine stratification weighting based on propensity score.

Study answer and limitations After weighting, 24 817 adults used a GLP-1 receptor agonist (mean age 59.9 years; 63.6% women) and 18 537 used an SGLT-2 inhibitor (59.8 years; 63.7% women). Among users of GLP-1 receptor agonists and SGLT-2 inhibitors, the weighted risk per 1000 people was, respectively, 4.15 and 4.26 for aspiration and 9.79 and 4.91 for discontinuation of endoscopy. Compared with SGLT-2 inhibitor use, GLP-1 receptor agonist use was not associated with an increased risk of pulmonary aspiration (risk ratio 0.98, 95% CI 0.73 to 1.31), although it was associated

COMMENTARY Balancing the harms and risks of periprocedural management

Glucagon-like peptide-1 (GLP-1) receptor agonists, which can slow gastric emptying and increase the risk of retained gastric contents, are increasingly prescribed for the treatment of diabetes and obesity, as well as emerging indications for cardiovascular and renal disease.¹⁻⁴ Many clinicians providing anaesthesia or sedation, however, are concerned about an increased risk of aspiration in patients using GLP-1 receptor agonists, owing to their mechanism of action. Unfortunately, whether, and to what extent, GLP-1 receptor agonists increase the risk of aspiration remains uncertain. Current evidence is limited to case reports and single centre observational studies at risk of confounding biases and that are focused on the presence of retained gastric contents and not whether aspiration occurs more frequently in those taking GLP-1 receptor agonists. This uncertainty is reflected in opinions and clinical practice guidelines that provide highly variable recommendations, spanning from conservative and precautionary guidance to the withholding of GLP-1 receptor agonists for three weeks before a procedure—including consideration for cancellation of a procedure owing to inadequate cessation of the drug to continuation of a procedure despite the drug not having been stopped during the periprocedural period.⁵⁻⁷ The one



Clinicians should recognise that clinically apparent aspiration is relatively rare (~5 per 1000)

area where agreement exists is that more, and better, data are required to inform the management of GLP-1 receptor agonists in patients requiring anaesthesia or sedation.

In their study, Alkabbani and colleagues addressed this need by estimating the risk of aspiration among people with type 2 diabetes who used GLP-1 receptor agonists or sodium-glucose cotransporter-2 (SGLT-2) inhibitors.⁸ The study makes meaningful methodological advancements, as the authors: used an active, clinically sensible, comparator group (people with diabetes using SGLT-2 inhibitors), which should help to reduce unmeasured confounding; specified aspiration as a primary outcome, which is more clinically and patient relevant

than focusing on the presence of gastric contents (an outcome more proximal on the causal pathway with unknown correlation with aspiration risk); and used a generalisable, population based design with adequate power to study aspiration. Across more than 43 000 individuals, data were not consistent, with an association between GLP-1 receptor agonist use and aspiration (pooled risk ratio 0.98, 95% confidence interval 0.73 to 1.31). An adjusted increase in discontinuation of the procedure (pooled risk ratio 1.99, 1.56 to 2.53) was reported, which is suggestive of increased rates of retained gastric contents in users of GLP-1 receptor agonists.

How can findings from this observational cohort study, considered in the context of existing evidence, help clinicians to provide safe anaesthesia and sedation care for patients taking GLP-1 receptor agonists?

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Crude and weighted risks of pulmonary aspiration and discontinuation of upper gastrointestinal endoscopy among users of GLP-1 receptor agonists and SGLT-2 inhibitors*

	Crude					Weighted				
	GLP-1 receptor agonist		SGLT-2 inhibitor		Risk ratio (95% CI)	GLP-1 receptor agonist		SGLT-2 inhibitor		Risk ratio (95% CI)
	Total no	No of events†	Total no	No of events†		Total no	No of events†	Total no	No of events†	
Pulmonary aspiration	24 824	103 (4.15)	18 541	92 (4.96)	0.84 (0.63 to 1.11)	24 817	103 (4.15)	18 537	79 (4.26)	0.98 (0.73 to 1.31)
Discontinuation of procedure	24 824	243 (9.79)	18 541	85 (4.58)	2.13 (1.66 to 2.72)	24 817	243 (9.79)	18 537	91 (4.91)	1.99 (1.56 to 2.53)

For each cohort, results were pooled across two databases (MarketScan Commercial Claims and Encounters and Optum's Clinformatics Data Mart) using fixed effect model.

CI=confidence interval; GLP-1=glucagon-like peptide-1; SD=standard deviation; SGLT-2=sodium-glucose cotransporter-2.

*Drug dispensed 30 days before endoscopy or drug supply extended into 30 day assessment period for drug use.

†Risk/1000 people.

with a higher risk for discontinuation of endoscopy (1.99, 1.56 to 2.53). Study limitations include lack of validation of the outcomes definition and possible residual confounding.

What this study adds This study found that pulmonary aspiration is rare and

not substantially higher among adults with type 2 diabetes prescribed GLP-1 receptor agonists compared with SGLT-2 inhibitors; however, endoscopy was more likely to be discontinued. These findings may inform practice recommendations on the preprocedural protocol for elective endoscopies.

Funding, competing interests, and data sharing Funded by the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, USA. See full paper on bmj.com for competing interests. The databases used in this study are accessible to other researchers by contacting the data-providers and acquiring data use agreements or licences.

Clinical implications

Firstly, clinicians should recognise that although consequences of aspiration can be severe, even in patients with risk factors for aspiration, clinically apparent aspiration is relatively rare (~5 per 1000, as in the current study).⁹ Across all patients having general anaesthesia for elective procedures, aspiration rates are an order of magnitude lower (~2.5 per 10000).¹⁰ Low baseline risk of aspiration means that even if GLP-1 receptor agonists did increase the relative risk of aspiration at a rate consistent with the upper 95% confidence limit reported by Alkabbani and colleagues (risk ratio 1.31, which could be considered a plausible extreme value based on their data), the absolute risk increase would be small (~0.1%; equivalent to a number needed to harm of ~1000).

Next, one must acknowledge that meaningful uncertainty remains. Observational studies that use routinely collected data are at risk of unmeasured confounding, and the codes used to identify aspiration are at risk of misclassification bias.¹¹ The impact of these biases, in both direction and magnitude, are difficult to

estimate. While a clear and consistent signal from the current study and related investigations is that patients taking GLP-1 receptor agonists likely have at least a twofold increased risk of retained gastric contents,^{12,13} the finding that aspiration risk was not increased questions the strength of association between retained gastric contents and meaningful increases in aspiration risk. Furthermore, Alkabbani and colleagues' data were obtained from before 2023, when the concern about aspiration risk attributable to GLP-1 receptor agonists was not widespread, and recommendations for preprocedural cessation were uncommon. This means that many patients in the study cohort who used GLP-1 receptors agonists plausibly continued their use through the procedural period, a bias that would increase the likelihood of finding a positive association between use of GLP-1 receptor agonists and aspiration.

Better evidence needed

Although the absolute risk of aspiration is likely low, clinicians must continue to provide individualised management of aspiration risk until causal estimates of risk

and benefits of different periprocedural GLP-1 management strategies are derived from randomised trials. Thus far, the management of periprocedural GLP-1 receptor agonists has largely been framed in terms of reducing aspiration risk. However, guidelines and related changes to care pathways (eg, prolonged holding periods for GLP-1 receptor agonists, cancelling procedures in at-risk patients) implemented in the absence of causal data should not be adopted blindly. Evidence based evaluation that also captures impacts on patient relevant measures that need to be balanced against risk of aspiration, such as impaired glucose control, surgical site infections, prolonged surgical wait times, and patient experience, is required. Although concerns of harm understandably trigger cautionary responses, management strategies must evolve with emerging evidence to ensure that all patients receive timely, safe, and appropriate access to sedation and anaesthesia for interventional and surgical procedures.

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Association of holidays and the day of the week with suicide risk

Lee W, Kang C, Park C, et al
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 Find this at doi: 10.1136/bmj-2024-077262

Study question Does suicide risk vary by day of the week and by national holidays?

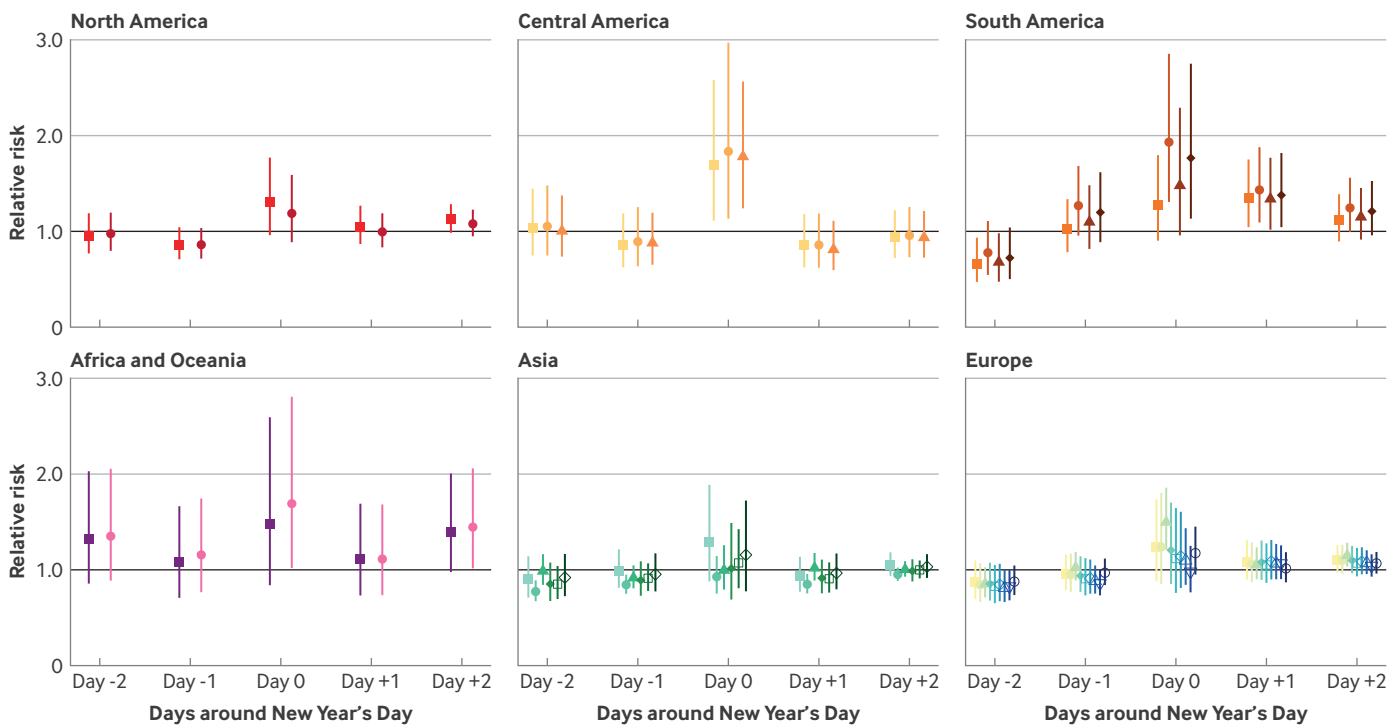
Methods This time series study was of 1 701 286 suicide cases in 26 countries and regions. Differences in suicide risk by day of the week (weekdays and weekends; reference Wednesday) and national holidays (New Year's Day, Christmas Day, and other national holidays) were assessed using a quasi-Poisson regression model for time series data.

Study answer and limitations During weekdays, Monday had the highest suicide risk, ranging from 1.02 (95% confidence interval (CI) 0.95 to 1.10) in Costa Rica to 1.17 (1.09 to 1.25) in Chile, compared with Wednesday. Suicide risks were lowest on Saturdays or Sundays in many countries in North America, Asia, and Europe. However, the risk increased during the weekends in South and Central American countries, Finland, and South Africa. Suicide risk increased on New Year's Day in most countries, ranging from 0.93 (95% CI 0.75 to 1.14) in Japan to 1.93 (1.31 to 2.85) in Chile. However, suicide risk during weekends and on Christmas Day and other national holidays differed by country and continent. Suicide risk was associated with a weak decrease on other national holidays, except for Central and South American countries,

where the risk generally increased one or two days after these holidays. Only a sample of locations was included, and therefore estimates might not be generalisable for each country. Also, some countries were limited to one or two cities or lacked data on recent periods.

What this study adds Suicide risk increased on Monday and New Year's Day at a global scale, with heterogeneous risk patterns on weekends, Christmas Day, and other national holidays. The findings support the need for more targeted interventions and pre-emptive prevention programmes to reduce suicide risk.

Funding, competing interests, and data sharing No competing interests declared. Data were collected under a specific data sharing agreement and are not publicly available.



- Canada (26 cities)
- Brazil (15 cities)
- South Africa (52 districts)
- Taiwan (3 cities)
- Germany (1 city)
- UK (10 regions)
- USA (134 cities)
- Chile (1 city)
- China (1 city)
- ◇ Vietnam (1 city)
- Italy (1 city)
- Costa Rica (1 city)
- ▲ Ecuador (2 cities)
- Japan (47 prefectures)
- Czech Republic (3 cities)
- ◇ Romania (8 cities)
- Guatemala (1 city)
- Paraguay (1 city)
- ▲ Korea (36 cities)
- Estonia (5 cities)
- ▲ Spain (50 cities)
- ▲ Mexico (10 cities)
- Australia (5 cities)
- Philippines (8 cities)
- ▲ Finland (310 municipalities)
- ▼ Switzerland (8 cantons)

Risk of suicide around New Year's Day with corresponding 95% confidence intervals (vertical lines). Reference days were non-holidays that are not included in New Year's Day, Christmas Day, and other national holidays that this study addressed