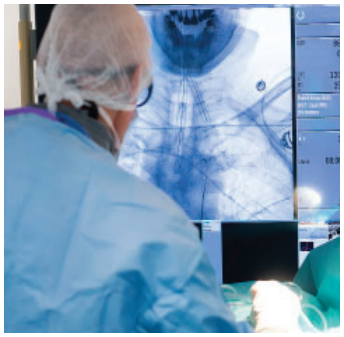
research

Effect of integrated interventions around pregnancy and in early childhood p 185



Risk of reintervention and rupture of abdominal aortic aneurysm after EVAR p 186

Covid-19 vaccines and risk of TTS and thromboembolism p 188

ORIGINAL RESEARCH Factorial, individually randomised controlled trial

Impact of a package of health, nutrition, psychosocial support, and WaSH interventions during preconception, pregnancy, and early childhood on birth outcomes and linear growth at age 24 months

Taneja S, Chowdhury R, Dhabhai N, et al

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Study question What is the effect of integrated and concurrent delivery of interventions during the preconception period alone, during pregnancy and early childhood, and throughout preconception, pregnancy, and early childhood on birth outcomes and linear growth at 24 months of age compared with routine care?

Methods This individually randomised controlled trial with factorial design was conducted in low and middle income neighbourhoods of Delhi, India. Married women aged 18-30 years were randomly assigned to receive preconception interventions or routine care. After ultrasonographic confirmation of pregnancy, the women were randomly assigned again to receive pregnancy and early childhood interventions or routine care. The primary outcomes were proportion of low birth weight, small for gestational age, and preterm infants, and mean birth weight, length-for-age z scores, and proportion stunted at 24 months.

Study answer and limitations The proportion with low birth weight was lower in the preconception intervention groups (506/2235) than in the no preconception intervention groups (502/1889; incidence risk ratio 0.85, 98.3% CI 0.75 to 0.97; absolute risk reduction −3.80%, 98.3% CI −6.99% to −0.60%). The proportion with low birth weight was lower in the pregnancy intervention groups (502/2096) than in the no pregnancy intervention groups (506/2028), but the upper limit of the confidence interval crossed the null effect (0.87, 0.76 to 1.01; −1.71%, −4.96% to 1.54%). There was a larger effect on proportion with low birth weight in the group that received interventions in the preconception and pregnancy periods (267/1141) than in the control group (267/934; 0.76, 0.62 to 0.91; −5.59%, −10.32% to −0.85%). The proportion stunted at 24 months was substantially lower in the pregnancy and early childhood intervention groups (79/746) than in the groups that did not receive these interventions (136/710; 0.51, 0.38 to 0.70; −8.32%, −12.31% to −4.32%), and in the group that received preconception, pregnancy, and early childhood interventions (47/453) compared with the control group (51/271; 0.49, 0.32 to 0.75; −7.98%, −14.24% to −1.71%). No effect on stunting at 24 months was observed in the preconception intervention groups (132/892) compared with the no preconception intervention groups (83/564).

What this study adds Integrated interventions delivered during preconception, pregnancy, and early childhood could substantially reduce the risk of low birth weight and stunting at 24 months of age.

Funding, competing interests, and data sharing See full paper on bmj.com for funding. No competing interests declared. Data shared with Healthy Birth, Growth, and Development Knowledge Integration repository (https://github.com/HBGDki).

Study registration Clinical Trial Registry—India CTRI/2017/06/008908

Tracking the performance of endovascular devices

ORIGINAL RESEARCH Observational surveillance study

Use of linked registry claims data for long term surveillance of devices after endovascular abdominal aortic aneurysm repair

Goodney P, Mao J, Columbo J, et al; on behalf of The Society for Vascular Surgery's Patient Safety Organization

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Study question What are the rates of reintervention and late rupture of abdominal aortic aneurysm associated with four devices used for endovascular repair (EVAR) in the United States using a linked registry claims dataset as a platform for real world, active device surveillance?

Methods This retrospective cohort study was based on data collected at 282 centres in the Vascular Quality Initiative Registry linked to US Medicare claims between 2003 and 2018. The study population comprised 20 489 patients treated with four different device types: 40.6% (n=8310) received the Excluder (Gore), 32.2% (n=6606) the Endurant (Medtronic), 16.0% (n=3281) the Zenith (Cook Medical), and 11.2% (n=2292) the AFX (Endologix). Given modifications to the AFX in late 2014, patients were categorised as having received the early AFX device compared with patients who received the other devices, using propensity matched Cox models. The main outcome measure was the proportion of patients undergoing reintervention and post-EVAR rupture of abdominal aortic aneurysm; all patients (100%) had complete follow-up via the registry or claims based outcome assessment, or both.

Study answer and limitations The risk of reintervention for patients who received the early AFX device was higher compared with the other devices in propensity matched Cox models (hazard ratio 1.61, 95% confidence interval 1.29 to 2.02) and analyses using a surgeon level instrumental variable of >33% AFX grafts used in their practice (1.75, 1.19 to 2.59). The linked registry claims surveillance data identified the increased risk of reintervention with the early AFX device as early as mid-2013, well before the first regulatory warnings were issued in the US in 2017. Limitations in this study that are inherent in the use of linked registry claims datasets for clinical analyses were partially mitigated by validation efforts confirming the ability to measure clinical outcomes with hybrid data sources.

What this study adds The linked registry claims surveillance data identified a device specific risk in long term reintervention after EVAR of abdominal aortic aneurysm. Device manufacturers and regulators can leverage linked data sources to monitor long term outcomes actively in real world practice after cardiovascular interventions.

COMMENTARY Registries linked to routinely collected data can help prevent avoidable harm

The study by Goodney and colleagues is an important evaluation of medium to long term outcomes after endovascular repair of abdominal aortic aneurysm.[1] It not only quantifies and explains the nature of the long term outcomes for patients, but also provides insight into how surgeons might harness routinely collected data to monitor the performance of surgical devices.

Starting in 2003, the authors used a patient registry to collect demographic and operative data on patients undergoing endovascular aneurysm repair (EVAR) in centres in the US and Canada. They were able to follow up patients after discharge from hospital through linkage to patient level data in the Medicare database. Almost a fifth of patients required another intervention related to their aortic aneurysm (aortic reintervention) within five years of their initial EVAR, and 2.4-4.3% developed a ruptured aneurysm. The authors found no evidence of a plateau in rates of complications and reinterventions.

These important observations might not surprise vascular surgeons, but do suggest research should focus on developing more durable aortic stent grafts and better methods of surveillance that are acceptable to patients and predict or identify clinically important complications early.

Utility of linked registry data

A key purpose of the study was to examine the performance of a particular underperforming EVAR device to establish whether the worse outcomes associated with this device could be identified within the linked registry data. The early AFX device (manufactured by Endologix) had a complication rate (aortic reintervention) nearly 10% higher in absolute terms than other devices within the first five years after surgery. Importantly, these findings were robust to any differences in surgical case mix. Although conventional adverse event reporting to the FDA ultimately led to the device being recalled, this recall was only done some years after its introduction. The authors argue that harnessing the linked registry data would have identified the under-performing device at least two years earlier, reducing patient harm.

Future research should focus on developing more durable aortic stent grafts and better methods of surveillance

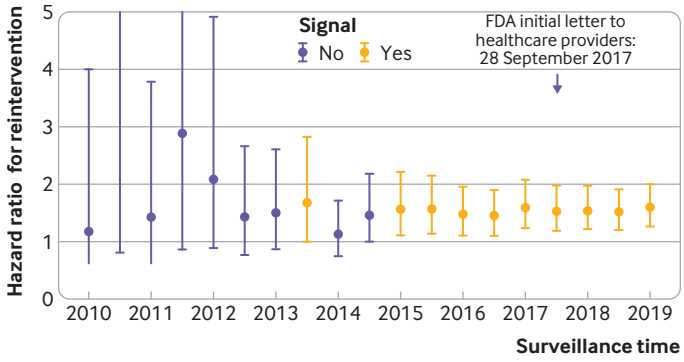
Endologix has improved its device, and a later iteration—also evaluated by Goodney and colleagues, appears to be performing well.

Goodney and colleagues' study also found that safety outcomes soon after surgery were a poor predictor of a device's long term performance. An inability to identify signs of late device failure in the early postoperative phase is a substantial problem because many device registries focus on in-hospital or 30 day outcomes and are not linked to routinely collected long term datasets. More reliable preclinical testing should be a priority, along with the identification and evaluation of surrogate markers of device performance that could be valuable early warnings of subsequent device failure.

Improved monitoring

Designing new surgical registries that can be linked to other important routinely collected datasets is only one aspect of efforts to improve device monitoring. In the UK, surgical registries have been developed for a variety of purposes, including assessment of surgeon and unit performance. However, assessment of device performance brings new challenges.[3 4] Research registries such as EUROSTAR and RETA, for example, successfully identified predictors of failure of early generation aortic stent grafts with inferior outcomes.[5 6] However, developing and maintaining

Robert J Hinchliffe
Robert.Hinchliffe@bristol.ac.uk
See bmj.com for author details



Number of years to detect complications signal (reintervention) for the early AFX (Endologix) device for endovascular repair. Whiskers represent 95% confidence intervals. FDA=US Food and Drug Administration

Funding, competing interests, and data sharing
This study was funded by the US Food and Drug Administration and the Society for Vascular Surgery Patient Safety Organization. Individual authors receive support from a variety of sources including the National Institutes of Health (PPG, JM), the American Heart Association (PPG), and the Veterans Administration. Reuse of the Vascular Quality Initiative-Medicare linked dataset is possible only through collaboration with the original requestor at Weill Cornell Medicine.

these registries required substantial resources and they were never linked to routinely captured data for long term monitoring purposes. The UK National Joint Registry has been successful in identifying poorly performing devices but has had to rely on industry funding to support its activities.[7]

Relevant data

Identifying long term complications related to a device or procedure relies on the capture of clinically important patient outcomes. Selected outcomes must be relevant to both patients and clinicians but also must be available and reliably recorded in routinely collected datasets. The impact of case mix on outcomes is also important but might not be clear when new technologies are introduced. Case selection is one reason why disease specific registries are preferable to registries that collect data only from patients who have successfully received an operation or device.

Although theoretical and regulatory frameworks exist for the development, evaluation, and introduction of new surgical techniques and devices, their governance and delivery are variable.[8 9] In the UK, high profile failures of surgical devices that caused serious patient harm and undermined confidence in device regulation led to a report by the Independent Medicines and Medical Devices Safety Review, published in 2020.[10] The review called for better regulation, including more testing of devices, improved use of registries, and a central database collecting identifiable patient information and details of all implants linked to those registries.

Goodney and colleagues' new study provides further evidence supporting the view that registries linked to routine data can help identify poorly performing devices and prevent harm. The challenge now is to develop and incorporate these linked registries into everyday clinical practice.

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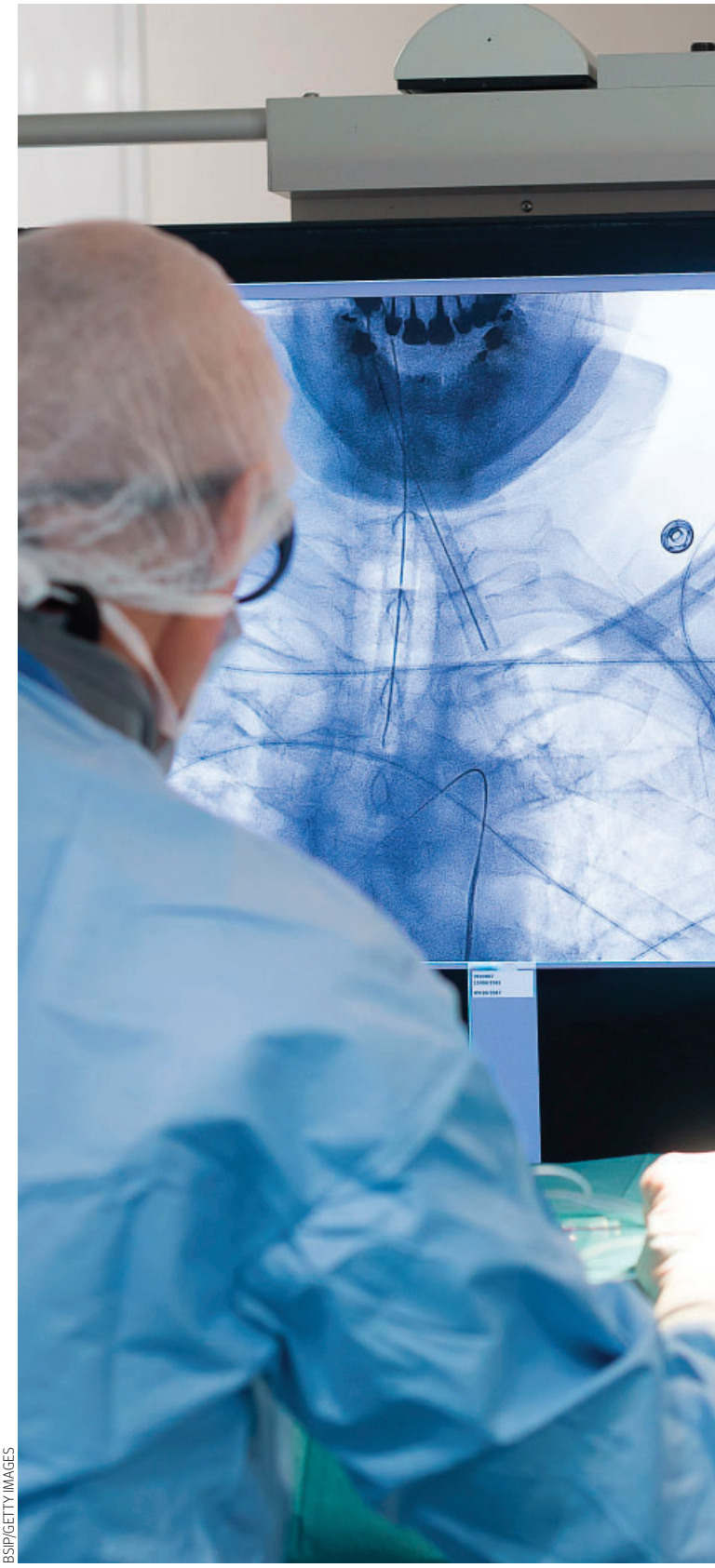

BSIP/GETTY IMAGES

Comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines

Li X, Burn E, Duarte-Salles T, et al

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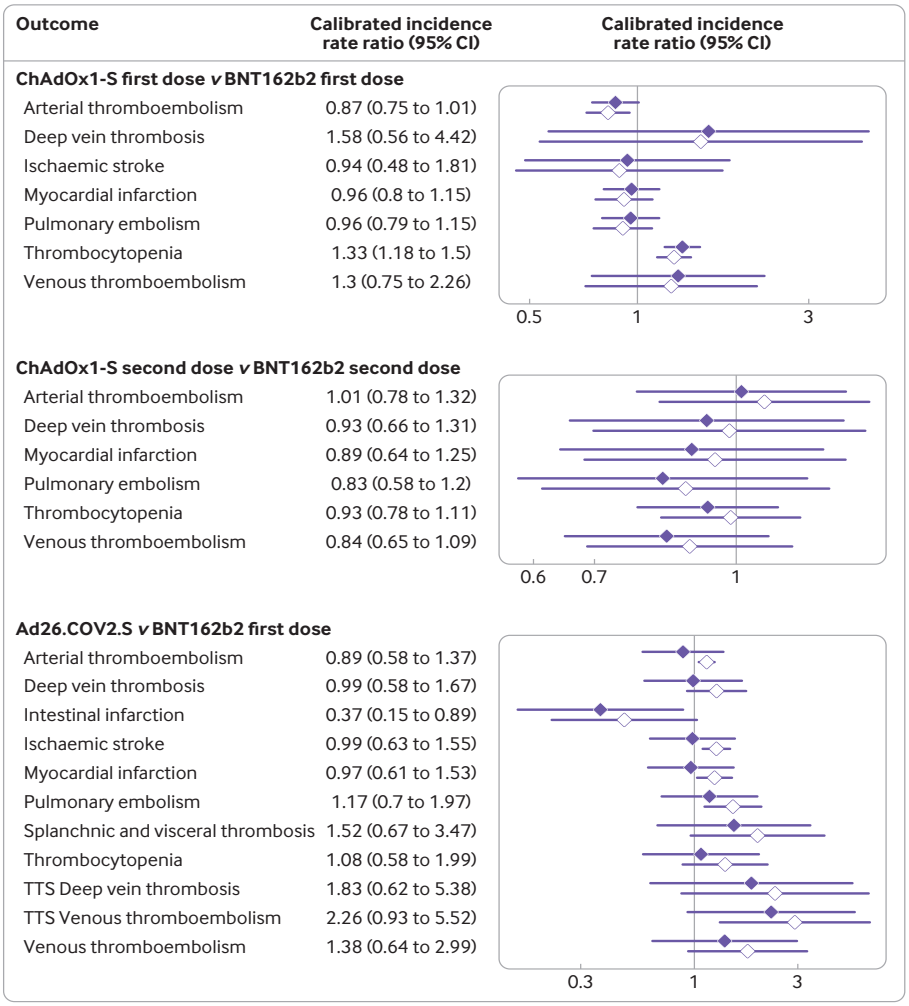
Study question What is the comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with use of adenovirus based versus mRNA based covid-19 vaccines?

Methods Using routinely collected health data from France, Germany, the Netherlands, Spain, UK, and US, researchers included adults (≥18 years) who received at least one dose of a covid-19 vaccine (ChAdOx1-S (Oxford-AstraZeneca), BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), or Ad26.COV2.S (Janssen/Johnson & Johnson)) from December 2020 to mid-2021. Propensity score matching was used to create comparable groups of individuals receiving adenovirus based and mRNA based vaccines. Incidence rate ratios of developing thrombosis with thrombocytopenia syndrome or venous or arterial thromboembolic events in the 28 days after covid-19 vaccination were estimated.

Study answer and limitations Overall, 1 332 719 of 3 829 822 recipients of first dose ChAdOx1-S were matched to 2 124 339 of 2 149 679 BNT162b2 recipients from Germany and the UK. Additionally, 762 517 of 772 678 people receiving Ad26.COV2.S were matched to 2 851 976 of 7 606 693 receiving BNT162b2 in Germany, Spain, and the US. All 628 164 Ad26.COV2.S recipients from the US were matched to 2 230 157 of 3 923 371 mRNA-1273 recipients. A total of 862 thrombocytopenia events were observed in the matched first dose ChAdOx1-S recipients from Germany and the UK, and 520 events after a first dose of BNT162b2. An increased risk of thrombocytopenia was observed after ChAdOx1-S vaccination compared with a first dose of BNT162b2, with a pooled calibrated incidence rate ratio of 1.33 (95% confidence interval 1.18 to 1.50). Additionally, a pooled calibrated incidence rate ratio of 2.26 (0.93 to 5.52) for venous thrombosis with thrombocytopenia syndrome was seen with Ad26.COV2.S vaccination compared with BNT162b2. One main weakness of this study was the potential misclassification of vaccinations and outcomes in observational data; however, the use of comparative safety analyses minimised the impact of this problem, because only vaccinated cohorts were included for analysis.

What this study adds Based on routinely collected data from Europe and the US, risk of thrombocytopenia increased by 30% after a first vaccine dose of ChAdOx1-S for covid-19 compared with a first dose of BNT162b2. Although rare, the observed risks of adenovirus based vaccines should be considered when planning further immunisation campaigns and future vaccine development.

Funding, competing interests, and data sharing
Funded by the European Medicines Agency. See full paper on bmj.com for competing interests and data sharing.



Meta-analytical estimates of incidence rate ratios of developing thrombosis with thrombocytopenia syndrome or venous or arterial thromboembolic events in the 28 days after covid-19 vaccination, according to information from routinely collected health databases. Lines with solid diamonds=calibrated estimates; lines with clear diamonds=uncalibrated estimates; TTS=thrombosis with thrombocytopenia syndrome; UK CPRD=Clinical Practice Research Datalink Aurum; Germany DA=IQVIA Disease Analyser Germany; Netherlands IPCI=Integrated Primary Care Information; France LPD=IQVIA Longitudinal Patient Data