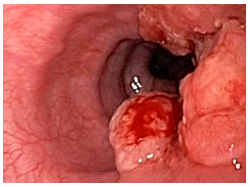
research



Chemotherapy for gastric and oesophageal cancer p 301

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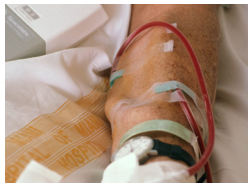
Antiseizure drugs and risk of neurodevelopmental disorders p 305



Inclusion of cystatin C in GFR estimating equations p 306

Intensification or optimisation: the unmet need of patients with gastro-oesophageal adenocarcinoma

ORIGINAL RESEARCH Randomised phase 3 trial

Camrelizumab+CAPOX with camrelizumab based maintenance *v* CAPOX as initial treatment for gastric or gastro-oesophageal junction adenocarcinoma

Peng Z, Zhang Y, Xu H, et al

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Find this at doi: 10.1136/bmj-2025-086115

Study question Does camrelizumab plus CAPOX (capecitabine plus oxaliplatin) with camrelizumab based maintenance improve overall survival compared with CAPOX alone in previously untreated patients with human epidermal growth factor receptor 2 (HER2) negative, unresectable, locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma?

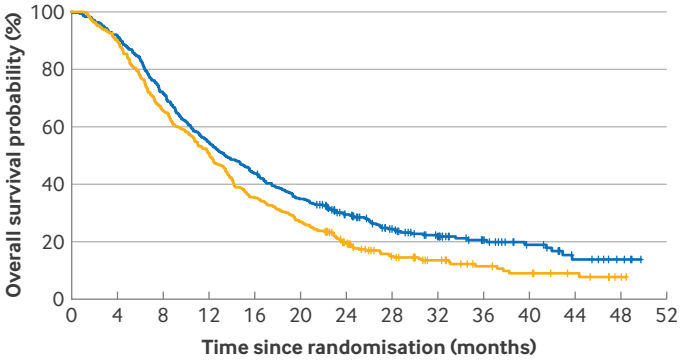
Methods In this randomised, open label, phase 3 trial conducted at 75 hospitals in China, adults were assigned (2:2:1) to camrelizumab plus CAPOX followed by maintenance camrelizumab plus apatinib, CAPOX alone, or camrelizumab plus CAPOX followed by maintenance camrelizumab alone. The primary endpoint was overall survival with camrelizumab plus CAPOX followed by camrelizumab plus apatinib versus CAPOX, assessed in participants with programmed death ligand 1 (PD-L1) combined positive score ›1 and in the overall population; comparisons involving the camrelizumab maintenance group were exploratory.

Study answer and limitations Among 878 treated participants, median overall survival was longer with camrelizumab plus CAPOX followed by camrelizumab plus apatinib than with CAPOX alone (PD-L1 combined positive score ›1: 15.0 *v* 12.5 months; overall population: 13.5 *v* 12.1 months). Overall survival was similar between maintenance camrelizumab plus apatinib and maintenance camrelizumab alone. A regimen containing apatinib was associated with higher rates of grade 3 or higher treatment related adverse events and treatment discontinuations. Limitations include the open label design, lack of blinded central review of tumour responses, and limited power and control of multiplicity for comparisons between the two camrelizumab based regimens.

What this study adds Camrelizumab plus CAPOX with camrelizumab based maintenance prolonged survival compared with CAPOX alone in patients with HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma. Intensification of maintenance with apatinib did not provide additional survival benefit, and increased toxicity.

Funding, competing interests, and data sharing Funded by Jiangsu Hengrui Pharmaceuticals. See full paper on bmj.com for competing interests. Anonymised participant data and the protocol, statistical analysis plan, and statistical code are available through the public repository Mendeley Data (https://data.mendeley.com/datasets/z22zyc2b2b/1).

Study registration ClinicalTrials.gov NCT03813784.



No at risk

Camre+CAPOX-camre+apa

352 323 253 192 154 122 89 62 46 30 19 9 4 0

CAPOX

349 314 229 177 124 94 60 36 24 15 11 7 2 0

	Camre+CAPOX-camre+apa	CAPOX
Events, No (%)	275 (78.1)	302 (86.5)
Median (95% CI), months	13.5 (11.9 to 15.6)	12.1 (10.7 to 13.5)
Hazard ratio (95% CI)	0.80 (0.68 to 0.94)	
One sided stratified log rank P value	P=0.004	

Kaplan-Meier estimates of overall survival in patients using camre+CAPOX followed by camre+apa versus CAPOX as preferred treatment for gastric or gastro-oesophageal junction adenocarcinoma. Log rank tests and Cox regression models were stratified by Eastern Cooperative Oncology Group performance status (0 *v* 1), presence versus absence of peritoneal metastasis, and PD-L1 expression status (positive *v* negative). P values are one sided and based on stratified log rank tests. CAPOX=capecitabine and oxaliplatin; camre+CAPOX-camre+apa=camrelizumab plus CAPOX followed by camrelizumab plus apatinib; CI=confidence interval

JOZEF POLC/ALAMY

Gastro-oesophageal adenocarcinoma (GOAC) is a global challenge, ranking among the leading causes of cancer mortality.[1] For decades, treatment options for patients with human epidermal growth factor receptor 2 (HER2) negative metastatic GOAC (mGOAC)—accounting for about 75% of cases—have relied exclusively on cytotoxic chemotherapy, leading to suboptimal survival outcomes. The introduction of immune checkpoint inhibitors in the treatment landscape of patients with mGOAC has led to considerable survival improvements across molecular subtypes.[2-6] The combination of oxaliplatin, a fluoropyrimidine and an immune checkpoint inhibitor (specifically an anti-programmed death protein 1 (PD-1) antibody), is currently a recommended upfront treatment option for patients with HER2 negative mGOAC, according to specific scoring systems and cut-off thresholds for programmed death ligand 1 (PD-L1).[2-6] To optimise quality of life and avoid dose-cumulative neurological and haematological toxicity, oxaliplatin is usually discontinued after an induction period of four to six months, whereas PD-1 inhibition is sustained for up to two years along with (optional) maintenance fluoropyrimidine.[3-5] Treatment benefit is mostly observed during the induction phase, while maintenance aims to preserve a balance between quality of life and consolidating treatment efficacy; nonetheless, resistance and consequent disease progression almost inevitably occur. In this context, even in most recent clinical trials, a relevant proportion (≤50%) of patients may be ineligible for subsequent treatments, mostly due to rapidly deteriorating clinical conditions.[2]

In their study, Peng and colleagues report the results of a randomised phase 3 trial in a Chinese population evaluating initial treatment with camrelizumab plus CAPOX (capecitabine plus oxaliplatin) followed by camrelizumab based maintenance with or without the vascular endothelial growth factor (VEGF) receptor-2 (VEGFR-2) inhibitor apatinib, compared with CAPOX alone in previously untreated HER2 negative mGOAC.[7] Survival mirrored

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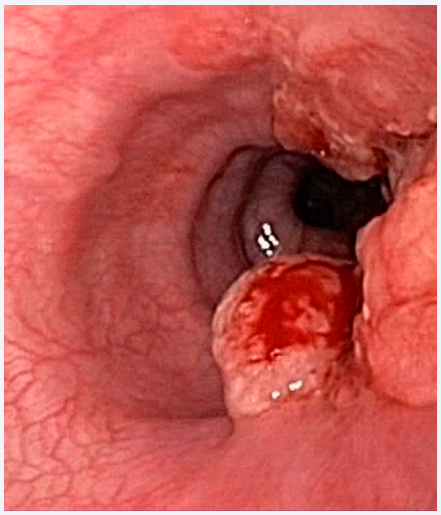

GASTROLAB/SPL

Upfront immune checkpoint blockade represents a substantial driver of survival in patients with mGOAC

previously reported data with different PD-1 antibodies with chemotherapy in the same setting, thus further confirming that the incorporation of PD-1 blockade to initial treatment improves survival outcomes.[2-5] Despite some uncertainty about how generalisable these findings are outside of China, the results reinforce a now consistent observation that upfront immune checkpoint blockade represents a substantial driver of survival in patients with mGOAC.

Although the implementation of VEGFR blockade to initial treatment did not result in overall survival gain in patients enrolled in two phase 3 trials, antiangiogenic agents, either as monotherapy or in combination with chemotherapy, are valuable treatment options in the second line and later line settings.[6-10]

VEGF expression drives an immunosuppressive microenvironment and its inhibition may restore intratumoral T cell infiltration, leading to enhanced sensitivity to immune checkpoint inhibitors. The addition of regorafenib to upfront treatment with FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and nivolumab was associated with promising activity and efficacy in a monocentric, single arm, phase 2 trial of patients with mGOAC, regardless of PD-L1 expression.[13] Based on such rationale, Peng and colleagues hypothesised that the addition of apatinib to camrelizumab based maintenance could enhance treatment efficacy by potentially overcoming VEGF mediated treatment resistance. Although the study was not powered for any direct comparison between the two immune checkpoint inhibitor based arms, apatinib intensified maintenance did not appear to drive any clinically significant survival benefit compared with camrelizumab alone at the price of increased overall and severe toxicity, leading to discontinuation of at least one study drug in 23% of patients—a factor that may have diluted survival gains.[7]

Strategic switching

In the ARMANI phase 3 trial, an early switch to paclitaxel and ramucirumab after a three month course of doublet oxaliplatin and fluoropyrimidine was associated with better overall survival when compared to the continuation of the same induction regimen in a similar population of patients with HER2 negative mGOAC.[14] A post hoc analysis of patients achieving stable disease as best objective response showed a hazard ratio for overall survival of 0.46 for the experimental arm, thus suggesting a clinically and biologically compelling hypothesis that there may be an even stronger rationale for maintenance switch to alternative, non-cross-resistant regimens in patients failing to prove in vivo sensitivity to oxaliplatin and fluoropyrimidines. Thus, patients with suboptimal early responses may require strategic switching before clinical deterioration precludes any further treatment. Future progress is therefore unlikely to occur from indiscriminately adding new drugs, but instead from identifying which patients require more treatment and when, and which patients require less.

The fundamental clinical question on how to balance treatment goals against sustainability is universally relevant. As treatment paradigms evolve and patients achieve unprecedented survival outcomes, tolerability and long term preservation of quality of life become even more central to any successful treatment.

Looking ahead, adaptive strategies are warranted. In conclusion, Peng and colleagues' study helps remind clinicians that modern oncology should aim to deliver the best treatment at the right time, favouring optimisation over mere intensification.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.s423

Pyrotinib or placebo in combination with trastuzumab and docetaxel for HER2 positive metastatic breast cancer

Ma F, Yan M, Li W, et al

Cite this as: *BMJ* 2026;392:e087259
Find this at doi: 10.1136/bmj-2025-087259

Study question Does the addition of pyrotinib to trastuzumab and docetaxel improve outcomes for untreated patients with human epidermal growth factor receptor 2 (HER2) positive metastatic breast cancer?

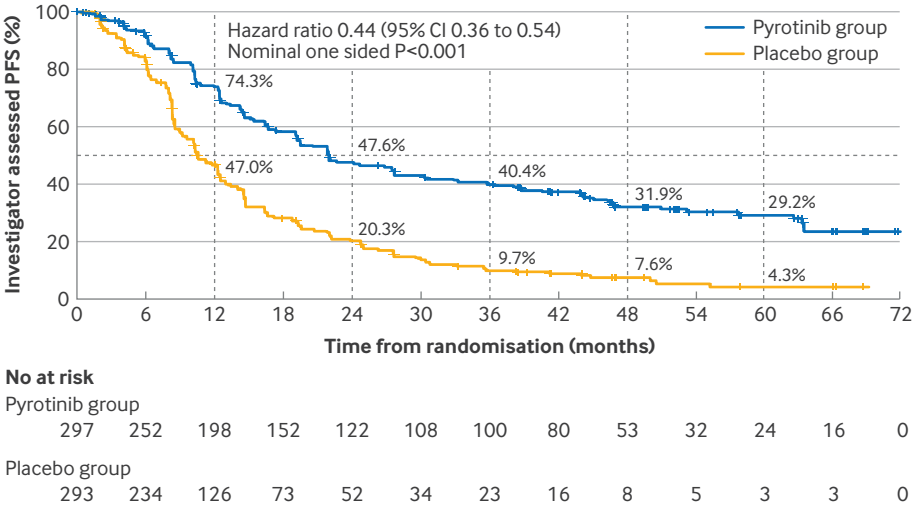
Methods This multicentre, double blind, phase 3 trial was performed in 40 centres in China from 6 May 2019 to 17 January 2022. 590 patients were randomised in a 1:1 ratio to receive initial treatment with either the HER inhibitor pyrotinib (400 mg orally once daily) or placebo, both in combination with intravenous trastuzumab (8 mg/kg for the first cycle, then 6 mg/kg in subsequent cycles) and docetaxel (75 mg/m^2) on day 1 of each 21 day treatment cycle. The primary endpoint was investigator assessed progression-free survival.

Study answer and limitations 590 patients were randomised and received treatment (297 in the pyrotinib group and 293 in the placebo group). As of 30 April 2024, during a median follow-up of 35.7 months in the pyrotinib group and 34.3 months in the placebo group, 59 (20%) and 87 (30%) patients died, respectively. Overall survival was longer in the pyrotinib group (hazard ratio 0.64 (95% confidence interval (CI) 0.46 to 0.89); P=0.004). Improvement in progression-free survival in the pyrotinib group was maintained (22.1 months (95% CI 19.3 to 27.8) *v* 10.5 months (9.5 to 12.4), hazard ratio 0.44 (0.36 to 0.53)). Over a median follow-up of 45.5 months, the pyrotinib based regimen showed consistent and prolonged survival benefit. The safety profile remained consistent with the interim analysis, and no new safety signals emerged during the extended follow-up period. The main limitations were the absence of an active comparator as the control and lack of long term definitive overall survival data.

What this study adds This analysis confirmed improved progression-free and overall survival benefit of dual blockade of HER2 with pyrotinib plus trastuzumab in combination with docetaxel in patients with untreated HER2 positive metastatic breast cancer, establishing this combination as an effective initial treatment option.

Funding, competing interests, and data sharing
Funded by Jiangsu Hengrui Pharmaceuticals, with additional grants from the National Natural Science Foundation of China, CAMS Innovation Fund for Medical Sciences, and National High Level Hospital Clinical Research Funding. See full paper on bmj.com for competing interests. Anonymised trial data are available in Mendeley Data, a public repository.

Study registration ClinicalTrials.gov NCT03863223.



Kaplan-Meier curve of PFS in patients with HER2 positive metastatic breast cancer assigned to pyrotinib or placebo combined with trastuzumab and docetaxel in the full analysis set to 30 May 2025. CI=confidence interval; PFS=progression-free survival

Prenatal antiseizure drug exposure and risk of neurodevelopmental disorders in children

Straub L, Hernandez-Diaz S, Bateman BT, et al

Cite this as: *BMJ* 2026;392:e085725
Find this at doi: 10.1136/bmj-2025-085725

Study question Does prenatal exposure to specific antiseizure drugs among pregnant patients with epilepsy increase the risk of neurodevelopmental disorders in offspring?

Methods This population based cohort study used healthcare data from publicly and commercially insured beneficiaries in the United States (2000-21). Pregnant patients with epilepsy were linked to their offspring, and exposure was classified by dispensing of carbamazepine, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate, or zonisamide during the second half of pregnancy (synaptogenesis period). The comparison group comprised pregnant patients with epilepsy without antiseizure drug dispensation from three months before pregnancy to delivery. Offspring outcomes were any neurodevelopmental disorder and specific disorders including attention deficit/hyperactivity disorder, autism spectrum disorder, behavioural disorder, developmental coordination disorder, intellectual disability, learning difficulty, and speech or language disorder, identified using validated algorithms.

Study answer and limitations The study cohort included 8887 prenatally unexposed children. Exposed pregnancies ranged from 219 for lacosamide to 5261 for levetiracetam. Valproate and zonisamide showed associations with several outcomes (adjusted hazard ratio range 1.26-4.50), whereas levetiracetam and phenytoin were not associated with an increased risk of any outcome. Several drugs were associated with a twofold to fourfold increased risk of intellectual disability, but estimates were imprecise because of the small number of children with this disorder. Although no meaningful associations were found for topiramate and lamotrigine across most outcomes, there was a potential signal for intellectual disability (both drugs) and learning difficulty (topiramate only; hazard ratio 1.23 based on small numbers). Carbamazepine and oxcarbazepine showed a modest risk increase for attention deficit/hyperactivity disorder and behavioural disorders (hazard ratio range 1.23-1.40). Limitations include reliance on claims requiring continuous child enrolment, potential exposure misclassification from dispensing based measures, sparse data for some drugs and outcomes leading to imprecise estimates, and residual confounding by epilepsy type or severity.

What this study adds The findings strengthen the evidence for increased risk of neurodevelopmental disorders after prenatal valproate exposure and suggest the need for further evaluation of zonisamide. Signals for other antiseizure drugs require confirmation as data accumulate.

Funding, competing interests, and data sharing
Funded by the National Institute of Mental Health. See bmj.com for competing interests. No additional data available.

Outcome	No of outcomes	Hazard ratio (95% CI)	Hazard ratio (95% CI)	No of outcomes	Hazard ratio (95% CI)	Hazard ratio (95% CI)
	Levetiracetam (n=5261)			**Topiramate (n=1036)**		
Any NDD	413		0.93 (0.82 to 1.06)	145		1.13 (0.93 to 1.36)
Speech or language disorder	261		0.97 (0.82 to 1.15)	75		1.10 (0.85 to 1.43)
ADHD	106		0.81 (0.64 to 1.02)	63		1.13 (0.85 to 1.50)
Behavioural disorder	89		1.04 (0.80 to 1.36)	35		1.03 (0.70 to 1.49)
Coordination disorder	59		0.96 (0.67 to 1.38)	<11		0.63 (0.30 to 1.34)
Autism spectrum disorder	40		0.67 (0.45 to 1.00)	18		1.02 (0.60 to 1.74)
Learning difficulty	15		1.01 (0.52 to 1.94)	<11		1.23 (0.54 to 2.79)
Intellectual disability	<11		1.14 (0.49 to 2.64)	<11		1.84 (0.75 to 4.51)
	Lamotrigine (n=4299)			**Valproate (n=800)**		
Any NDD	404		1.05 (0.92 to 1.19)	144		1.29 (1.06 to 1.56)
Speech or language disorder	246		1.11 (0.93 to 1.32)	79		1.52 (1.17 to 1.98)
ADHD	136		1.04 (0.84 to 1.29)	78		1.26 (0.97 to 1.64)
Behavioural disorder	84		1.03 (0.79 to 1.35)	49		1.31 (0.94 to 1.82)
Coordination disorder	56		1.06 (0.72 to 1.55)	14		1.67 (0.89 to 3.13)
Autism spectrum disorder	55		1.10 (0.77 to 1.58)	34		2.60 (1.67 to 4.04)
Learning difficulty	18		1.10 (0.59 to 2.05)	15		1.49 (0.77 to 2.88)
Intellectual disability	16		2.38 (1.20 to 4.73)	11		1.72 (0.77 to 3.83)

MAKSYM YEMELYANOV/ALAMY

Hazard ratios (95% confidence intervals) of any neurodevelopmental disorder and individual neurodevelopmental disorders in children prenatally exposed to specific antiseizure drug of interest (results shown for levetiracetam, lamotrigine, topiramate, and valproate only). Results from main adjusted analyses are presented for publicly and commercially insured children combined. Individual drugs are sorted by number of exposed pregnancies in both cohorts combined (from highest to lowest); individual neurodevelopmental disorders are sorted based on absolute risk observed in overall population at 8 years (from largest to smallest). Event numbers <11 suppressed according to Centers for Medicaid & Medicare Services policy. ADHD=attention deficit/hyperactivity disorder; CI=confidence interval; NDD=neurodevelopmental disorder

ORIGINAL RESEARCH Prospective, longitudinal cohort study

Accuracy of glomerular filtration rate estimation based on creatinine and cystatin C for monitoring moderate chronic kidney disease in adults

Scandrett K, Sitch AJ, Barratt J, et al

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Find this at doi: 10.1136/bmj-2025-085005

Study question Does inclusion of cystatin C in glomerular filtration rate (GFR) estimating equations improve longitudinal accuracy of GFR monitoring in moderate chronic kidney disease?

Methods In a prospective, longitudinal (three year) cohort study, 875 adults (median age 67 years, 57.7% men, 88.3% white participants, and 25.1% with diabetes) with moderate chronic kidney disease were recruited from primary, secondary, and tertiary care across six centres in England. Iohexol clearance was the reference GFR measure. Measured GFR was compared with estimated GFR based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and European Kidney Function Consortium (EKFC) estimating equations.

Study answer and limitations Median measured GFR decreased from 48.1 mL/min/1.73 m^2 at baseline to 43.6 mL/min/1.73 m^2 at three years. Median change in measured GFR exceeded median change in estimated GFR for all equations. All equations achieved agreement (n=875) exceeding 72.5% with measured GFR (defined as slope change within ±3 mL/min/1.73 m^2/year of reference measured GFR slope change). Dual biomarker equations ($CKD\text{-}EPI_{creatinine\text{-}cystatin}$, $CKD\text{-}EPI(2021)_{creatinine\text{-}cystatin}$, and $EKFC_{creatinine\text{-}cystatin}$) showed better agreement with change in measured GFR than $CKD\text{-}EPI_{creatinine}$ (all P<0.001). Progression of chronic kidney disease (decline in measured GFR of ›25% with decline in disease category) was observed in 139 (15.9%) participants. All GFR equations had poor sensitivity (‹54.1%) but good specificity (›90.4%) for identifying progression of chronic kidney disease. Measures of agreement and sensitivity estimates may have been influenced by stable kidney function in most participants.

What this study adds Equations that included both cystatin C and creatinine showed better agreement with changes in measured GFR than equations based on one biomarker. All GFR estimating equations underestimated the temporal reduction in GFR.

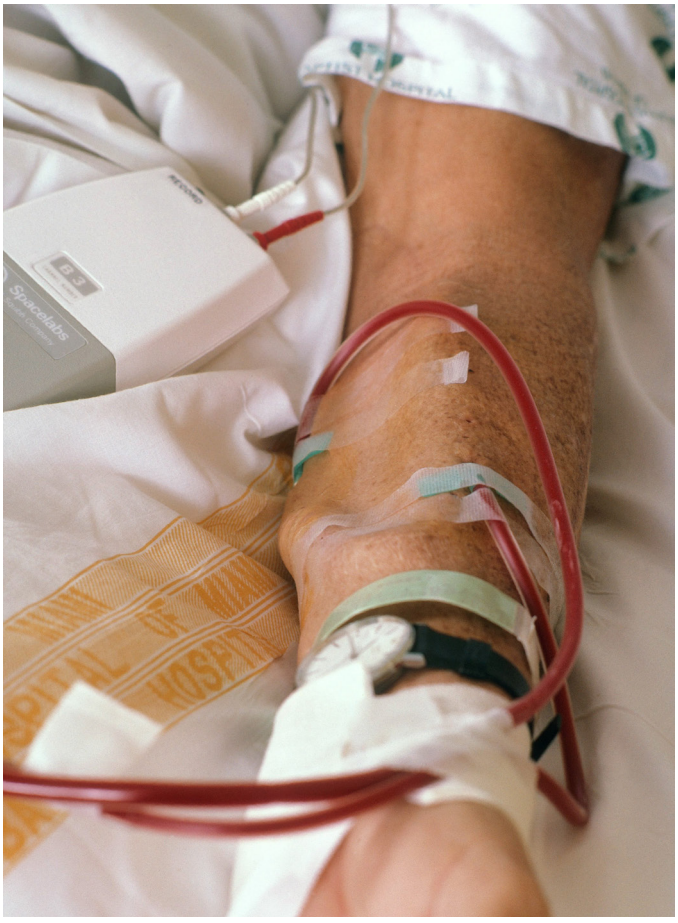
Funding, competing interests, and data sharing Funded by the National Institute for Health and Care Research. See full paper on bmj.com for competing interests. An anonymised dataset and statistical code is available on the University of Birmingham eData Repository (see full paper on bmj.com for details).

Study registration ISRCTN Registry ISRCTN42955626.

Proportion of participants with estimated GFR change per year (slope) within +3 mL/min/1.73 m^2 of measured GFR slope (n=875)

GFR equation*	Proportion of participants showing agreement (% (95% CI))	P value†
$CKD\text{-}EPI_{creatinine}$	73.1 (70.1 to 76.1)	—
$CKD\text{-}EPI_{cystatin}$	75.7 (72.7 to 78.5)	0.16
$CKD\text{-}EPI_{creatinine\text{-}cystatin}$	78.6 (75.8 to 81.3)	‹0.001
$CKD\text{-}EPI(2021)_{creatinine}$	72.6 (69.5 to 75.5)	0.33
$CKD\text{-}EPI(2021)_{creatinine\text{-}cystatin}$	78.1 (75.2 to 80.8)	‹0.001
$EKFC_{creatinine}$	76.5 (73.5 to 79.2)	‹0.001
$EKFC_{cystatin}$	77.1 (74.2 to 79.9)	0.02
$EKFC_{creatinine\text{-}cystatin}$	80.2 (77.4 to 82.8)	‹0.001

CI=confidence interval; GFR=glomerular filtration rate.
*Estimating equations: CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; EKFC=European Kidney Function Consortium.
†P values indicate significance compared with performance of CKD-EPI creatinine (McNemar's test).



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