Journal of Translational Medicine

RESEARCH

Open Access

# Association of genetically proxied cancer-targeted drugs with cardiovascular diseases through Mendelian randomization analysis

Chuchun Fang[1,4,5†], Xuewei Liu[2,3,4†], Chen Yu[6], Songlin Li[1,4,5], Xueying Liu[1,4,5], Shifeng Qiu[1,4,5], Hongbin Liang[1,4,5], Caiwen Ou[2,3,4*] and Jiancheng Xiu[1,4,5*]

## Abstract

**Background** Cancer-targeted therapies are progressively pivotal in oncological care. Observational studies underscore the emergence of cancer therapy-related cardiovascular toxicity (CTR-CVT), impacting patient outcomes. We aimed to investigate the causal relationship between different types of cancer-targeted therapies and cardiovascular disease (CVD) outcomes through a two-sample Mendelian randomization (MR) study.

**Methods** This genome-wide association study was conducted using a two-sample Mendelian randomization framework. Genetic instruments for drug target gene expression were extracted from the eQTLGen consortium (31684 individuals, 37 cohorts). Genome-wide association study (GWAS) summary statistics for 19 cardiovascular diseases were derived from the FinnGen database. Primary analysis was carried out using the summary-data-based MR (SMR) method, with sensitivity analysis for validation. Colocalization analysis identifies shared causal variants between exposure eQTLs and CVD-associated single-nucleotide polymorphisms (SNPs).

**Results** Among the 39 drug target genes, 8 were identified with detectable cis-eQTLs and were subsequently validated through positive control analysis for further investigation. In the SMR and sensitivity analyses, genetically proxied VEGFA inhibition showed significantly strong association with stroke (odds ratio [OR] = 1.17, 95% confidence interval [CI] = 1.09–1.26, $p = 1.33 \times 10^{-5}$). Additionally, the inhibition of FGFR1, FLT1, and MAP2K2 exhibited suggestive association with corresponding cardiovascular disease outcomes. Nevertheless, only VEGFA expression and stroke shared a causal variant (93.6%), whereas FGFR1, MAP2K2, and FLT1 did not share causal variants with corresponding cardiovascular diseases in the colocalization analysis.

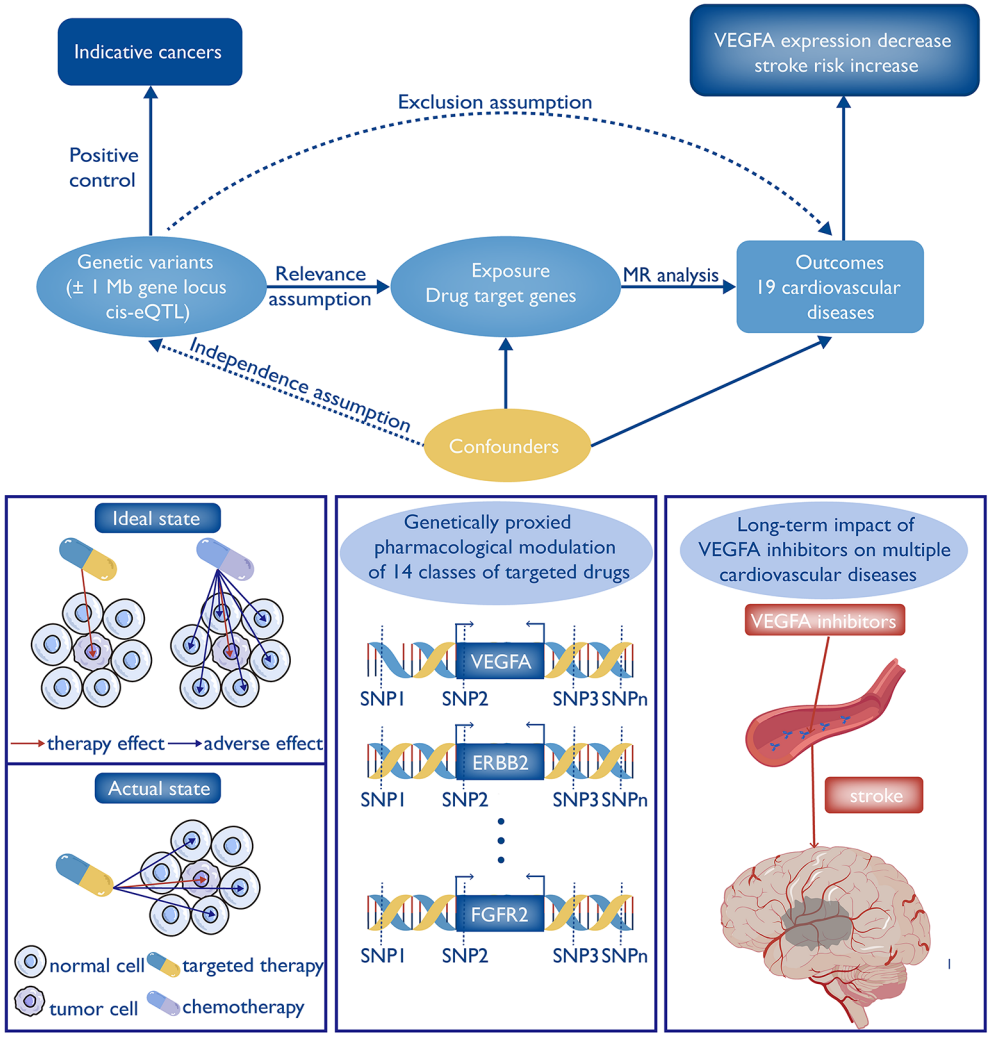
**Conclusions** This genetic association study revealed evidence supporting the genetic association between the use of VEGFA inhibitors and increased stroke risk, highlighting the need for enhanced pharmacovigilance. These findings underscore the delicate balance between cardiovascular toxicity risk and the benefits of cancer-targeted therapy.

†Chuchun Fang and Xuewei Liu contributed equally to this work.

*Correspondence:
Caiwen Ou
oucaiwen@smu.edu.cn
Jiancheng Xiu
xiujch@163.com

Full list of author information is available at the end of the article

## Graphical Abstract




**Central illustration** Compared with traditional chemotherapy, targeted therapy is expected to selectively impact tumour cells. However, in reality, targeted therapy can impair normal cells, and this effect extends to other organs through the circulation. SNPs within ±1 Mb of the gene locus were defined as cis-eQTLs to pharmacologically proxy the modulation effect of targeted drug exposure. Drug–target Mendelian randomization (MR) was conducted on multiple cardiovascular diseases, revealing a significant causal association between VEGFA inhibition and stroke risk. Three assumptions should be satisfied: relevance, exclusion, and independence. eQTL: expression quantitative trait loci; MR: Mendelian randomization; SNP = single–nucleotide polymorphism; VEGFA: vascular endothelial growth factor A.

**Keywords** Cancer-targeted therapy, Cardiovascular diseases, Mendelian randomization, eQTL

## Background

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality in oncology patients worldwide [1, 2]. This stems from anticancer therapy side effects or increased susceptibility to cardiovascular risk factors, including dyslipidaemia, diabetes, cachexia, genetic variants, and immune system disorders [3–6]. The burgeoning field of cardio-oncology, evolving with novel cancer therapies, emphasizes the need for interdisciplinary collaboration in managing cancer patients due to treatment-related

adverse events known as cancer therapy-related cardiovascular toxicities (CTR-CVTs) [7]. Traditional cancer treatments encompass surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy [8]. This study specifically investigated the adverse effects of targeted therapy on the cardiovascular system.

Studies have investigated the cardiovascular toxicity mechanisms induced by targeted drugs, including direct toxicity to the heart and vasculature, as well as disturbances in cardiovascular, immune, and metabolic homeostasis [3]. For example, observational studies have shown that immune checkpoint inhibitors (ICIs), raise risks of myocardial infarction, coronary revascularization, ischaemic stroke, mediated by accelerated progression of atherosclerosis, and myocarditis [9, 10]. A human epidermal growth factor receptor 2 (HER2) inhibitor enhances overall survival in patients with HER2-positive cancer, but it is implicated in asymptomatic left ventricular ejection fraction reduction, heart failure, arrhythmia, and long-term cardiopulmonary function impairment [11, 12]. Recognizing diverse manifestations and mechanisms across drug classes is crucial in the management of cardio-oncology patients.

In traditional observational studies, associations are demonstrated rather than causalities, and challenges such as reverse causations and complicated confounding biases may arise. While randomized controlled trials (RCTs) are considered the gold standard for investigating causal associations between traits, their implementation is often challenging due to their time-consuming and laborious nature. Therefore, Mendelian randomization (MR) has emerged as an optimal approach to genetically validate whether the observed relationship between exposure and outcome is causal. Drug-target MR analysis employs SNPs as IVs to proxy the pharmacological inhibitory effect of a drug on its target protein. Genetic variants, validated to associate with the expression of drug target genes, are termed expression quantitative trait loci (eQTLs). By satisfying three major assumptions—relevance, exclusion, and independence—MR analysis can overcome confounding bias and reverse causation. This is due to the random assignment at meiosis and the prior assignment to disease of genetic variants, facilitating the exploration of long-term risk modulation by targeted drugs [13, 14]. Additionally, the summary-data-based Mendelian Randomization (SMR) method is a robust and efficient MR approach that excels in data accessibility, statistical power, efficiency, and scalability. It integrates summary-level data from genome-wide association studies (GWAS) with expression quantitative trait locus (eQTL) data to evaluate causal relationships between gene expression and complex traits [15, 16].

In this study, the potential causal associations between cancer-targeted drugs and a broad spectrum of cardiovascular diseases were investigated using a two-sample MR framework. The cis-eQTLs were used as genetic variants for target genes of cancer-targeted therapies.

## Methods

### Study design

Two-sample MR analysis was conducted to investigate the causal relationship between cancer-targeted therapies and 19 CVDs. Initially, drug target genes for each cancer-targeted therapy were identified from the DrugBank [17] (https://go.drugbank.com/) and ChEMBL [18, 19] (https://www.ebi.ac.uk/chembl/) databases. Subseq uently, the top cis-eQTL were extracted as IVs to proxy the pharmacological modulation of each drug target proteins. Gathering GWASs for CVDs outcomes from the FinnGen dataset (https://r9.finngen.fi/), we utilized the SMR method to estimate the effect sizes of genetically proxied drug expression and CVDs outcomes. The study adhered to three key assumptions: relevance, exclusion, and independence. A detailed flowchart is presented in Fig. 1, and a central illustration is provided. No ethical approval was required for our study, since all analyses relied on publicly available summary-level data.

### Genetic instruments for cancer-targeted therapies

Major cancer-targeted therapies are categorized into specific classes (Table 1), including human epidermal receptor 2 (HER2)-targeted therapies, vascular endothelial growth factor (VEGF) inhibitors, multitargeted kinase inhibitors targeting breakpoint cluster region–Abelson oncogene locus (BCR-ABL), Bruton tyrosine kinase (BTK) inhibitors, proteasome inhibitors and monoclonal antibodies for multiple myeloma, rapidly accelerated fibrosarcoma (RAF) and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors, immune checkpoint inhibitors (ICIs), cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, anaplastic lymphoma kinase (ALK) inhibitors, and epidermal growth factor receptor (EGFR) inhibitors. This classification follows the guidelines on cardio-oncology published by the European Society of Cardiology (ESC) in 2022 [7]. Additionally, several targeted drugs with pancancer treatment potential were considered, including fibroblast growth factor receptor (FGFR) inhibitors [20], tumour-associated calcium signal transducer 2 (TACSTD2) inhibitors [21], neurotrophic tyrosine receptor kinase (NTRK) inhibitors [22] and poly ADP−ribose polymerase (PARP) inhibitors [23]. Having determined the specific categorization of cancer-targeted therapies, we performed detailed research on the DrugBank and ChEMBL databases to identify drug target genes for corresponding cancer-targeted therapies.

The expression quantitative trait loci (eQTLs) for drug target genes used as the proxies of exposure to each

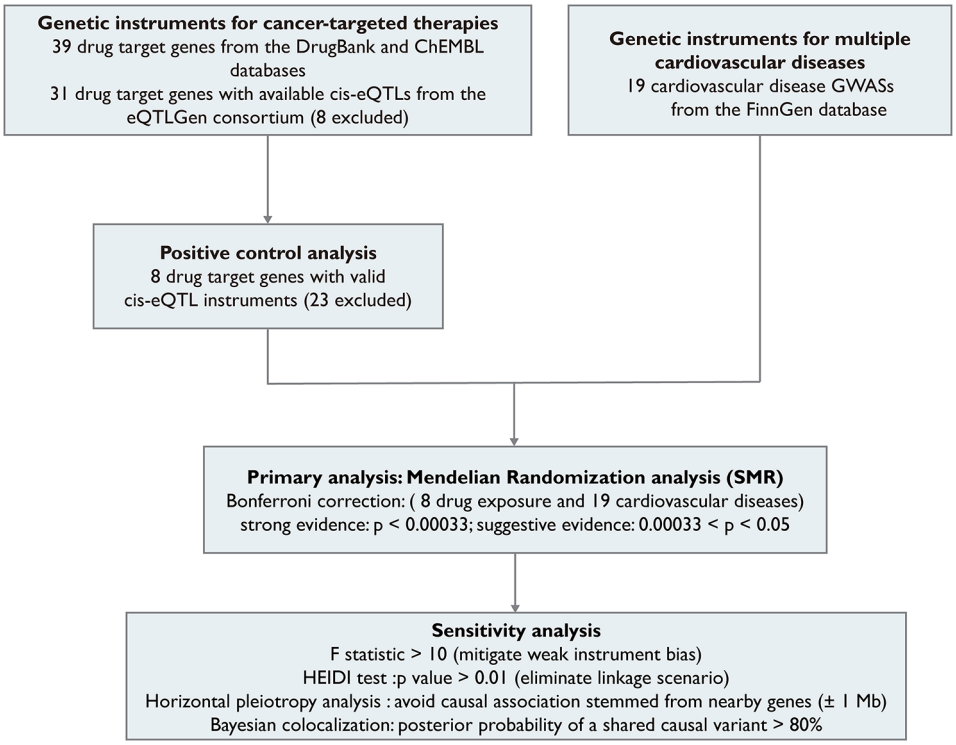



**Fig. 1** Study overview. Drug target genes were identified from both the DrugBank and ChEMBL databases, and cis-eQTLs were extracted from the eQTLGen consortium to serve as genetic instruments. Positive control analyses were conducted to validate the genetic instruments. Summary GWASs for cardiovascular diseases were obtained from the FinnGen dataset. For each exposure, we performed MR analyses utilizing the SMR method and multiple sensitivity analyses. eQTL = expression quantitative trait loci; SMR = summary-data-based Mendelian randomization; GAWS = genome-wide association study

cancer-targeted therapy were obtained from the publicly available eQTLGen consortium ($n$=31,684) [24]. Our study focused exclusively on cis-eQTLs located within 1 Mb windows flanking each encoded gene. We identified common SNPs (minor allele frequency>1%) that were significantly associated with the expression of drug target genes at a genome-wide level ($p<5\times10^{-8}$). Using the SMR approach, we adhered to the strong relevance assumption of Mendelian Randomization by selecting the top significantly associated cis-eQTL near the target gene as a single genetic instrument.

### Outcome data sources

The publicly available GWAS summary-level data for 19 CVDs outcomes were retrieved from the FinnGen consortium [25] The specified CVD outcomes, along with their respective case and control numbers, are as follows: heart failure (27,304 cases, 349,973 controls), myocardial infarction (24,185 cases, 313,400 controls), stroke (39,818 cases, 271,817 controls), coronary heart disease (43,518 cases, 333,759 controls), ischaemic heart disease (63,744 cases, 313,533 controls), valvular heart disease (20,929 cases, 286,109 controls), cardiomyopathy (5,874 cases, 286,109 controls), myocarditis (1,521 cases, 191,924 controls), pericarditis (979 cases, 286,109 controls), hypertension (111,581 cases, 265,626 controls), pulmonary hypertension (234 cases, 265,626 controls), venous thromboembolism (19,372 cases, 357,905 controls), pulmonary embolism (9,243 cases, 367,108 controls), peripheral vascular disease (2,230 cases, 349,539 controls), conduction disorders (9,949 cases, 286,109 controls), atrial fibrillation and flutter (45,766 cases, 191,924 controls), pleural effusion (4,513 cases, 361,836 controls), dyslipidaemia (37,742 cases, 324,150 controls), and cardiovascular death (19,295 cases, 357,982 controls) (Additional file 2: Table S2) [7, 26–28].The study population was restricted to individuals of European ancestry. Additionally, all GWASs conducted as part of the FinnGen research project underwent analysis using REGENIE and were adjusted for covariates including sex, age, genotype batch, and first ten principal components.

### Positive control analysis

A positive control analysis was conducted to validate the robustness of the genetic instrument for drugs by examining the anticipated relationship between the expression of drug target genes and the corresponding cancers under drug exposures. Thus, we selected the expression of drug target genes as exposures and the corresponding indicative cancers as outcomes, utilizing summary-data-MR

**Table 1** Target genes for cancer-targeted drugs from the DrugBank and ChEMBL

| Drug class | Encoding genes of target proteins | | Gene location (hg19) |
|---|---|---|---|
| | DrugBank | ChEMBL | |
| Human epidermal receptor 2 (HER2)-targeted therapies | ERBB2 | ERBB2 | chr17:37865423 |
| Vascular endothelial growth factor (VEGF) inhibitors | VEGFA | VEGFA | chr6:43746072 |
| | FLT1 | FLT1 | chr13:28971877 |
| | KDR | KDR | chr4: 55,968,200 |
| | FLT4 | FLT4 | chr5:180052565 |
| Multitargeted kinase inhibitors targeting breakpoint cluster region-Abelson oncogene locus (BCR-ABL) | BCR | BCR | chr22:23591057 |
| | ABL1 | ABL1 | chr9:133676197 |
| Bruton tyrosine kinase (BTK) inhibitors | BTK | BTK | chrX:100,622,809 |
| Immune checkpoint inhibitors (ICIs) | CTLA4 | CTLA4 | chr2:204735596 |
| | PDCD1 | PDCD1 | chr2:242796546 |
| | CD274 | CD274 | chr9: 5,460,534 |
| Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors | CDK4 | CDK4 | chr12:58145653 |
| | CDK6 | CDK6 | chr7:92350071 |
| Multiple myeloma therapies | PSMB1 | PSMB1 | chr6:170853317 |
| | PSMB2 | PSMB2 | chr1:36087315 |
| | PSMB5 | PSMB5 | chr14:23495095 |
| | PSMB8 | PSMB8 | chr6:32810487 |
| | PSMB9 | PSMB9 | chr6:32819637 |
| | PSMB10 | PSMB10 | chr16:67969697 |
| | SLAMF7 | SLAMF7 | chr1:160716824 |
| | XPO1 | XOPO1 | chr2:61735372 |
| | CD38 | CD38 | chr4:15815483 |
| Epidermal growth factor receptor (EGFR) inhibitors | EGFR | EGFR | chr7:79994513 |
| Anaplastic lymphoma kinase (ALK) inhibitors | ALK | ALK | chr2:29780036 |
| Rapidly accelerated fibrosarcoma and mitogen-activated extracellular signal-regulated kinase inhibitors | BRAF | BRAF | chr7:140524753 |
| | RAF1 | RAF1 | chr3:12665412 |
| | MAP2K1 | MAP2K1 | chr15:66731902 |
| | MAP2K2 | MAP2K2 | chr19:4107222 |
| Fibroblast growth factor receptor (FGFR) inhibitors | FGFR1 | FGFR1 | chr8:38297504 |
| | FGFR2 | FGFR2 | chr10:123297910 |
| | FGFR3 | FGFR3 | chr4:1802816 |
| | FGFR4 | FGFR4 | chr5:176519516 |
| Tumour-associated calcium signal transducer 2 (TACSTD2) inhibitors | TACSTD2 | TACSTD2 | chr1:59042132 |
| Neurotrophic tyrosine receptor kinase (NTRK) inhibitors | NTRK1 | NTRK1 | chr1:156818537 |
| | NTRK2 | NTRK2 | chr9:87460985 |
| | NTRK3 | NTRK3 | chr15:88609114 |
| Poly ADP ribose polymerase (PARP) inhibitors | PARP1 | PARP1 | chr1:226572086 |
| | PARP2 | PARP2 | chr14:20818902 |
| | PARP3 | PARP3 | chr3:51979622 |

We obtained totally 39 drug target genes for each cancer-targeted therapy obtained from the DrugBank and ChEMBL databases. Gene location was identified as the middle position for each gene, obtained from https://grch37.ensembl.org/. BRAF = v-Raf murine sarcoma viral oncogene homologue B1; CD38 = cluster of differentiation 38; CD274 = cluster of differentiation 274; CI = confidence interval; CTLA4 = cytotoxic T-lymphocyte-associated antigen 4; ERBB2 = receptor tyrosine-protein kinase erbB-2; FLT1 = FMS-like tyrosine kinase 1; FLT4 = FMS-like tyrosine kinase 4; KDR = Kinase insert domain receptor; MAP2K1 = mitogen-activated protein kinase kinase 1; MAP2K2 = mitogen-activated protein kinase kinase 2; PDCD1 = programmed cell death protein 1; PSMB = proteasome 20 S subunit beta; RAF = rapidly accelerated fibrosarcoma; SLAMF7 = signalling lymphocytic activation molecule family 7; VEGFA: vascular endothelial growth factor A; XPO1 = exportin 1

(SMR) software, version 1.3.1 [15], for a 2-sample MR analysis. Detailed information regarding the GWASs for these positive control outcomes is presented in the supplemental materials (Additional file 2: Table S2). Genes that did not exhibit the expected significant association with cancers were excluded from further primary MR analysis.

## Statistical analysis

### *Primary MR analysis of drug target genes expression in CVDs outcomes*

The SMR method was applied to investigate the associations between a 1 SD decrease in drug target gene expression levels and CVDs outcomes mentioned above. The effect sizes of genetic associations between drug target

genes expression and CVDs outcomes were converted to odds ratios (ORs), which were standardized to demonstrate inhibitory effects on corresponding indicative cancers. Consequently, the primary results in terms of ORs illustrated the potential direction of cancer-targeted therapy exposures concerning the risk of CVDs.

Considering multiple hypothesis testing, we implemented Bonferroni correction, setting the critical significance level at 0.00033 (8 drug target genes and 19 CVDs outcomes) [29]. A significance level of $p<0.00033$ indicated strong evidence, whereas $0.00033<p<0.05$ indicated suggestive evidence.

#### Sensitivity analysis

The strength of the genetic instrument for drug exposure was measured by the F-statistic, excluding eQTLs with an F statistic less than 10 to mitigate weak instrument bias [30]. The heterogeneity in dependent instruments (HEIDI) test was then employed to identify whether the associations between drug target genes expression and CVDs outcome stemmed from linkage scenario [15]. A p-value above 0.01 was used as the threshold, indicating that we could not reject the null hypothesis of a single causal variant underlying the relationship between gene expression and trait variation. This supports the absence of significant linkage disequilibrium in the association between drug exposure and CVD outcomes.

Given the potential for one genetic instrument to be linked with the expression of multiple genes, violating the exclusion assumption of MR analysis, we assessed horizontal pleiotropy by extracting nearby genes within 1 Mb on each side [31]. For those nearby genes strongly associated with the top eQTL ($p<0.05$), SMR analysis was performed to determine whether the genetic instrument influenced the CVDs outcome via the expression of nearby genes rather than target genes.

For significant causal associations, Bayesian colocalization [32, 33] was applied to further evaluate the probability that drug genes expression and CVDs outcome share a common causal variant via the R package 'coloc' (http://cran.r-project.org/web/packages/coloc), including SNPs within ±1 Mb of the drug target gene. As described by Giambartolomei et al. [32], Bayesian colocalization analysis comprises five mutually exclusive hypotheses: (1) H0: There is no causal variant associated with either trait; (2) H1: There is a causal variant only associated with trait 1; (3) H2: There is a causal variant only associated with trait 2; (4) H3: Trait 1 and trait 2 are associated with the region via two independent variants; (5) H4: Trait 1 and trait 2 are associated with the region via one shared causal variant. The posterior probabilities corresponding to these hypotheses are denoted as PPH0, PPH1, PPH2, PPH3, and PPH4, quantifying the evidence supporting each hypothesis. A gene was assumed to be colocalized with the CVDs outcome on the basis of a PPH4>80% [34]. We also performed colocalization analysis for nearby genes with significant associations via horizontal pleiotropy analysis. We also performed two-sample Mendelian randomization analysis using various methods provided in the R package TwoSampleMR (version 0.5.7), including Inverse Variance Weighted (IVW), MR-Egger, Weighted Median, Simple Mode, and Weighted Mode. While these methods operate within the same analytical framework, their differing assumptions can lead to biases in the estimations.

#### Phenotype scanning

We performed phenotype scanning using the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/) to explore associations between top cis-eQTLs and other traits. The analysis adhered to the following criteria: [1] associations were considered significant if $p<5\times10^{-8}$, and [2] the top cis-eQTLs were linked to known risk factors for cardiovascular diseases.

#### Reverse MR analysis

Reverse Mendelian Randomization (MR) analysis was conducted for significant associations identified in the phenotype scanning. Given that the eQTLGen summary data contained only cis-associations, which are unsuitable for reverse MR analysis requiring genome-wide genetic variations as outcomes, we used protein quantitative trait loci (pQTLs) data from deCODE ($n=35,559$) as outcome SNPs [35].

## Results

#### Genetic instruments selection and validation for cancer-targeted therapy

Among the 39 cancer therapy-associated genes detailed in the DrugBank and ChEMBL (Table 1), eight were excluded due to the absence of genetic variants in expression. Subsequently, for 31 of 39 drug target genes, with available genetic variants, the most significant cis-eQTLs, with F statistics surpassing 10, were utilized as genetic instruments to minimize weak instrument bias. Positive control analyses validated the efficacy and robustness of the genetic instrument. Eight of the 31 drug target genes, including VEGFA, ERBB2, FLT1, FLT4, PSMB1, MAP2K2, FGFR1, and FGFR2, significantly associated with indicative cancers ($p<0.05$), were analysed further. Odds ratios (ORs) were used to genetically proxy the inhibitory effect per 1 SD decrease in gene expression (Table 2 and Additional file 2: Table S3).

#### Primary SMR analysis

As shown in Fig. 2 and Additional file 2: Table S4, genetically proxies for VEGFA inhibition were significantly associated with increased stroke risk (OR=1.17,

95% CI=1.09–1.26, $p=1.33\times10-5$), supported by the Bonferroni-corrected p values and HEIDI test ($p>0.01$, eliminating the linkage scenario). Additionally, genetically proxied VEGFA inhibition was suggestively associated with increased risk for coronary heart diseases (OR=1.13, 95% CI=1.05–1.21, $p=5.44\times10^{-4}$), hypertension (OR=1.08, 95% CI=1.03–1.14, $p=1.78\times10^{-3}$), ischaemic heart diseases (OR=1.09, 95% CI=1.03–1.16, $p=3.40\times10^{-3}$), myocardial infarction (OR=1.12, 95% CI=1.02–1.23, $p=1.32\times10^{-2}$), dyslipidaemia (OR=1.09, 95% CI=1.01–1.16, $p=1.84\times10^{-2}$), and atrial fibrillation (OR=1.10, 95% CI=1.01–1.20, $p=2.42\times10^{-2}$).

Genetically proxied ERBB2 inhibition was suggestively associated with a lower risk of atrial fibrillation (OR=0.59, 95% CI=0.43–0.82, $p=1.42\times10^{-3}$) (Additional file 2: Table S5 and Additional file 1: Figure S1). Genetically proxied FLT1 inhibition was suggestively protective against coronary heart diseases (OR=0.94, 95% CI=0.89–0.99, $p=3.26\times10^{-2}$) and myocardial infarction (OR=0.92, 95% CI=0.85–1.00, $p=4.70\times10^{-2}$), but was a risk factor for valvular heart diseases (OR=1.10, 95% CI=1.01– 1.19, $p=2.33\times10^{-2}$) (Additional file 2: Table S6). Genetically proxied FLT4 inhibition showed suggestive evidence of a positive association with myocarditis (OR=1.56, 95% CI=1.06–2.29, $p=2.45\times10^{-2}$) (Additional file 2: Table S7 and Additional file 1: Figure S2). Genetically proxied MAP2K2 inhibition was suggested to negatively associated with hypertension (OR=0.95, 95% CI=0.90–1.00, $p=3.44\times10^{-2}$), while positively associated with myocardial infarction (OR=1.11, 95% CI=1.01–1.21, $p=2.23\times10^{-2}$) (Additional file 2: Table S9). Genetically proxied FGFR1 inhibition showed suggestively protective effects on stroke (OR=0.89, 95% CI=0.84–0.95, $p=4.35\times10^{-4}$) and hypertension (OR=0.94, 95% CI=0.90–0.98, $p=2.26\times10^{-3}$) (Additional file 2: Table S10). No significant associations were detected between genetically proxied PSMB1 or FGFR2 inhibition and CVDs outcomes (Additional file 2: Table S8 and S11, Additional file 1: Figure S3-S4).

### Sensitivity analysis

Horizontal pleiotropy was examined to ascertain whether the aforementioned significant associations originated from nearby genes linked to the top cis-eQTLs of drug target genes within a±1 Mb window. For VEGFA, ERBB2, FLT1, FLT4, FGFR1, and MAP2K2, we identified 12, 20, 2, 9, 5, and 7 adjacent genes, respectively, including the drug target genes themselves. Subsequently, cis-eQTLs at $p<5\times10^{-8}$ were extracted (Additional file 2: Table S12). SMR analyses revealed significant associations between VEGFA and stroke, FLT1 and myocardial infarction, FLT1 and valvular heart diseases, FGFR1 and stroke, as well as MAP2K2 and myocardial infraction. Notably, these associations were observed with respect to the drug target genes themselves rather than with adjacent genes and corresponding CVDs outcomes, suggesting the absence of horizontal pleiotropy (Additional file 2: Table S13). The results from the IVW method were consistent with those from the SMR analysis, highlighting significant associations. These included genetically

**Table 2** MR association between inhibition of drug target genes and indicative cancers

| Exposure and outcome | SNVs, No. | top eQTL SNP | F statistic | Beta[a] (95% CI) | OR[b] (95% CI) | *p* value |
|---|---|---|---|---|---|---|
| **VEGFA expression** | | | | | | |
| Ovary cancer | 214 | rs11965885 | 872.6 | -0.44 (-0.62- -0.25) | 0.65 (0.44–0.94) | 0.02 |
| Breast cancer | 214 | rs11965885 | 872.6 | -0.15 (-0.22- -0.09) | 0.86 (0.75–0.98) | 0.02 |
| **ERBB2 expression** | | | | | | |
| Colorectal cancer | 272 | rs903506 | 66.40 | -0.93 (-1.21- -0.64) | 0.40 (0.22–0.71) | 0.002 |
| Prostate cancer | 272 | rs903506 | 66.40 | -0.50 (-0.71- -0.28) | 0.61 (0.39–0.95) | 0.02 |
| **FLT1 expression** | | | | | | |
| Melanoma | 523 | rs56728557 | 510.48 | -0.20 (-0.28- -0.12) | 0.82 (0.69–0.97) | 0.02 |
| **FLT4 expression** | | | | | | |
| Head and neck cancer | 255 | rs2387281 | 493.71 | -0.35 (-0.51- -0.19) | 0.70 (0.51–0.97) | 0.03 |
| **PSMB1 expression** | | | | | | |
| Multiple myeloma | 859 | rs4710839 | 1731.11 | -0.36 (-0.52- -0.19) | 0.70 (0.50–0.99) | 0.04 |
| **MAP2K2 expression** | | | | | | |
| Melanoma | 169 | rs10250 | 526.34 | -0.23 (-0.33- -0.12) | 0.80 (0.64–0.99) | 0.04 |
| **FGFR1 expression** | | | | | | |
| Biliary tract cancer | 323 | rs10958704 | 1178.17 | -0.41 (-0.56- -0.26) | 0.66 (0.49–0.91) | 0.01 |
| **FGFR2 expression** | | | | | | |
| Biliary tract cancer | 268 | rs1896422 | 2896.70 | -0.24 (-0.34- -0.14) | 0.79 (0.64–0.97) | 0.03 |
| Breast cancer | 268 | rs1896422 | 2896.70 | -0.12 (-0.15- -0.09) | 0.89 (0.83–0.94) | 0.00006 |

Abbreviation CI=confidence interval; eQTL=expression quantitative trait loci; ERBB2=receptor tyrosine-protein kinase erbB-2; FGFR1=fibroblast growth factor receptor 1; FGFR2=fibroblast growth factor receptor 2; FLT1=FMS-like tyrosine kinase 1; FLT4=FMS-like tyrosine kinase 4; OR=odds ratio; SNV=single-nucleotide variant; VEGFA=vascular endothelial growth factor A

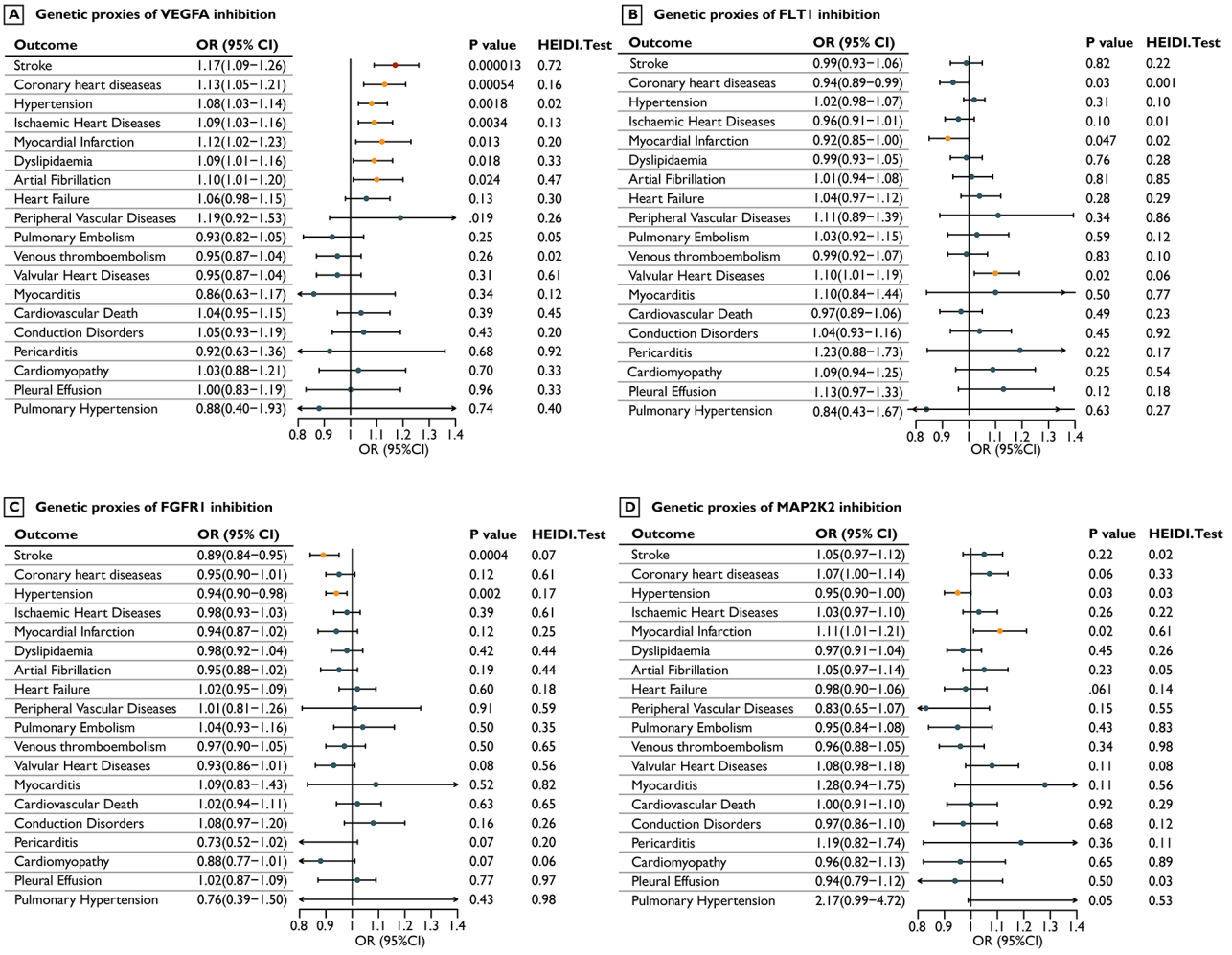



**Fig. 2** Causal associations between cancer-targeted therapies and cardiovascular diseases. A Mendelian randomization study estimated ORs for the effect of a 1 SD decrease in the expression of (**A**) VEGFA, (**B**) FLT1, (**C**) FGFR1, and (**D**) MAP2K2 on 19 cardiovascular diseases. The results were obtained from SMR analysis at a Bonferroni correction p value < 0.00033 (8 exposures and 19 outcomes) and a HEIDI test p value > 0.01 to avoid linkage disequilibrium. The red points indicate SMR P values < 0.00033 and HEIDI test p-value > 0.01, the yellow points indicate SMR 0.00033 < P values < 0.05 and HEIDI test p values > 0.01, and the blue points indicate other values. OR = odds ratio; CI = confidence interval; HEIDI = heterogeneity in the dependent instrument

proxied VEGFA inhibition with an increased stroke risk (OR = 1.14, 95% CI = 1.10–1.17, $p = 0.016$), MAP2K2 inhibition with an increased risk of myocardial infarction (OR = 1.09, 95% CI = 1.01–1.19, $p = 0.037$), and FGFR1 inhibition with a decreased stroke risk (OR = 0.92, 95% CI = 0.87–0.98, $p = 0.007$). Additionally, the Weighted Median method confirmed the significant association between genetically proxied FLT1 inhibition and an increased risk of valvular heart disease (OR = 1.08, 95% CI = 1.01–1.16, $p = 0.035$), aligning with the SMR analysis. However, no significant association was identified between FLT1 expression and myocardial infarction risk using the two-sample MR method (Additional File 2: Table S14). Furthermore, none of the top cis-eQTLs for these drug target genes with significant associations were linked to other traits recognized as cardiovascular disease risk factors (Additional File 2: Table S15).

## Colocalization analysis

Further colocalization analysis revealed a robust 93.6% posterior probability of a shared causal variant between VEGFA expression and stroke risk, providing robust support for the observed MR association (Fig. 3). In contrast, associations with PPH4 less than 80% were considered nonsignificant. These included the association between FLT1 expression and myocardial infarction risk (PPH4 = 3.4%), FLT1 expression and valvular heart disease risk (PPH4 = 6.6%), FGFR1 expression and stroke risk (PPH4 = 65.5%), and MAP2K2 expression and myocardial infarction risk (PPH4 = 5.7%) (Fig. 3, Additional File 2: Table S13).

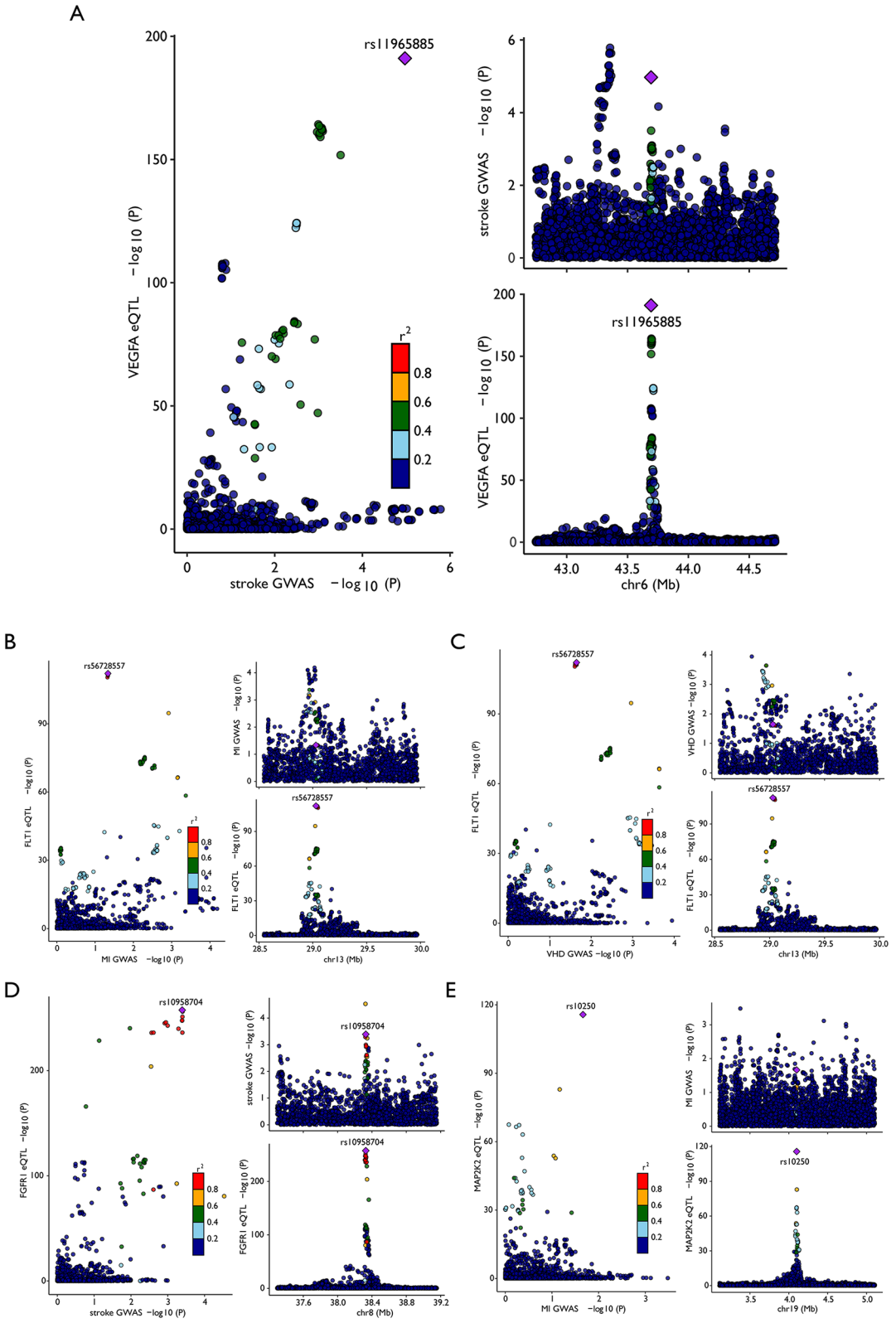



**Fig. 3** Colocalization analysis between significant drug target genes and CVD outcomes. The figure depicts colocalization between the drug target gene eQTL signal and the outcome GWAS. The purple diamond points indicate the lead SNP with the minimal P value in the eQTL. The eQTL P values were extracted from the eQTLGen consortium (31,684 samples), and the stroke GWAS P values were extracted from the FinnGen database (39,818 cases, 27,1817 controls). eQTL: expression quantitative trait loci; GWAS: genome-wide association study

### Reverse MR analysis of the effect of stroke risk on VEGFA protein levels in plasma

We analyzed pQTL data from the deCODE database for three VEGFA protein isoforms: VEGF121, L-VEGF165, and VEGF. Reverse MR analysis found no evidence of a causal association between stroke risk and VEGFA protein levels (Additional File 2: Table S16).

## Discussion

In this study, we investigated the effects of genes encoding cancer-targeted drugs on 19 adverse cardiovascular outcomes, confirming a significant causal link between genetically proxied VEGFA inhibition and increased stroke risk. This finding was consistent with the results of colocalization analysis, revealing that the posterior probability of a shared causal variant shared between VEGFA expression and stroke reached 93.6%. To our knowledge, this study represents the pioneering and most extensive MR study examining cancer-targeted drugs and cardiovascular outcomes.

Suggestive evidence has emerged for associations between genetically proxied FLT1 inhibition and decreased myocardial infarction risk, as well as increased valvular heart disease risk; genetically proxied FGFR1 inhibition and decreased stroke risk; and genetically proxied MAP2K2 inhibition and increased myocardial infarction risk. The protective effects of cancer-targeted therapies on cardiovascular diseases may be attributed to their anti-inflammatory properties and metabolic regulation [36, 37], while the harmful effects could be due to off-target effects and shared signaling pathways with cancer-targeted therapies [38, 39]. However, colocalization analysis revealed that the posterior probability of a shared causal variant was not significant between these drug genes and the corresponding CVDs outcomes. These conflicting results may arise from false-probability in suggestive associations, addressable through p-value adjustment via Bonferroni correction, or the existence of linkage disequilibrium, thereby violating MR assumptions [40]. Further investigations are needed to elucidate the reason underlying the absence of evidence for colocalization when a nonzero MR estimate is revealed.

Bevacizumab, the first approved angiogenesis inhibitor, is a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor A ligand (VEGFA), and has demonstrated enhanced overall survival in various cancers [41, 42]. In a cohort study with 2526 stage IV colorectal cancer patients, the combination of first-line cytotoxic chemotherapy with bevacizumab correlated with an elevated stroke risk, compared with that of patients without bevacizumab (4.9% vs. 2.5%, p value < 0.01), rather than with cardiac events [43]. Another post hoc meta-analysis of 5 randomized clinical trials in metastatic carcinoma patients, revealed a significantly increased risk of arterial thromboembolic events (ATEs) (hazard ratio [HR] = 2.0, 95% confidence interval [CI] = 1.05–3.75, $p = 0.031$) with bevacizumab treatment. Subsequent ATE classification revealed that the majority of patients experienced stroke, indicating a greater risk in bevacizumab-treated patients than in controls [44]. Totzeck et al. [45] and Saran et al. [46] also consistently showed a heightened stroke risk in patients with malignant tumours treated with bevacizumab combinations. Our MR results align with these findings, indicating a significant association between genetically proxied VEGFA inhibition and increased stroke risk. However, a meta-analysis of 77 studies and another meta-analysis of 5 clinical trials failed to establish significant association between bevacizumab application and increased risk of stroke [47, 48]. Given the uncertain association and causation unavailability in these studies, our MR study serves as a supplementary and extensive approach with respect to conventional studies.

The positive association between genetically proxied VEGFA inhibition and stroke risk remains elusive, but insights into the angiogenesis mechanism of VEGFA in malignant carcinoma may shed light on potential explanations. VEGFA is a dimeric glycoprotein in vascular endothelial growth factor (VEGF) family, that regulates angiogenesis and vascular permeability by interacting with its receptor tyrosine kinases, VEFGR1 and VEGFR2 (main receptors) [49]. As VEGFR2 is expressed on vascular endothelial cells beyond tumour neovascularization, VEGFA inhibition also affects the cardiovascular system with adverse effects. Inhibiting VEGFA leads to reduced nitric oxide (NO), mediated by the PI3K/Akt signalling pathway [49, 50]. Additionally, VEGFA inhibition disrupts phospholipase A2 (PLA2) activation via the PLCγ/PKC signalling pathway, reducing prostaglandin I2 (PGI2) [50]. Diminished levels of the crucial vasodilators NO and PGI1, contribute to endothelial dysfunction, reducing vascular permeability and endothelial cell survival [50]. Furthermore, VEGFA inhibition increases mitochondrial oxidative stress, inflammation, and blood viscosity through overproduction of erythropoietin [51, 52]. While these mechanisms have not been thoroughly investigated, our MR results underscore the potential involvement of VEGFA in stroke pathogenesis.

### Study strengths

Our MR study exhibits several strengths. First, we employed eQTLs affecting gene expression as genetic instruments to proxy for the inhibition of cancer-targeted drug exposure, mitigating concerns of reverse causation and confounding bias. Second, we performed positive control analyses that examined the expected effects of cancer-targeted therapies on the indicated cancers, to verify the validity and robustness of the selected

genetic instrumental variables. Third, multiple sensitivity analyses, including the F statistic, HEIDI test, horizontal pleiotropy, and Bayesian colocalization, were conducted to ensure the efficacy of the MR results. Fourth, we restricted our cardiovascular disease GWASs to individuals of European ancestry, which minimized bias due to population stratification. Finally, our MR study provides a more economical, efficient and safe evaluation of the safety and side effects of cancer-targeted drugs than traditional randomized clinical trials.

### Study limitations

This study has several limitations. First, our exploration focused primarily on on-target actions, investigating the potential drug effects of intended drug targets on CVDs risk, opening the possibility of biological modulating effects through unintended drug targets, known as off-target actions. Second, although both cis-eQTL and outcome GWAS data predominantly involve the European population to mitigate population stratification bias, caution is necessary when generalizing MR results to other populations. Third, genetic instrumental variants reflect the life-long and low-dose effects of drug exposure on CVDs outcomes, potentially diverging from the short-term and high-dose effects of targeted drugs. Thus, MR results may contradict or not be fully comparable to those of relevant observational studies or clinical trials, and the effect size may not perfectly reflect the actual effect of targeted drug exposure. Nevertheless, these results provide valuable insights into the long-term adverse cardiovascular effects of cancer-targeted treatments. Fourth, the incidence of cardiovascular diseases varies with age. While Mendelian randomization (MR) analysis assumes that the effects of genetic variants on exposure are lifelong and independent of environmental factors, including age, genetic effects may interact with age. Age-stratified analyses could therefore provide additional insights into these relationships. Unfortunately, the FinnGen database we used does not provide age-specific stratified data, which limits our ability to perform such analyses in the current study. Future studies incorporating detailed age-specific data would be valuable in further exploring these associations. Finally, for genes that did not show significant associations with CVDs outcomes, we should not dismiss the potential modulatory effects of these target genes on the cardiovascular system for the lack of evidence of significant association.

## Conclusions

Our study provides MR evidence suggesting an adverse association between VEGFA-targeted inhibitors and stroke risk. Although the statistical evidence from the MR analysis alone is not sufficient to draw definitive conclusions, our findings highlight the potential role of VEGFA in stroke, particularly in the context of cardiovascular diseases associated with cancer-targeted therapies. Therefore, our research may contribute to the early identification of specific cardiovascular diseases in individuals receiving cancer-targeted therapies, enhance the effectiveness of preventive and treatment measures, and support the development of personalized and precision medicine. Additionally, our study emphasizes the importance of strengthening pharmacovigilance and further investigating the underlying mechanisms that modulate these effects.

#### Abbreviations

| | |
|---|---|
| ALK | Anaplastic lymphoma kinase |
| BCR-ABL | Breakpoint cluster region-Abelson oncogene locus |
| BRAF | v-Raf murine sarcoma viral oncogene homologue B1 |
| BTK | Bruton tyrosine kinase |
| CD38/274 | Cluster of differentiation 38/274 |
| CDK4/6 | Cyclin-dependent kinase 4/6 |
| CI | Confidence interval |
| CTR-CVT | Cancer therapy-related cardiovascular toxicity |
| CTLA4 | Cytotoxic T-lymphocyte-associated antigen 4 |
| CVD | Cardiovascular disease |
| EGFR | Epidermal growth factor receptor |
| ERBB2 | Receptor tyrosine-protein kinase erbB-2 |
| eQTL | Expression quantitative trait loci |
| FGFR | Fibroblast growth factor receptor |
| FLT1/4 | FMS-like tyrosine kinase 1/4 |
| GAWS | Genome-wide association study |
| HEIDI | Heterogeneity in the dependent instrument |
| HER2 | Human epidermal receptor 2 |
| ICIs | Immune checkpoint inhibitors |
| IV | Instrument variant |
| KDR | Kinase insert domain receptor |
| MAP2K1/2 | Mitogen-activated protein kinase kinase 1/2 |
| MR | Mendelian randomization |
| NTRK | Neurotrophic tyrosine receptor kinase |
| OR | Odds ratio |
| PARP | Poly ADP ribose polymerase |
| PDCD1 | Programmed cell death protein 1 |
| pQTLs | Protein quantitative trait loci |
| PSMB | Proteasome 20 S subunit beta |
| RAF | Rapidly accelerated fibrosarcoma |
| SD | Standard deviation |
| SLAMF7 | Signalling lymphocytic activation molecule family 7 |
| SMR | Summary-data-based Mendelian randomization |
| SNP | Single nucleotide polymorphism |
| TACSTD2 | Tumour-associated calcium signal transducer 2 |
| VEGFA | Vascular endothelial growth factor A |
| XPO1 | Exportin 1 |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-024-06027-4.

Supplementary Material 1

Supplementary Material 2

#### Acknowledgements

This study was facilitated by the FinnGen study and eQTLGen Consortium. We want to acknowledge the participants and investigators who contributed to these studies.

**Author contributions**
C.F. and X.L. took responsibility for the analyses of the data and the writing of the paper. C.Y., S.L., and X.L. undertook the collection of data. S.Q. and H.L. interpreted the data. J.X. and C.O. conceived the study design, reviewed the paper and made critical revisions to the manuscript. All the authors read and approved the final version of the manuscript.

**Funding**
This research was funded by the National Key R&D Program of China (2018YFC1312803), the Guangzhou Key Research and Development Program (202206080014), and the Clinical Research Program of Nanfang Hospital, Southern Medical University (2021CR007).

**Data availability**
All the data used in this study are publicly available. Additional file 2: Table S2 describes the data used and the relevant information used to retrieve the summary statistics. Code was implemented in summary-data-MR (SMR) software, version 1.3.1. Bayesian colocalization was applied via the R package 'coloc' (http://cran.r-project.org/web/packages/coloc) in the R V.4.0.0 computing environment. The code to reproduce the analysis are available at https://github.com/lxwrainbow/cancer-targeted-drugs-SMR.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

**Author details**
[1]Department of Cardiology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China
[2]The First School of Clinical Medicine, Southern Medical University, Guangzhou 510515, China
[3]The Tenth Affiliated Hospital of Southern Medical University (Dongguan People's Hospital), Southern Medical University, Dongguan 523018, China
[4]Guangdong Provincial Key Laboratory of Shock and Microcirculation, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China
[5]State Key Laboratory of Organ Failure Research, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China
[6]Department of Cardiology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, China

Received: 4 August 2024 / Accepted: 23 December 2024
Published online: 06 January 2025

**References**

1. Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J. 2019;40(48):3889–97.
2. Lenneman CG, Sawyer DB. Cardio-Oncology: an update on cardiotoxicity of Cancer-Related treatment. Circ Res. 2016;118(6):1008–20.
3. Karlstaedt A, Moslehi J, de Boer RA. Cardio-onco-metabolism: metabolic remodelling in cardiovascular disease and cancer. Nat Rev Cardiol. 2022;19(6):414–25.
4. Islam MA, Amin MN, Siddiqui SA, Hossain MP, Sultana F, Kabir MR. Trans fatty acids and lipid profile: a serious risk factor to cardiovascular disease, cancer and diabetes. Diabetes Metab Syndr. 2019;13(2):1643–7.
5. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med. 2015;162(2):123–32.
6. Masoudkabir F, Sarrafzadegan N, Gotay C, Ignaszewski A, Krahn AD, Davis MK, et al. Cardiovascular disease and cancer: evidence for shared disease pathways and pharmacologic prevention. Atherosclerosis. 2017;263:343–51.
7. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022;43(41):4229–361.
8. Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. Tumor-treating fields: a fourth modality in Cancer Treatment. Clin Cancer Res. 2018;24(2):266–75.
9. Drobni ZD, Alvi RM, Taron J, Zafar A, Murphy SP, Rambarat PK, et al. Association between Immune checkpoint inhibitors with Cardiovascular events and atherosclerotic plaque. Circulation. 2020;142(24):2299–311.
10. Rubio-Infante N, Ramírez-Flores YA, Castillo EC, Lozano O, García-Rivas G, Torre-Amione G. Cardiotoxicity associated with immune checkpoint inhibitor therapy: a meta-analysis. Eur J Heart Fail. 2021;23(10):1739–47.
11. Yang Z, Wang W, Wang X, Qin Z. Cardiotoxicity of epidermal growth factor receptor 2-Targeted drugs for breast Cancer. Front Pharmacol. 2021;12:741451.
12. Yu AF, Flynn JR, Moskowitz CS, Scott JM, Oeffinger KC, Dang CT, et al. Long-term Cardiopulmonary consequences of Treatment-Induced Cardiotoxicity in survivors of ERBB2-Positive breast Cancer. JAMA Cardiol. 2020;5(3):309–17.
13. Schmidt AF, Finan C, Gordillo-Marañón M, Asselbergs FW, Freitag DF, Patel RS, et al. Genetic drug target validation using mendelian randomisation. Nat Commun. 2020;11(1):3255.
14. F PS. DGM, C P, A K. Mendelian Randomization as an Approach to Assess Causality Using Observational Data. Journal of the American Society of Nephrology: JASN [Internet]. 2016 Nov [cited 2023 Nov 7];27(11). Available from: https://pubmed.ncbi.nlm.nih.gov/27486138/
15. Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE, et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. Nat Genet. 2016;48(5):481–7.
16. Chen J, Ruan X, Sun Y, Lu S, Hu S, Yuan S, et al. Multi-omic insight into the molecular networks of mitochondrial dysfunction in the pathogenesis of inflammatory bowel disease. EBioMedicine. 2024;99:104934.
17. Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res. 2018;46(D1):D1074–82.
18. Gaulton A, Hersey A, Nowotka M, Bento AP, Chambers J, Mendez D, et al. The ChEMBL database in 2017. Nucleic Acids Res. 2017;45(D1):D945–54.
19. Davies M, Nowotka M, Papadatos G, Dedman N, Gaulton A, Atkinson F, et al. ChEMBL web services: streamlining access to drug discovery data and utilities. Nucleic Acids Res. 2015;43(Web Server issue):W612–20.
20. Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer. Nat Rev Cancer. 2017;17(5):318–32.
21. Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, et al. Sacituzumab Govitecan in Metastatic Triple-negative breast Cancer. N Engl J Med. 2021;384(16):1529–41.
22. Solomon JP, Benayed R, Hechtman JF, Ladanyi M. Identifying patients with NTRK fusion cancer. Ann Oncol. 2019;30(Suppl8):viii16–22.
23. Slade D. PARP and PARG inhibitors in cancer treatment. Genes Dev. 2020;34(5–6):360–94.
24. Võsa U, Claringbould A, Westra HJ, Bonder MJ, Deelen P, Zeng B, et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. Nat Genet. 2021;53(9):1300–10.
25. Kurki MI, Karjalainen J, Palta P, Sipilä TP, Kristiansson K, Donner KM, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. Nature. 2023;613(7944):508–18.
26. C GCDCSD, O A C et al. D L,. Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA: a cancer journal for clinicians [Internet]. 2016 Jul [cited 2023 Aug 29];66(4). Available from: https://pubmed.ncbi.nlm.nih.gov/26919165/
27. Moslehi JJ. Cardiovascular toxic effects of targeted Cancer therapies. N Engl J Med. 2016;375(15):1457–67.
28. Pun SC, Neilan TG. Cardiovascular side effects of small molecule therapies for cancer. Eur Heart J. 2016;37(36):2742–5.
29. Sedgwick P. Multiple hypothesis testing and Bonferroni's correction. BMJ. 2014;349:g6284.

30. Carter AR, Sanderson E, Hammerton G, Richmond RC, Davey Smith G, Heron J, et al. Mendelian randomisation for mediation analysis: current methods and challenges for implementation. Eur J Epidemiol. 2021;36(5):465–78.
31. Chauquet S, Zhu Z, O'Donovan MC, Walters JTR, Wray NR, Shah S. Association of Antihypertensive Drug Target genes with Psychiatric disorders: a mendelian randomization study. JAMA Psychiatry. 2021;78(6):623–31.
32. Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. PLoS Genet. 2014;10(5):e1004383.
33. Deng YT, Ou YN, Wu BS, Yang YX, Jiang Y, Huang YY, et al. Identifying causal genes for depression via integration of the proteome and transcriptome from brain and blood. Mol Psychiatry. 2022;27(6):2849–57.
34. Lin J, Zhou J, Xu Y. Potential drug targets for multiple sclerosis identified through mendelian randomization analysis. Brain. 2023;146(8):3364–72.
35. Ferkingstad E, Sulem P, Atlason BA, Sveinbjornsson G, Magnusson MI, Styrmisdottir EL, et al. Large-scale integration of the plasma proteome with genetics and disease DECODE. Nat Genet. 2021;53(12):1712–21.
36. Kim YC, Guan KL. mTOR: a pharmacologic target for autophagy regulation. J Clin Invest. 2015;125(1):25–32.
37. Feng FY, de Bono JS, Rubin MA, Knudsen KE. Chromatin to clinic: the Molecular Rationale for PARP1 inhibitor function. Mol Cell. 2015;58(6):925–34.
38. Palaskas NL, Ali HJ, Koutroumpakis E, Ganatra S, Deswal A. Cardiovascular toxicity of immune therapies for cancer. BMJ. 2024;385:e075859.
39. Rochette L, Guenancia C, Gudjoncik A, Hachet O, Zeller M, Cottin Y, et al. Anthracyclines/trastuzumab: new aspects of cardiotoxicity and molecular mechanisms. Trends Pharmacol Sci. 2015;36(6):326–48.
40. Zuber V, Grinberg NF, Gill D, Manipur I, Slob EAW, Patel A, et al. Combining evidence from mendelian randomization and colocalization: review and comparison of approaches. Am J Hum Genet. 2022;109(5):767–82.
41. Garcia J, Hurwitz HI, Sandler AB, Miles D, Coleman RL, Deurloo R, et al. Bevacizumab (Avastin®) in cancer treatment: a review of 15 years of clinical experience and future outlook. Cancer Treat Rev. 2020;86:102017.
42. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov. 2004;3(5):391–400.
43. Meyerhardt JA, Li L, Sanoff HK, Carpenter W, Schrag D. Effectiveness of bevacizumab with first-line combination chemotherapy for Medicare patients with stage IV colorectal cancer. J Clin Oncol. 2012;30(6):608–15.
44. Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst. 2007;99(16):1232–9.
45. Totzeck M, Mincu RI, Rassaf T. Cardiovascular adverse events in patients with Cancer treated with Bevacizumab: a Meta-analysis of more than 20 000 patients. J Am Heart Assoc. 2017;6(8):e006278.
46. Saran F, Chinot OL, Henriksson R, Mason W, Wick W, Cloughesy T, et al. Bevacizumab, temozolomide, and radiotherapy for newly diagnosed glioblastoma: comprehensive safety results during and after first-line therapy. Neuro Oncol. 2016;18(7):991–1001.
47. Abdel-Qadir H, Ethier JL, Lee DS, Thavendiranathan P, Amir E. Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: a systematic review and meta-analysis. Cancer Treat Rev. 2017;53:120–7.
48. Cortes J, Calvo V, Ramírez-Merino N, O'Shaughnessy J, Brufsky A, Robert N, et al. Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: a meta-analysis. Ann Oncol. 2012;23(5):1130–7.
49. Claesson-Welsh L, Welsh M. VEGFA and tumour angiogenesis. J Intern Med. 2013;273(2):114–27.
50. Pandey AK, Singhi EK, Arroyo JP, Ikizler TA, Gould ER, Brown J, et al. Mechanisms of VEGF (vascular endothelial growth factor) inhibitor-Associated Hypertension and Vascular Disease. Hypertension. 2018;71(2):e1–8.
51. Marto JP, Strambo D, Livio F, Michel P. Drugs Associated with ischemic stroke: a review for clinicians. Stroke. 2021;52(10):e646–59.
52. Campia U, Moslehi JJ, Amiri-Kordestani L, Barac A, Beckman JA, Chism DD, et al. Cardio-Oncology: vascular and metabolic perspectives: A Scientific Statement from the American Heart Association. Circulation. 2019;139(13):e579–602.

## Publisher's note