DDCM：A computational strategy for drug repositioning based on support vector regression algorithm

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Supplementary Materials

Table S1. Training dataset

Data type	Source	Number
disease	DO	710
drug	DrugBank	1775
disease-drug	CTD/DrugBank	19632
drug pathway	KEGG/CTD	2187
drug-target gene	DrugBank	50876
disease pathway	KEGG/CTD	2339
disease pathogenic gene	OMIM/DO/CTD	5715

Table S2. Literature Validation of Potential Therapeutic Drugs for NSCLC.

Potential therapeutic drugs	Generic Name	Literature
DB02424	Geldanamycin	[1]
DB01394	Colchicine	
DB01177	Idarubicin	[2]
DB13811	Oblimersen	[3, 4]
DB06810	Plicamycin	
DB01254	Dasatinib	[5-8]
DB06176	Romidepsin	[9, 10]
DB00590	Doxazosin	
DB11919	6-O-benzylguanine	[11]
DB00448	Lansoprazole	[12]
DB01099	Flucytosine	
DB04815	Clioquinol	
DB08901	Ponatinib	[13-15]
DB05220	Alisertib	[16, 17]
DB04944	Acadesine	
DB11890	Cilengitide	[18]
DB06444	Dexanabinol	
DB11648	Afuresertib	
DB01179	Podofilox	
DB05088	Tetrathiomolybdate	[19]
DB01162	Terazosin	
DB00352	Tioguanine	[20]
DB00338	Omeprazole	[21]
DB09350	Piperonyl butoxide	
DB00947	Fulvestrant	[22, 23]

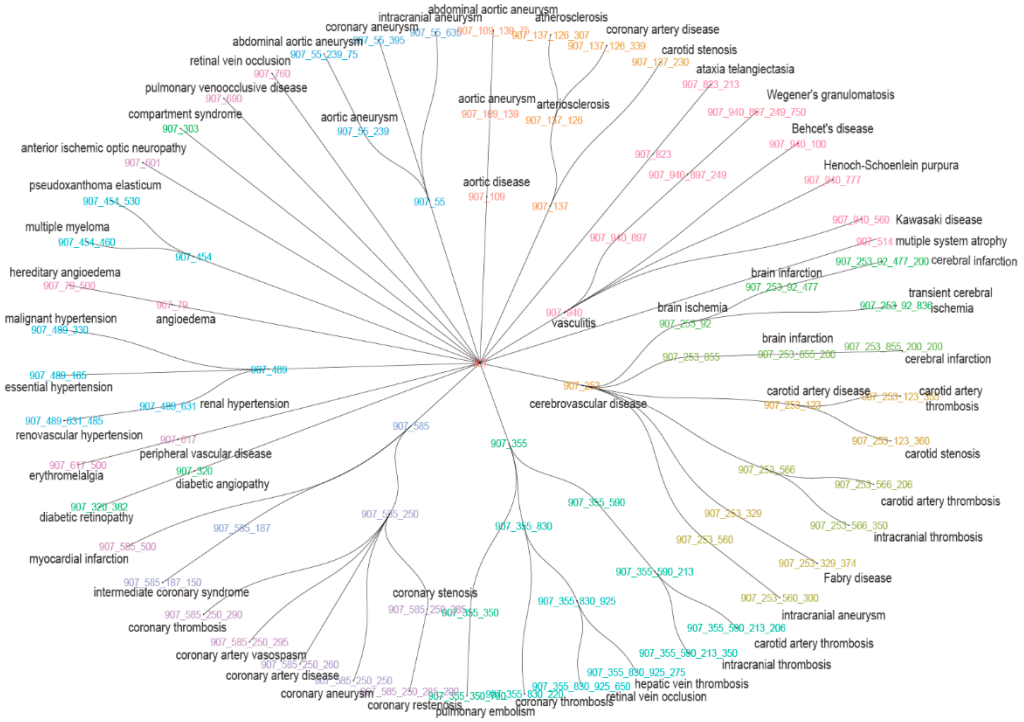
Table S3. The cerebrovascular disease-associated gene set has literature validating it as a therapeutic target for the disease.

Gene Family	Literature
GRIN	[24]
CALM	[25]
OPR	[26]
MAO	[27-29]
ADR	[30]
DRD	[31]
HTR	[32]

Table S4. Comparison of prediction performance of different methods

Method	AUC
SVM	$9.84e-01$
KNN	$9.50e-01$
RW	$8.91e-01$
DDCM	$9.96e-01$

A



B

cerebrovascular disease

	DrugBank ID	Score
1	DB00788	0.790
2	DB01191	0.559
3	DB01191	0.556
4	DB01191	0.540
5	DB01191	0.530
6	DB00579	0.458
7	DB00579	0.451
8	DB00579	0.441
9	DB00261	0.375
10	DB00261	0.366
...	...	...

vasculitis

	DrugBank ID	Score
1	DB00477	0.699
2	DB00477	0.696
3	DB00477	0.690
4	DB01140	0.646
5	DB00816	0.570
6	DB00816	0.567
7	DB00261	0.535
8	DB00261	0.512
9	DB05015	0.479
10	DB00679	0.492
...	...	...

coronary thrombosis

	DrugBank ID	Score
1	DB01362	0.612
2	DB01362	0.607
3	DB00650	0.384
4	DB00650	0.377
5	DB09313	0.362
6	DB00227	0.322
7	DB00694	0.298
8	DB00717	0.293
9	DB00694	0.291
10	DB00694	0.290
...	...	...

C

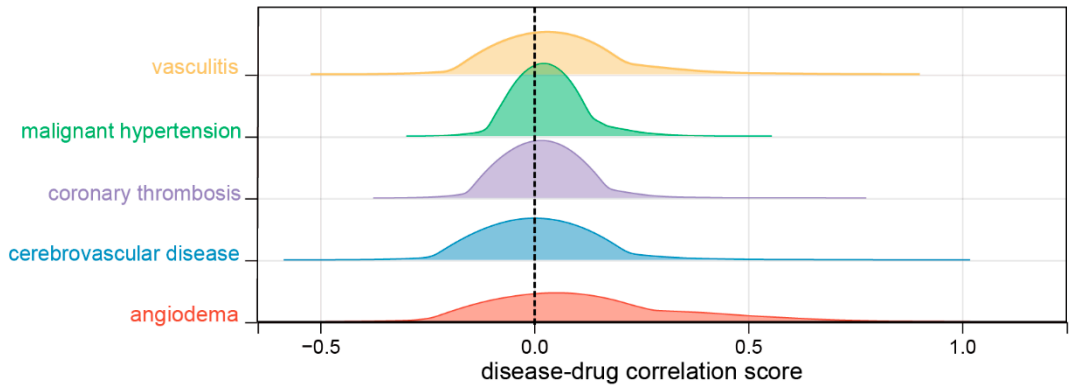
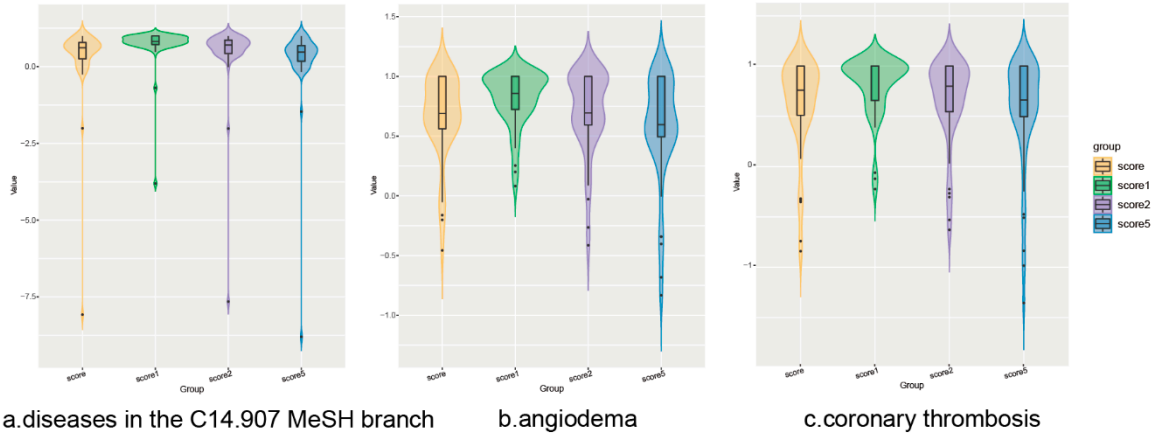


Figure S1. (A) The distribution of the disease data adopted in the MeSH branch C14.907 in the branch. **(B)** The disease-drug correlation score for a certain disease calculated using the DDCM method. (The figure shows the partial disease-drug correlation score results for cerebrovascular disease, vasculitis and coronary thrombosis .) **(C)** The distribution of disease-drug correlation scores for different diseases (The figure shows the distribution of disease-drug correlation scores for five

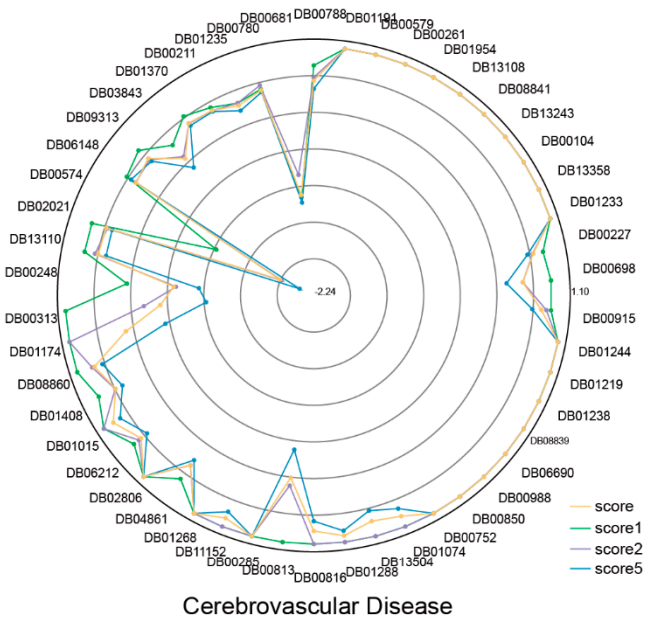
diseases, vasculitis, malignant hypertension, coronary thrombosis, cerebrovascular disease, and angioedema.)

A



a.diseases in the C14.907 MeSH branch b.angiodema c.coronary thrombosis

B



Stability Criteria

Potential Therapeutic Criteria

1	DB01191
2	DB00579
3	DB00261
4	DB01954
5	DB13108
6	DB08841
7	DB13243
8	DB00104
9	DB13358
10	DB01233
11	DB01244
12	DB01219
13	DB01238
14	DB08839
15	DB06690
16	DB00988
17	DB00850
18	DB00752
19	DB01074
20	DB01288
21	DB00285
22	DB11152
23	DB01268
24	DB02806
25	DB01015

C

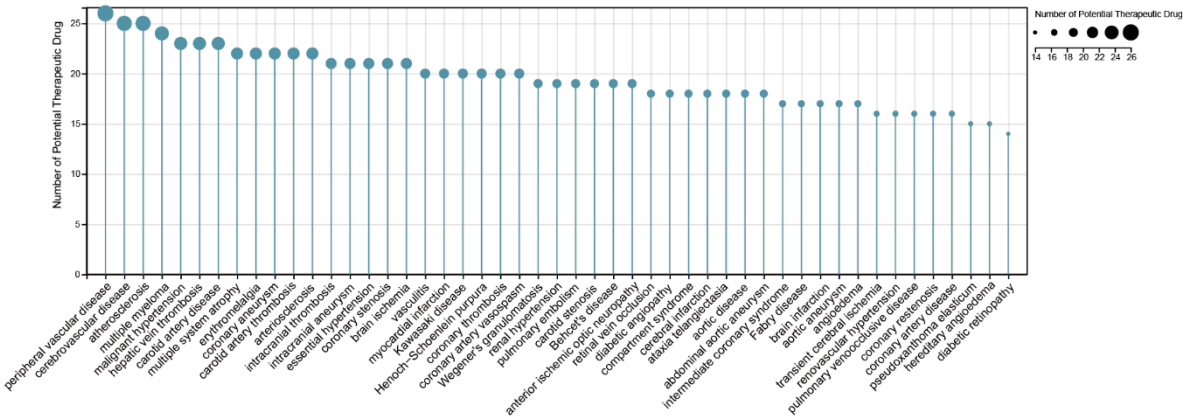


Figure S2. (A) a The overall distribution of disease-drug correlation scores for the drugs of interest for the selected diseases in the C14.907 branch of MeSH before and after random perturbation. b and c the distribution of disease-drug correlation scores for the relevant drugs in this branch for angioedema and coronary thrombosis, respectively, before and after receiving random perturbation. **(B)** The radar plot of stable drug candidates for cerebrovascular disease and the potential

therapeutic drug criteria, where drugs with stability scores close to 1 multiple times are considered relatively stable. After the potential therapeutic criteria a total of 25 potential therapeutic drugs for final cerebrovascular disease were identified. **(C)** the number of potential therapeutic drugs for a disease.

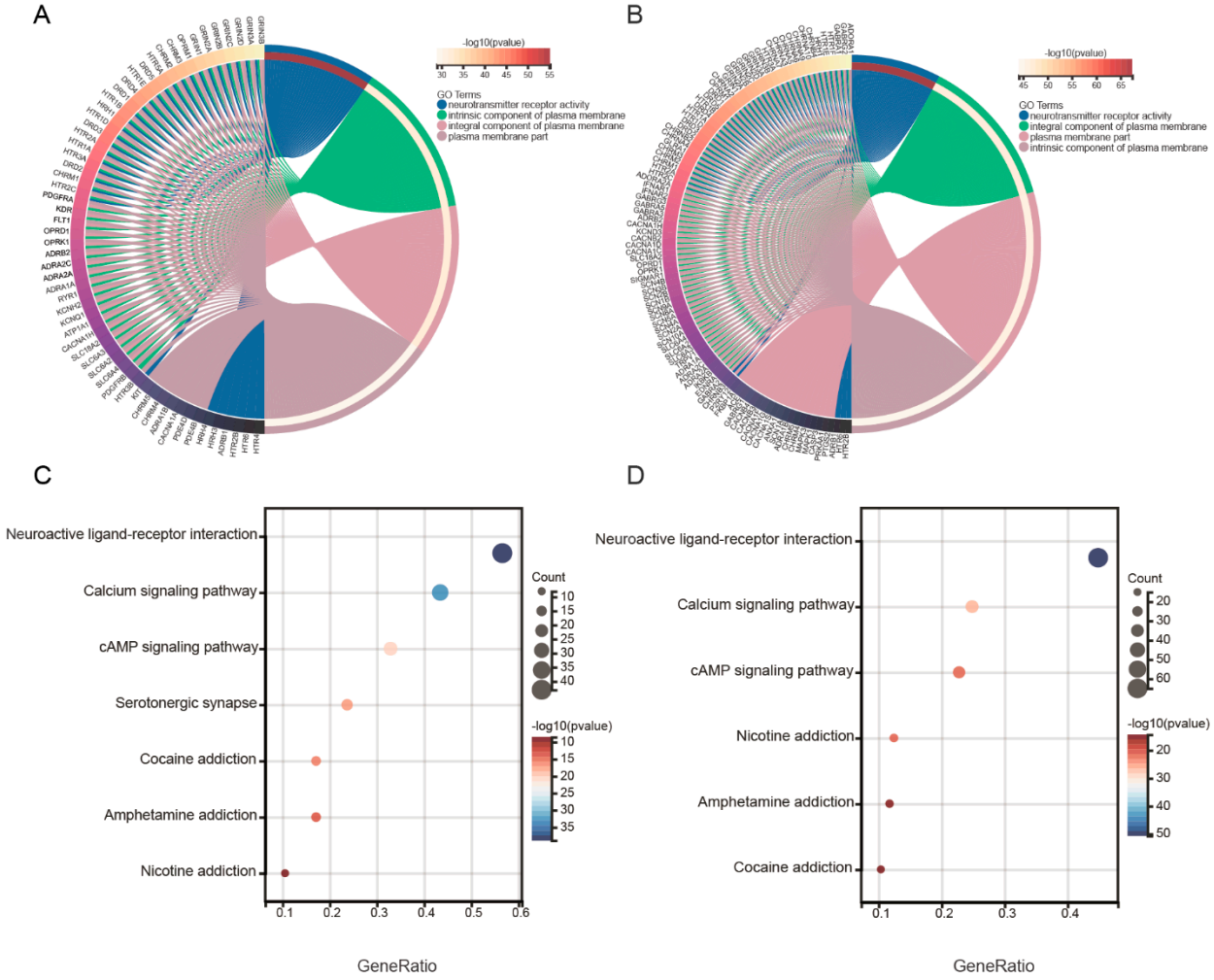


Figure S3. (A) and **(B)** The GO enrichment analysis of the drug targets of predicted potential therapeutic drugs and the drug targets of known therapeutic drugs for cerebrovascular disease, respectively. **(C)** and **(D)** The KEGG enrichment analysis of the drug targets of predicted potential therapeutic drugs and the drug targets of known therapeutic drugs for cerebrovascular disease, respectively.

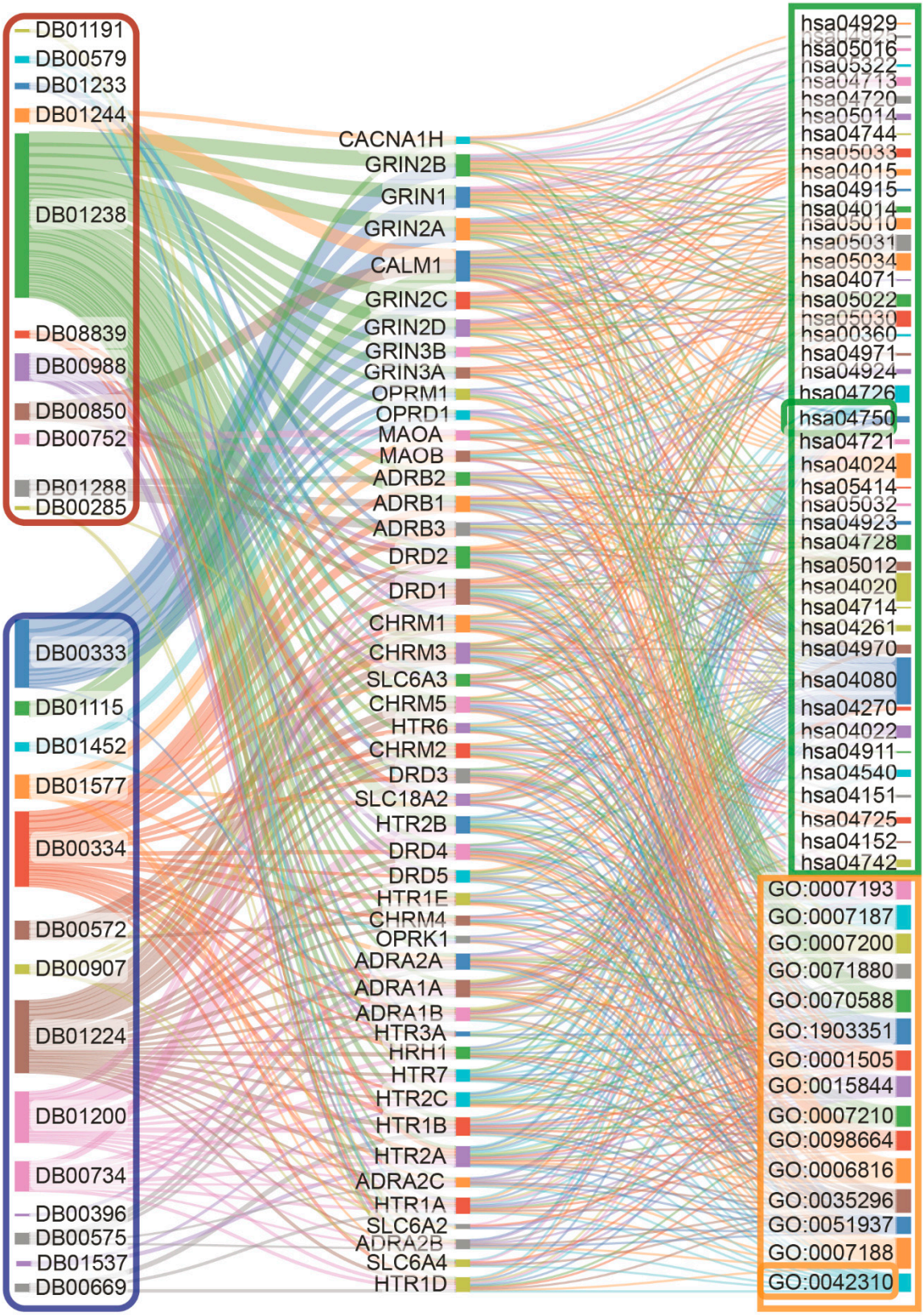


Figure S4. The Sankey plot shows the partial results of GO and KEGG enrichment of the set of genes predicted by the DDCM method for cerebrovascular disease after intersecting and then merging the potential therapeutic and known therapeutic drugs with the disease pathogenic genes, respectively. The red and blue rounded rectangles are the predicted potential therapeutic drugs and known therapeutic drugs for cerebrovascular disease, respectively. The green and yellow rectangles are the KEGG pathways and GO terms that are significantly enriched for this gene set, respectively.

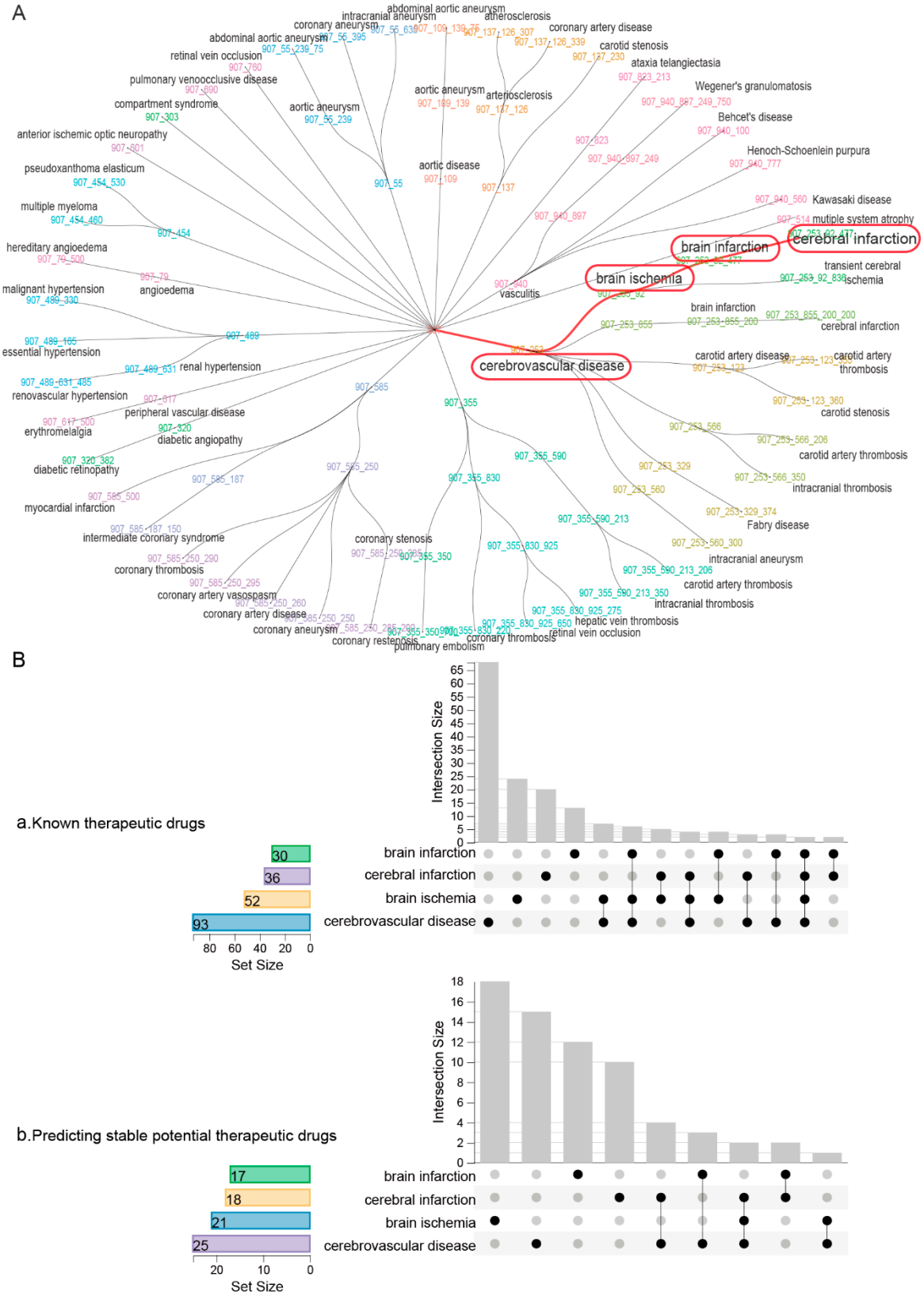


Figure S5. **(A)** The relationship between four cardiovascular diseases (cerebrovascular disease, brain ischemia, brain infarction and cerebral infarction) under the C14.907 branch of MeSH. **(B)** a. Overlap of known therapeutic drugs for the four diseases. b. Overlap of the number of potential therapeutic drugs predicted by the DDCM method for the four diseases.

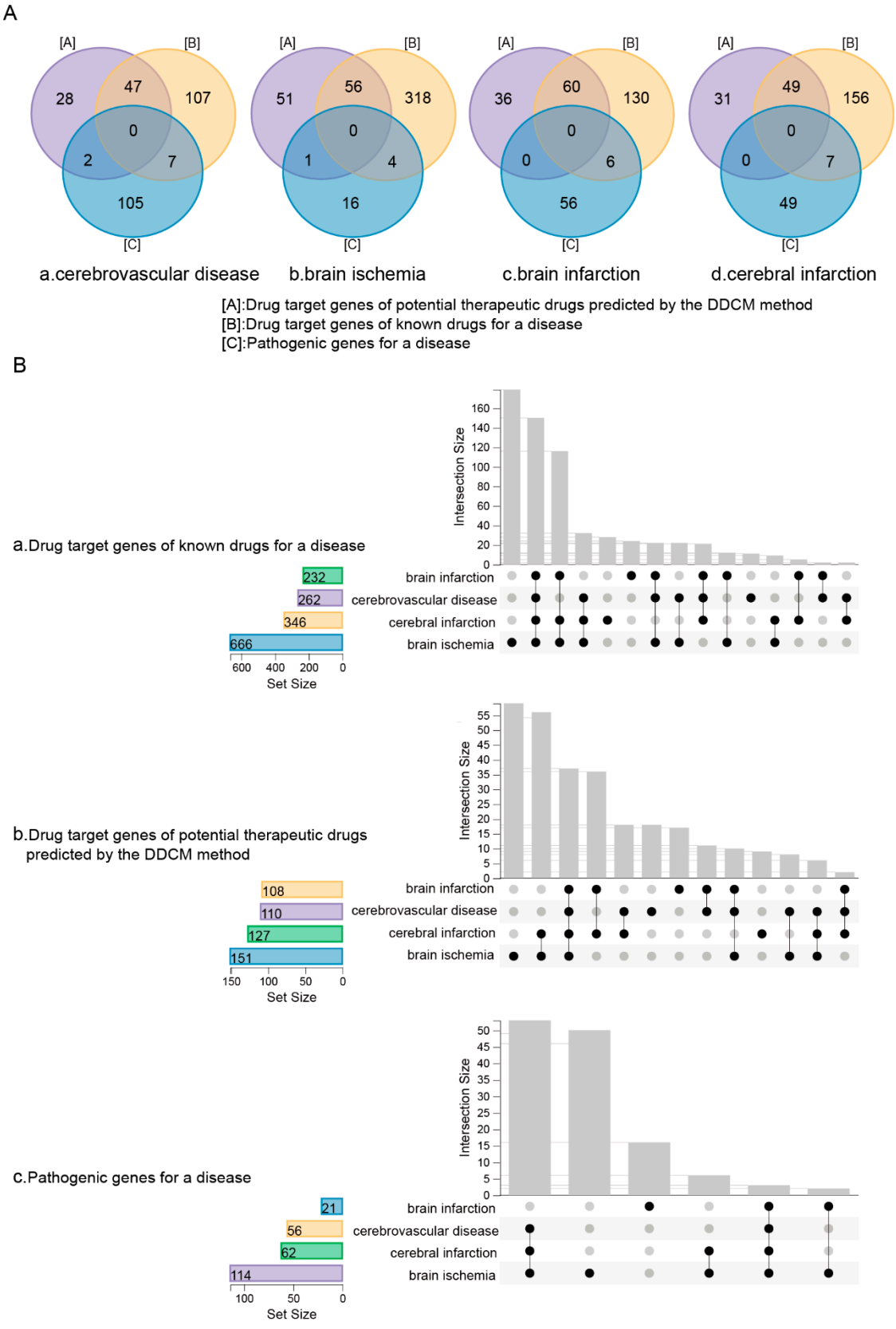


Figure S6. (A)(a-d) The venn diagrams indicate the degree of overlap of the predicted potential therapeutic drug targets, drug targets of known drugs, and disease pathogenic genes for cerebrovascular disease, brain ischemia, brain infarction and cerebral infarction, respectively. **(B)**(a-c) The diagrams represents the overlap of drug targets of known therapeutic drugs, drug targets of predicted potential therapeutic drugs, and pathogenic genes for each of the four diseases (cerebrovascular disease, brain ischemia, brain infarction and cerebral infarction).

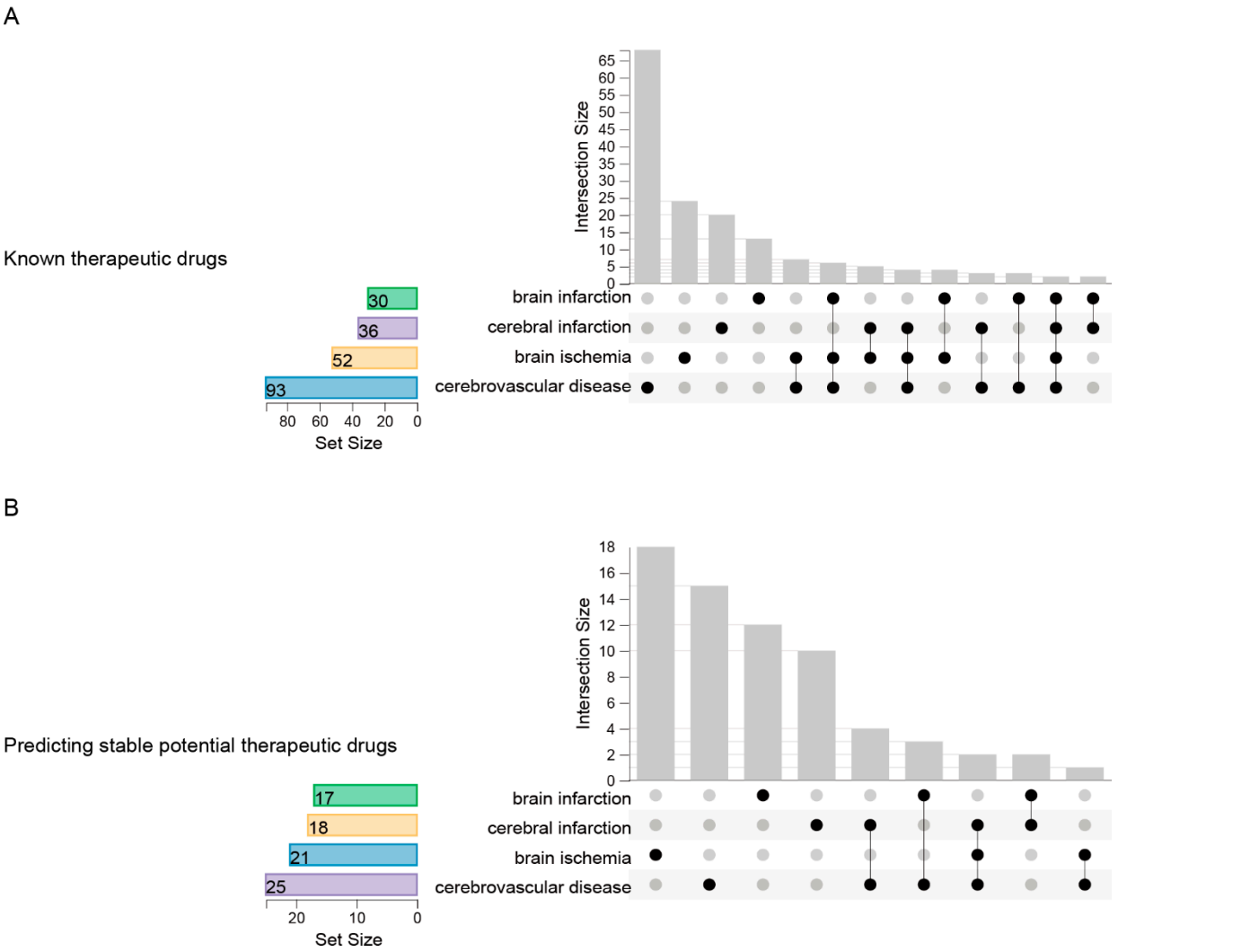


Figure S7. (A) Overlap of known therapeutic drugs for the four diseases. **(B)** Overlap of the number of potential therapeutic drugs predicted by the DDCM method for the four diseases.

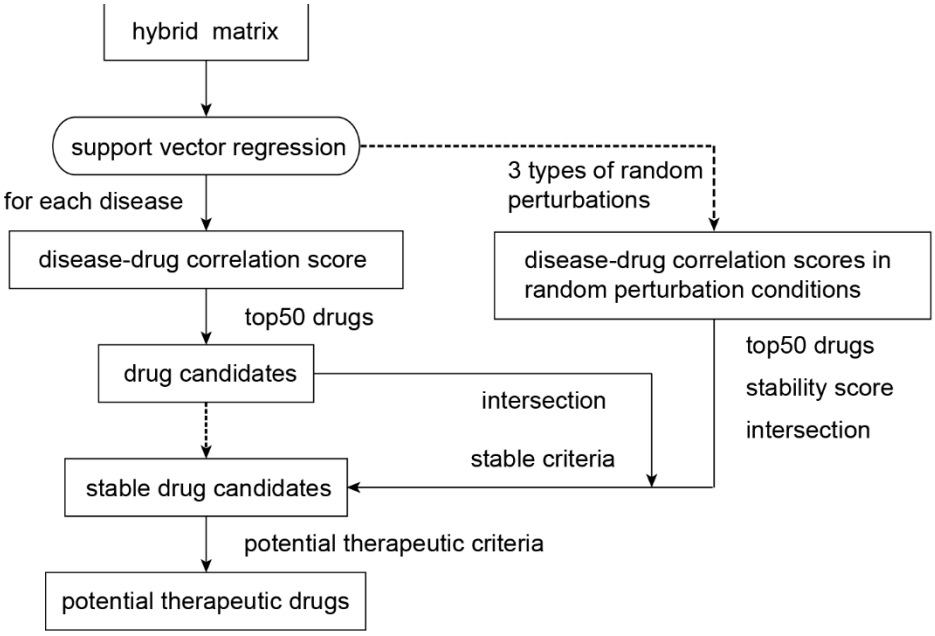


Figure S8. Stepwise screening process for potential therapeutic drugs for each disease.

Document S1
The whole set of findings on vascular disease.

1. Results

1.1. Screening for potential therapeutic drugs for vascular disease

To further explore the generalizability of the drug repositioning strategy, we applied this method to 49 vascular diseases from MeSH branch (C14.907) (Supplementary Figure S1, File S5 1_C14.907_CorScore, File S5 2_stability_scores_boxplot). Around these diseases, we mainly analyzed cerebrovascular disease, 25 potential therapeutic drugs were eventually identified (Supplementary Figure S2; File S2 Table S6). The GO enrichment analysis of these screened potential therapeutic drug targets showed that the drug target genes of the predicted drugs for the cerebrovascular disease were mainly enriched in some GO terms relateared to activity of some ions, proteins, and channels. In addition, information on drug targets of known therapeutic drugs for disease and disease pathogenic genes was noticed. Similarly, it could be seen that analogous enrichment trends in GO enrichment analysis of drug targets of known drugs. This situation was also manifested in the KEGG enrichment analysis. It could also be noticed that the drug targets of screened potential therapeutic drugs and known therapeutic drugs for the disease were mainly enriched in some pathways related to drug addiction and signal transduction (Supplementary Figure S3).

For cerebrovascular disease, the drug targets of its associated drugs with pathogenic gene enrichment to the KEGG pathway with GO terms such as hsa04750: Inflammatory mediator regulation of TRP channels, GO:0042310: vasoconstriction, etc. (Supplementary Figure S4) had corresponding literature support. Numerous studies have shown that certain stimuli contribute to the development of vascular disease. Atherosclerosis is thought to be the main factor responsible for most cardiovascular diseases. The role of infection is thought to provide a key inflammatory stimulus[33]. Nitsa A et al. proved that vitamin D deficiency has been associated with activation of the pro-inflammatory mechanism, promoting atherogenesis[34].Kim JH et al. studied and learned that greater peripheral vasoconstriction with mental stress, denoted by a low sPAT ratio, is associated with a higher risk of adverse cardiovascular outcomes in patients with coronary artery disease[35].

At the genetic level, it was observed that the genomes associated with cerebrovascular disease could be broadly classified into several gene families, almost every gene family had been validated in the literature as causative genes or therapeutic targets associated with vascular disease (Supplementary TableS3).

Esteban G et al. proved that JL72 is a good and selective MAO-A inhibitors, thus possible modulators of the monoaminergic neurotransmission that behaves as a multitarget ligand able to modulate monoaminergic transmission and besides showing an anti-inflammatory profile, both pathways known to be altered in neurological disorders. This suggests that JL72 is a promising lead compound for further development of drugs to be used in the therapy of cerebrovascular and neurological diseases[27]. From our screened potential therapeutic drugs for cerebrovascular disease: Tranylcypromine (DB00752) is a monoamine oxidase inhibitor. Tranylcypromine has two targets: MAO-A and MAO-B. This monoamine oxidase inhibitor is effective in the treatment of major depression, dysthymic disorder, and atypical depression. It also is useful in panic and phobic disorders (From AMA Drug Evaluations Annual, 1994, p311). This suggested that tranylcypromine may hold promise as a therapeutic drug for cerebrovascular diseases from pharmacological aspects such as monoamine oxidase inhibitors.

Combined with the above analysis, this proved the accuracy and stability of the prediction results from a functional perspective. The pharmacotherapeutic mechanisms of some drugs could be explained by the rich functional classes of their drug target genes.

On the other hand, for screened potential therapeutic drugs for a disease, by searching PubMed to find relevant literature, we found that some of the screened potential therapeutic drugs had been shown to have a therapeutic effect on the disease in animal experiments or there were relevant experiments to support the indirect therapeutic promotion of the drug for the treatment of the disease. For instance, in cerebrovascular disease 's prediction of stable drug outcomes by the DDCM method, we found that these drugs were confirmed by the corresponding literature through a search of the literature.Tyramine(DrugBankID:DB08841[36]),Dantrolene(DrugBankID:DB01219[37]),Aripiprazole(DrugBankID:DB01238 [38]).

1.2. Drug research of similar vascular disease in MeSH branches

For these cardiovascular diseases in the MeSH branch, four diseases from one of the sub-branches of this branch were selected for analysis from different perspectives. These four diseases were cerebrovascular disease, brain ischemia, brain infarction and cerebral infarction in the same branch based on the hierarchical relationship of the MeSH branch (Supplementary Figure S5).

The overlap between the drug target genes of the predicted potential therapeutic drugs and the target genes of the known drugs and the genes of the diseases was examined for the four diseases, and it could be found that the degree of overlap between the predicted potential therapeutic drugs and the drug targets of the known drugs for these four similar diseases was relatively large, while the degree of overlap with the pathogenic genes was smaller (Supplementary Figure S6A a-d). This indicated that the therapeutic mechanisms of both predicted potential therapeutic drugs and known therapeutic drugs were similar, while differed from the pathogenic mechanisms of the diseases. In addition, the drug targets of the predicted potential therapeutic drugs, the drug targets of the known therapeutic drugs, and the pathogenic genes of the four diseases overlapped to some extent (Supplementary Figure S6B a-c), indicating that the four diseases were similar in their respective therapeutic and pathogenic mechanisms, which was further illustrated by the similarity of the four diseases since they were taken from the same branch of MeSH.

By predicting potential therapeutic drugs for these diseases, common therapeutic drugs could be found between these four cardiovascular diseases. Also, there was some degree of overlap in the known therapeutic drugs for these diseases (Supplementary Figure S7 A,B).

Among the known drugs for the four diseases, where Aspirin (DB00945) and Nimodipine (DB00393) are the known drug for cerebrovascular disease, brain ischemia, brain infarction, and cerebral infarction. (Aspirin is a salicylate used to treat pain, fever, inflammation, migraines, and reducing the risk of major adverse cardiovascular events. Nimodipine is a calcium channel blocker used to improve neurological outcomes in patients with subarachnoid hemorrhage due to a ruptured intracranial aneurysm.)

Among the predicted potential therapeutic drugs for the four diseases, Dopamine (DB00988) was one of the predicted potential therapeutic drugs common to cerebrovascular disease, brain ischemia, and cerebral infarction. Dopamine is a catecholamine neurotransmitter used to treat hemodynamic imbalances, poor perfusion of vital organs, low cardiac output, and hypotension. Frishman WH et al proved that dopamine is a parenteral agent that selectively activates both DA1 and beta 2 adrenergic receptors and is being evaluated in patients with CHF and in individuals with postoperative left ventricular dysfunction. A group of selective DA2 receptor agonists is being evaluated as long-term treatment for systemic hypertension[39].

We have demonstrated a degree of overlap between the potential therapeutic drugs predicted by the DDCM approach for these four diseases under the same MeSH branch, as well as confirmed by certain literature.

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