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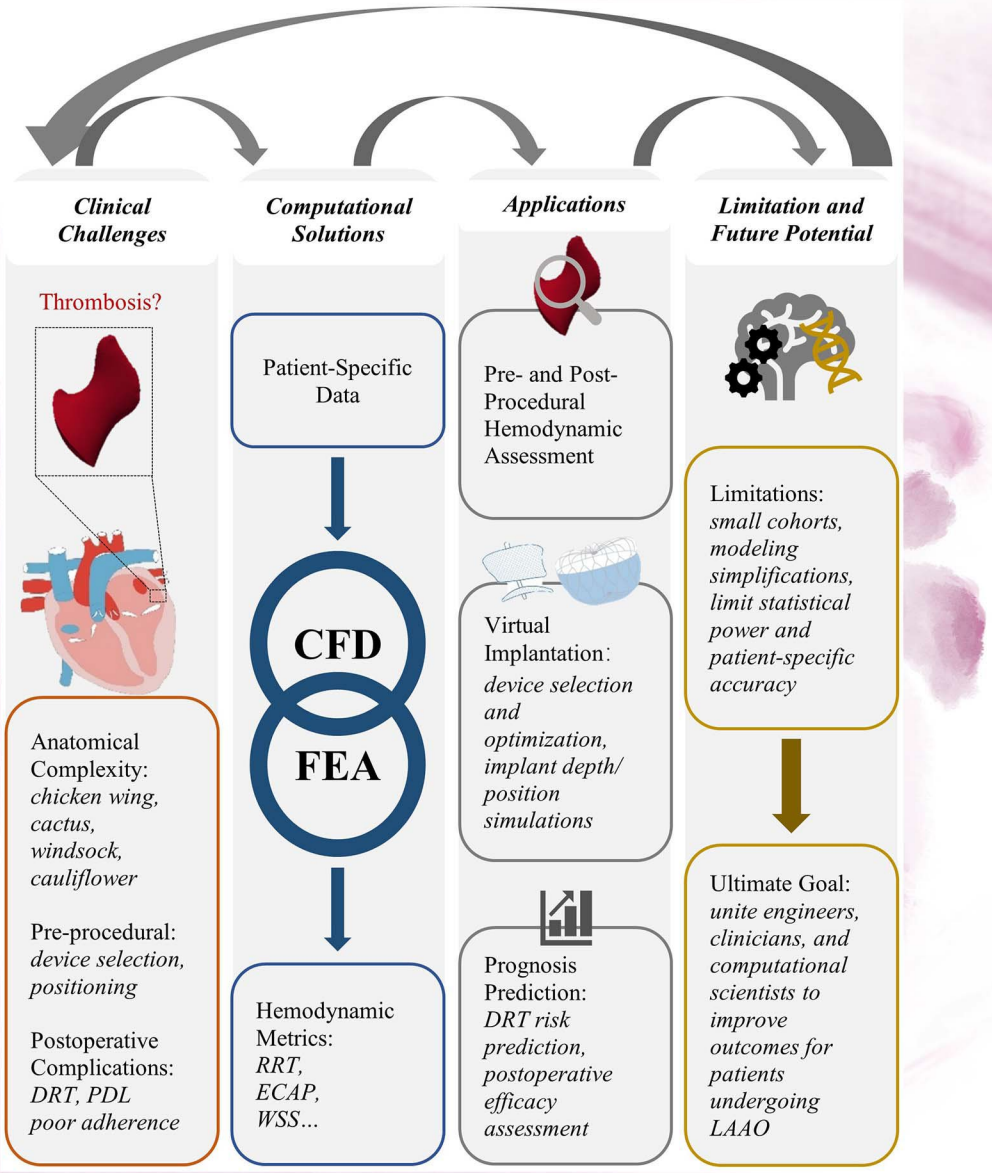

Computer simulations in left atrial appendage occlusion: Current applications and future potential

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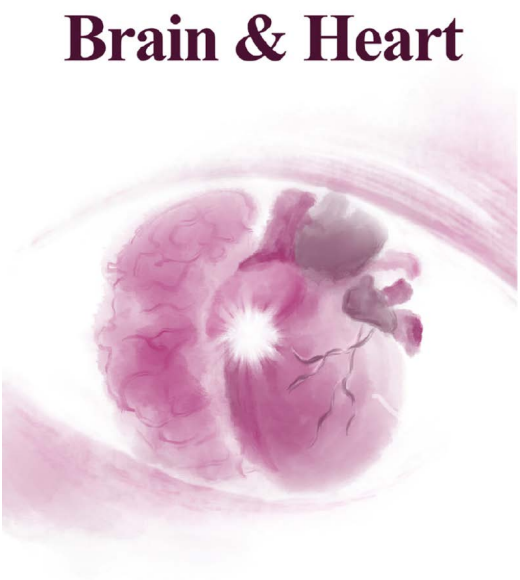

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AccScience Publishing
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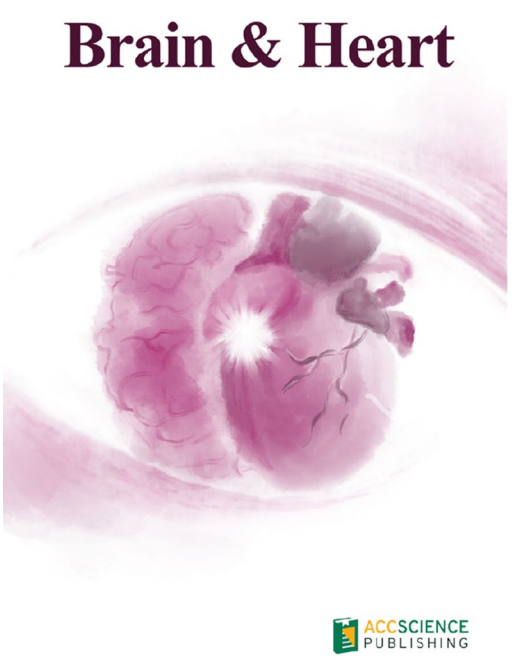

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REVIEW ARTICLE

Serum autoantibodies as biomarkers in atherosclerotic disease

Takaki Hiwasa*

Department of Neurological Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan

Abstract

Atherosclerosis-related diseases such as acute ischemic stroke (AIS), acute myocardial infarction, and chronic kidney disease remain major global health burdens, yet the potential role of autoantibodies in these conditions has only recently begun to be recognized. This review summarizes the methodology and characteristics of atherosclerosis autoantibody biomarkers reported in our previous studies. In our earlier research, we performed a large-scale screening of serum autoantibody markers for atherosclerotic diseases, such as AIS, using expression cloning and protein array methods, and identified 106 antibodies. Among these, 34 markers were selected as potentially useful diagnostic markers, with serum antibody levels found to be higher in patients with atherosclerosis-related diseases than in healthy donors. The autoantibody markers were highly sensitive, with elevated levels observed not only in patients with AIS but also in those with transient ischemic attack, a prodromal stage of AIS. Thus, the autoantibodies may serve as predictive markers for AIS. The potential use of autoantibodies as targets for prevention and/or treatment is also discussed in this review.

Keywords: Autoantibodies; Prognostic biomarkers; Cancer prognosis; Atherosclerosis-related diseases; Serum antibody markers

***Corresponding author:**
Takaki Hiwasa
(hiwasa_takaki@faculty.chiba-u.jp)

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1. Introduction

Acute ischemic stroke (AIS), acute myocardial infarction (AMI), and chronic kidney disease (CKD) are primarily caused by atherosclerosis,[1] a major complication of diabetes mellitus (DM).[2] Autoantibodies have rarely been investigated because these atherosclerosis-related diseases have not been recognized as autoimmune diseases. It was previously believed that the development of autoantibodies occurred only in autoimmune diseases and cancer.[3,4] Since 2003, we have been the first researchers worldwide to conduct large-scale screening for atherosclerosis-associated autoantibodies and to examine serum antibody levels. When some autoantibodies were found to exhibit higher serum levels in patients with atherosclerosis-related diseases than in healthy donors (HDs), they were reported as promising atherosclerosis autoantibody biomarkers (AABs). This review summarizes the methodology and characteristics of these AABs reported in our previous studies.

2. Reasons for searching for autoantibodies in atherosclerosis

In 2002, we began searching for antigens recognized by immunoglobulin (Ig) G antibodies present in the sera of patients with esophageal cancer (EC) using the

serological identification of antigens by recombinant complementary DNA (cDNA) expression cloning (SEREX) method.[5,6] When serum antibody levels were measured against the identified antigens, we found that antibodies were present at varying degrees against most human proteins. Serum samples with high antibody levels were not significantly observed in patients with cancer or autoimmune diseases, but were found in HDs or other patients. These findings led us to consider that serum antibodies might reflect an individual's medical history. Thus, specific autoantibodies may be elevated in association with serious diseases such as cerebrovascular and cardiovascular diseases (CVDs), which are mainly caused by atherosclerosis. Therefore, we began searching for atherosclerosis-associated autoantibodies.

3. Advances in comprehensive screening technology for autoantigens

3.1. Screening method 1: Serological analysis of tumor antigens by recombinant cDNA expression cloning

Chen *et al*.[7] introduced the expression cloning method to identify tumor antigens recognized by serum immunoglobulin G (IgG) from patients with cancer. First, a cDNA library was constructed using mRNA from cancer cells and inserted into λZAP II or Uni-ZAP phages. *Escherichia coli* (*E. coli*) was infected with the phage cDNA library and plated onto agar plates. After induction of cDNA expression, the expressed protein products were blotted onto nitrocellulose membranes, which were then reacted with patient serum IgG and detected using alkaline phosphatase (ALP)-conjugated secondary antibodies (anti-human IgG and a substrate. Each monoclonalized phage clone contained only one cDNA, which could be converted to pBluescript plasmids using helper phages. The cDNA insert in each plasmid was sequenced, and the corresponding gene was identified using BLAST. SEREX is a comprehensive method for screening autoantigens. Most procedures in the SEREX method involve the use of genes and bacteria, making it possible to perform large-scale, high-throughput screening of antigenic proteins that are otherwise difficult to analyze.

Even if the obtained SEREX clone does not contain a full-length cDNA, the clone clearly contains the epitope recognized by serum antibodies. Therefore, SEREX clones can be used to prepare antigenic recombinant gene products, which can then serve as antigens to measure antibody levels. The prokaryotic expression vectors, pGEX-4T and pGEX-6P, are particularly useful for obtaining large amounts of recombinant proteins because they efficiently express cDNA as proteins in *E. coli*.

3.2. Screening method 2: Protein array

Large-scale protein arrays enable the selection of antigenic proteins recognized by IgG antibodies in patient sera. In the previous research, we used the ProtoArray Human Protein Microarrays (version 4.0, Thermo Fisher Scientific, USA), which contained 9,480 proteins.[8,9] The data were processed using Prospector software (Thermo Fisher Scientific, USA), which employs *M*-statistics to distinguish positive from negative reactions.[8] Representative ProtoArray results are publicly available in the Figshare database (https://figshare.com/articles/dataset/Results_of_protein_array_for_atherosclerosis/25906330). We selected antigenic proteins that showed more than 50% reactivity against patient sera and less than 10% reactivity against HD sera.[9] As the epitope sites in protein array-selected proteins are unknown, the full-length proteins were prepared by recombining the full-length cDNA into pGEX-4T and used them as antigens.

3.3. Peptide antigens

When a small peptide containing only one epitope is available, more specific antibody levels against the restricted epitope can be measured compared with those measured using large proteins containing multiple epitopes. Possible epitope sites in antigen-candidate proteins were predicted using the ProPred program (http://www.imtech.res.in/raghava/propred/).[10] Peptide arrays covering the full-length candidate proteins were also used and were successfully applied to identify useful peptides containing one or a few epitopes.[11] The peptide arrays were synthesized on cellulose membranes using 9-fluorenylmethyloxycarbonyl amino acids with the Auto Spot Robot ASP222 (ABIMED Analysen-Technik GmbH, Germany), as described in the previous study.[12] Finally, biotinylated synthetic 14–18mer peptides containing the screened amino acid sequences were used to measure antibody levels. The amino acid sequences and purities of the peptides used are listed in Table 1.

4. Advances in measurement technology for antibody levels

4.1. Enzyme-linked immunosorbent assay

After preparing protein and peptide antigens, serum autoantibody levels in patients and controls were compared to select useful antigens. In a previous study, enzyme-linked immunosorbent assay (ELISA)—a widely used method—was employed to measure antibody levels. First, antigen proteins were immobilized in the

Table 1. Amino acid sequences and purities of the peptides used

Name	Peptide structure	Purity (%)
CPSF2	Biotin-QVRLKDSLVSSLQFC-COOH	99.0
SOSTDC1	Biotin-KITVVTACKCKRYTR-COOH	84.3
CTNND1	Biotin-LRNVSSERSEARRKL-COOH	92.8
XRCC4	Biotin-KRFILVLNEKKTKI-COOH	91.6
CLDND1	Biotin-FRYNGTVGLWRRCIT-COOH	97.6
FOXJ2	Biotin-KMVNRLNWSSIEQSQ-COOH	98.3
SH3BP5	Biotin-MGRMRQLEKKLKRA-COOH	94.9
IFI16	Biotin-GKKYKNIVLLKGLE-COOH	98.6
LIMA1	Biotin-TKILRAQSRSASGRK-COOH	94.7
CCNG2	Biotin-KKHSKINDTEFFYWR-COOH	95.1
DIDO1	Biotin-AMAASKKTAPPGSAVGKQ-COOH	98.4
ASXL2	Biotin-QRFMLGFAGRRTSK-COOH	97.0

wells of a 96-well microtiter plate via hydrophobic bonds between the antigenic protein and the polycarbonate plate. Subsequently, the plate was incubated, washed, and blocked with a blocking reagent such as albumin (ALB) or fetal bovine serum. After further incubation and washing, serum was added. Following another wash, bound IgG antibodies were detected by incubating horseradish peroxidase-conjugated anti-human IgG antibodies and adding a peroxidase substrate. The absorbance of each well was measured using a microplate reader.[13-15] This method was established; however, IgG subtypes varied among individuals, and some exhibited stronger hydrophobicity than ALB and blocking reagents. Such highly hydrophobic IgGs can bind directly to the polycarbonate plate even after blocking and react with the secondary detection antibody—anti-human IgG—without antigen mediation. This results in variable background levels depending on the individual serum, interfering with accurate antibody level measurement.

4.2. Amplified luminescent proximity homogeneous assay-linked immunosorbent assay (AlphaLISA)

AlphaLISA (Revvity, USA) is a recently developed method for measuring antigen and antibody levels. In AlphaLISA, glutathione-conjugated and streptavidin-conjugated donor beads bind to glutathione-S-transferase fused antigenic proteins and biotin-tagged antigenic peptides, respectively. Anti-human IgG-conjugated acceptor beads bind to serum IgG antibodies. When serum antibodies recognize antigens, the two beads approach each other, producing luminescent light. Chemical emission at 615 nm, induced by excitation at 680 nm, is measured using an EnSpire Alpha microplate reader (Revvity, USA), as described in previous studies.[16-19] The resultant photon counts reflect the extent of antigen–antibody binding. The dynamic range of AlphaLISA is typically three orders of magnitude (1,000–1,000,000 emission photon counts), but consistent results can be obtained even outside this range.

The experimental procedure requires only the mixing of antigens, sera, and the two beads, without plate washing; therefore, background levels are very low and stable. As AlphaLISA uses 384-well plates, it is suitable for high-throughput mass screening. The amount of antigen required for AlphaLISA is 1/5–1/20 of that required for ELISA.[20] An additional advantage is that antibody levels can be measured even with partially purified antigens, because only antigens bound to donor beads through tags produce photons on binding to IgG antibodies. However, the results can be affected by temperature, oxygen, and light. Therefore, technical expertise and appropriate laboratory conditions are required to mitigate these effects. The introduction of AlphaLISA and its sophisticated technology has greatly facilitated the selection of antibody markers.

A flowchart of antibody marker screening and selection is shown in Figure 1, and representative AlphaLISA results are shown in Figure 2.

5. List of AABs

To date, several autoantibody biomarkers in metabolic and atherosclerotic diseases have been reported. For example, antibodies against phospholipids,[21] apolipoprotein A-1,[22,23] oxidized low-density lipoprotein,[24,25] and heat shock proteins (HSPs)[24,26] have been identified for CVD; antibodies against HSP60 for stroke;[27] and antibodies against insulin,[28] glutamic acid decarboxylase (GAD),[29] and protein tyrosine phosphatase IA-2[30,31] for DM. It has also been reported that some autoantibodies in patients with systemic lupus erythematosus were associated with CVD.[32,33]

In our previous study, we performed large-scale SEREX screening and protein array analysis to screen antigenic proteins recognized by serum IgG in patients with atherosclerosis and/or AIS. Table 2 lists the identified AABs in our prior studies. These antigenic proteins can be functionally classified into several groups:

(i) Cytoskeletal proteins and their binding proteins: ACTR3B, ANK1, CEP290, DST, ECSCR, KIF20B, LIMA1, NAV2, TPM3, and TUBB2C
(ii) Proteases and their inhibitors: ADAMTS7, BMP1, MMP1, NRD1, PCSK9, PRCP, and SERPINE1
(iii) Bone morphogenetic protein (BMP)-related proteins: BMP1, CRIM1, DAN, SOSTDC1, and TMEFF1

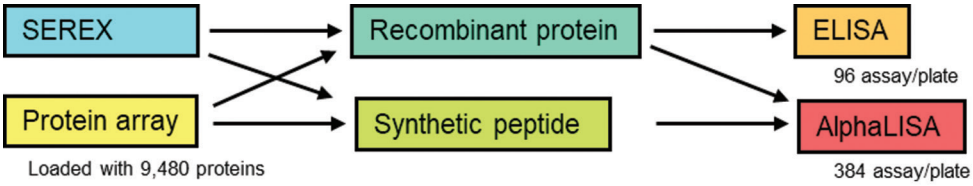

Figure 1. Flow chart of antibody marker screening and selection. The first screening was performed using SEREX and protein array methods. Subsequently, the antigens, such as recombinant proteins and synthetic peptides, were prepared and used to evaluate serum antibody levels using ELISA or AlphaLISA. Given the relatively low sensitivity of ELISA, synthetic peptides with low antigenicity are not suitable for use as antigens. Image created by the author.
Abbreviations: AlphaLISA: Amplified luminescent proximity homogeneous assay-linked immunosorbent assay; ELISA: Enzyme-linked immunosorbent assay; SEREX: Serological analysis of recombinant expression cloning.

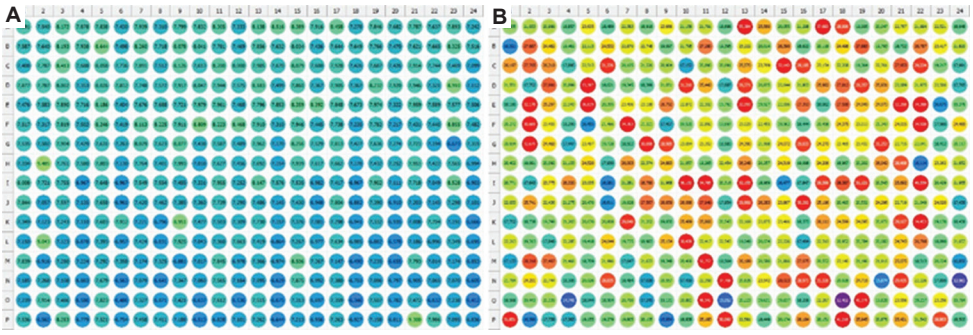

Figure 2. Representative results of AlphaLISA. (A) GST and (B) GST-RNF151 were mixed with serum samples, with one serum sample added per well of the 384-well plate. Glutathione-conjugated donor beads and anti-human immunoglobulin G-conjugated acceptor beads were then added. The AlphaLISA signals are shown, where wells with higher photon counts appear in deeper red. Image created by the author.
Abbreviations: AlphaLISA: Amplified luminescent proximity homogeneous assay-linked immunosorbent assay; GST: Glutathione-S-transferase.

(iv) Cytokines: ADIPOQ, CCL8, CSF2, and FGF7
(v) HSPs: DNAJA1, DNAJC2, HSP8, and HSPB1
(vi) Nuclear export: NEMF, RANBP2L1, RBCK, and XPO1
(vii) Glycolysis/tricarboxylic acid cycle enzymes: ALDOA, FH, PCK1, and PFKFB3
(viii) DNA repair-related proteins: RPA1, RPA2, XRCC4, and FOXJ2
(ix) Intracellular trafficking-related proteins: COPE, SH3BP5, and SNX16
(x) Translation factors: EEF1A1, EEF1G, and EIF2A
(xi) Transcription factors: ASXL2, MYBBP1A, and TFAM
(xii) Ubiquitination-related proteins: ATXN3, SPATA2, and UBE2E3
(xiii) Membrane channels: ATP2B4 and MAGT1.

The frequent identification of cytoskeletal proteins may partly be attributable to their abundant expression. In addition to anti-HSP60 antibodies,[27] we have identified four more HSPs associated with atherosclerosis. The presence of serum antibodies against secreted or membrane-integrated proteins such as cytokines, BMP-related proteins, proteases and their inhibitors, and membrane channel proteins suggests possible direct binding between antigens and serum antibodies. Thus, serum antibodies may affect the functions of these antigens.

6. Disease specificity or commonality of AABs

6.1. Association of AABs with diseases

Table 3 summarizes the association of AABs with atherosclerosis-related diseases such as AIS, transient ischemic attack (TIA), CVD (e.g., AMI and unstable angina pectoris), DM, CKD (types 1, 2, and 3), and cancers (e.g., EC and colorectal cancer [CRC]).

All 34 AABs in Table 3 showed significantly higher levels in patients with AIS than in HDs, and similar increases were observed in patients with TIA for 27 AABs. The serum levels of AP3D1-Abs, ASXL2-Abs, ATP2B4-Abs, BMP1-Abs, KIAA0513-Abs, SC65-Abs, SNX16-Abs, TMEFF1-Abs, COPE-Abs, LRPAP1-Abs, CLDND1-Abs, DNAJC2-Abs, UBE2E3-Abs, and FOXJ-Abs were commonly elevated in patients with all atherosclerotic diseases and gastrointestinal cancers compared with HDs. CPSF2-Ab levels were significantly higher in patients with ischemic stroke (AIS and TIA) and DM, but not in those with CVD or CKD, relative to HDs. The levels of LGSLS9-Abs, PCK1-Ab, and SOSTDC1-Abs were not elevated in patients with CVD compared with HDs. The levels of CTNND1-Abs, XRCC4-Abs, and DIDO1-Abs were elevated in patients with ischemic stroke and CKD but not in those with CVD and DM. MMP1-Ab levels were elevated in AIS, CVD, and DM but not in CKD,

Table 2. List of atherosclerosis autoantibody biomarkers

Abbreviated name	Accession number	Full name	Screening method	Reference
ACTR3B	NM_020445.6	Actin-related protein 3 homolog B	SEREX	17
ADAMTS7	NM_014272.3	ADAM metallopeptidase with thrombospondin type 1 motif, 7	SEREX	34
ADIPOQ	NM_001177800	Adiponectin, C1Q, and collagen domain containing	Prediction[a]	35
ALDOA	NM_184041	Aldolase A	SEREX	36
ANK1	BC030957.1	Ankyrin 1, erythrocytic	Protein array	10
AP3D1	NM_003938.8	Adaptor-related protein complex 3 subunit delta 1	SEREX	37
ASXL2	NM_018263.6	Additional sex combslike 2	SEREX	18
ATP2B4	NM_001001396.2	ATPase, Ca^{2+}transporting, plasma membrane 4	Protein array	38
ATXN3	BC033711.1	Ataxin 3	Protein array	39
BAZ1B	NM_032408	Bromodomain adjacent to zinc finger domain, 1B	SEREX	34
BMP1	NM_006129.4	Bone morphogenetic protein 1	SEREX	15,38
BRAT1	NM_152743	BRCA1-associated ATM activator 1	SEREX	40
CBX1	NM_001127228	Chromobox homolog 1	SEREX	16
CBX5	NM_012117	Chromobox homolog 5	SEREX	16
CCL8	NM_005623	C-C motif chemokine ligand 8	Prediction	UP[b]
CCNG2	BC032518.1	Cyclin G2	Protein array	10
CEP290	NM_014684	Centrosomal protein 290 kDa	SEREX	34
CLDND1	NM_019895.1	Claudin domain-containing 1	Protein array	10
COPE	CR456886	Coatomer protein complex subunit epsilon	SEREX	41
CPSF2	NM_017437.1	Cleavage and polyadenylation specific factor 2, 100 kDa	Protein array	34
CRIM1	NM_016441.2	Cysteine-rich transmembrane BMP regulator 1 (chordin-like)	SEREX	34
CSF2	NM_000758.4	Colony-stimulating factor 2	Prediction	42
CTNNA1	NM_001903.5	Catenin alpha 1	SEREX	17
CTNND1	NM_001085458	Catenin delta 1	Protein array	10
DAN/NBL1	X66872.1	DAN family BMP antagonist	Prediction	43
DEF8	NM_207514	Differentially expressed in FDCP 8 homolog (mouse)	SEREX	34
DHPS	NM_001930	Deoxyhypusine synthase	Protein array	20
DIDO1	BC000770.1	Death inducer-obliterator-1	Protein array	34
DNAJA1	NM_001539	DnaJ heat shock protein family (Hsp40) member A1	SEREX	44
DNAJC2	NM_014377	DnaJ heat shock protein family (Hsp40) member C2	SEREX	44
DST	NM_015548	dystonin	SEREX	34
ECSCR	NM_001077693.4	Endothelial cell surface expressed chemotaxis and apoptosis regulator	SEREX	39
EEF1A1	NM_001402.5	Eukaryotic translation elongation factor 1 alpha 1	SEREX	45
EEF1G	NM_001404.4	Eukaryotic translation elongation factor 1-gamma	SEREX	34
EIF2A	NM_032025.3	Eukaryotic translation initiation factor 2A, 65 kDa	SEREX	34
FER1L3	NM_133337	Myoferlin	SEREX	34
FGF7	NM_002009.4	Fibroblast growth factor 7	Prediction	39
FH	NM_000143	Fumarate hydratase	SEREX	36
FOXJ2	NM_018416.2	Forkhead box J2	Protein array	34
GOPC	NM_001017408	Golgi-associated PDZ and coiled-coil motif containing	SEREX	34
H3F3B	NM_005324	H3 histone, family 3B	SEREX	34
HM13	AF483215	Histocompatibility (minor) 13	SEREX	34

(Cont'd)

Table 2. ***(Continued)***

Abbreviated name	Accession number	Full name	Screening method	Reference
HSPA8	NM_006597	Heat shock 70 kDa protein 8	SEREX	34
HSPB1	NM_001540.3	Heat shock 27kda protein 1	SEREX	34
IFI16	NM_001206567.2	Interferon-gamma inducible protein 16	SEREX	39
JMJD6	NM_015167	Jumonji C-domain-containing 6	SEREX	46
KIAA0020	NM_014878	Pumilio RNA-binding family member 3	SEREX	4
KIAA0513	BC030280.1	Kiaa0513	Protein array	9
KIF20B	NM_001284259.2	Kinesin family member 20B	SEREX	39
LGALS9	NM_009587	galectin 9	SEREX	15
LIMA1	NM_001113546	LIM domain and actin binding 1	SEREX	39
LRPAP1	NM_002337	Low-density lipolipoprotein receptor–related protein–associated protein 1	SEREX	45,47
MAGT1	NM_032121.5	Magnesium transporter 1	SEREX	34
MMP1	NM_002421	Metalloproteinase 1	SEREX	16
MYBBP1A	BC050546.1	MYB binding protein 1a	Protein array	10
NAV2	NM_145117.4	Neuron Navigator 2	SEREX	34
NEK7	NM_133494	NIMA (never in mitosis gene a)-related kinase 7	SEREX	UP
NEMF	NM_004713	Nuclear export mediator factor	SEREX	39
NRD1	NM_002525.3	Nardilysin	Prediction	48
PABPC1	NM_002568.4	Poly (A) binding protein cytoplasmic 1	SEREX	49
PACRG	BC030642	PARK2 co-regulated (PACRG)	Protein array	39
PARC	NM_015089	p53-associated parkin-like cytoplasmic protein	SEREX	34
PCK1	NM_002591.4	Phosphoenolpyruvate carboxykinase 1	SEREX	50
PCSK9	NM_174936.3	Proprotein convertase subtilisin/kexin type 9	Prediction	51
PDCD11	NM_014976.2	Programmed cell death 11	SEREX	17
PFKFB3	NM_004566	6-phosphofructo-2-kinase/fructose -2,6-biphosphatase 3	SEREX	34
PHB2	NM_007273.2	Prohibitin 2	Protein array	39
PHF20	NM_016436	PHD finger protein 20	SEREX	34
PHLDA1	BC018929.1	Pleckstrin homology-like domain family A	Protein array	39
PPP1R15A/ GADD34	NM_014330	Protein phosphatase 1 regulatory subunit 15A	SEREX	15,52
PRCP	NM_005040.1	Prolylcarboxypeptidase	Protein array	53
PSAP	NM_002778	Prosaposin	SEREX	34
RANBP2L1	NM_005054	RAN binding protein 2-like 1	SEREX	34
RBCK1	NM_031229	Ranbp-type and C3HC4-type zinc finger containing 1	SEREX	34
RBPJ	NM_005349	Recombination signal binding protein for immunoglobulin kappa J region	SEREX	34
RNF151	NM_174903	Ring finger protein 151	SEREX	UP
ROCK1	NM_005406	Rho-associated, coiled-coil containing protein kinase 1	SEREX	34
RPA1	NM_002945	Replication protein A1	SEREX	34
RPA2	NM_002946	Replication protein A2	SEREX	15
RPL3 R	NM_000967	Ribosomal protein Ll3t	SEREX	34
SC65	BC007942	Synaptonemal complex protein SC65	SEREX	15
SERPINE1	NM_000602	Serpin peptidase inhibitor, clade E member 1	SEREX	19
SH3BP5	NM_004844	SH3 domain-binding protein 5	Protein array	11

(Cont'd)

Table 2. ***(Continued)***

Abbreviated name	Accession number	Full name	Screening method	Reference
SMARCA4	NM_001128847	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4	SEREX	34
SNX16	NM_022133.4	Sorting nexins 16	SEREX	54
SOSTDC1	NM_015464	Sclerostin domain-containing 1	Protein array	10
SPARC	NM_003118	Secreted protein acidic and cysteine-rich	SEREX	34
SPATA2	NM_006038.1	Spermatogenesis associated 2	Protein array	39
SPOCK1	NM_004598	SPARC (osteonectin), cwcv, and kazal-like domains proteoglycan 1	SEREX	45
TBC1D2	NM_001267571	TBC1 domain family, member 2	SEREX	34
TBC1D4	NM_014832	TBC1 domain family, member 4	SEREX	34
TEX261	NM_144582	Testis expressed 261	SEREX	34
TFAM	NM_003201	Transcription factor A, mitochondrial	Protein array	10
THBS1	NM_003246	Thrombospondin 1	SEREX	34
TMEFF1	NM_003692	Transmembrane protein with EGF-like and two follistatin-like domains 1	SEREX	34
TOP3B	NM_003935	DNA topoisomerase III beta	Protein array	10
TPM3	NM_153649	Tropomyosin 3, transcript variant 2	SEREX	39
TSTD2	NM_139246.3	Thiosulfate sulfurtransferaselike domaincontaining 2	Protein array	55
TUBB2C	NM_006088	Tubulin, beta2C	SEREX	45
TYMS	NM_001071	Thymidylate synthetase	SEREX	34
UBE2E3	NM_006357	Ubiquitin-conjugating enzyme E2 E3	Protein array	8
WD36	NM_139281.2	T-cell activation WD repeat protein	SEREX	15
WDR1	NM_017491	WD repeat domain 1	SEREX	40
XPO1	NM_003400.3	Exportin 1	SEREX	34
XRCC4	NM_022406	X-ray repair cross-complementing 4	SEREX	34
ZFP36L1	NM_004926	ZFP36 ring finger protein like 1	SEREX	34

Notes: [a]Predicted molecules as atherosclerosis autoantigens. [b]"UP" indicates unpublished data.

EC, or CRC. The levels of IFI16-Abs, LIMA1-Abs, RPA1-Abs, RPA2-Abs, PPPIR15A-Abs, FIR1L3-Abs, HSPB1-Abs, CCNG2-Abs, DHPS-Abs, and TUBB2C-Abs were associated with all atherosclerotic diseases but not with EC. Each antibody biomarker represents different disease specificity; therefore, a combined analysis of multiple AAMs may provide greater diagnostic precision.

6.2. Common association of AABs with atherosclerotic diseases and cancer

Approximately half of the AABs were commonly associated with DM and cancer (Table 3). Substantial evidence indicates that cancer is associated with atherosclerosis-related diseases. For example, DM is a risk factor for cancers such as EC and CRC,[56,57] and cancer survivors have a higher risk of developing cardiovascular risk factors compared with individuals without cancer.[58] Molecular pathways and many etiological and mechanistic processes are shared between atherosclerosis and cancer.[59] The common association of some AABs with both atherosclerosis and cancer further supports the close relationship between these two disease groups.

7. Correlation of AABs levels with patients' data

Spearman's correlation analysis of AAB levels shown in Table 4 was performed against patient data, including age; an obesity index (body mass index [BMI]); a stenosis index (maximum intima–media thickness [max-IMT]); a hypertension index (blood pressure [BP]); an atherosclerosis risk factor (smoking period [years]); inflammation markers (C-reactive protein and white blood cell count); liver metabolism markers (ALP, thymol turbidity test, zinc sulfate turbidity test, cholinesterase, ALB, ALB/globulin ratio, and total protein); glucose metabolism markers (blood sugar [BS] and glycated hemoglobin [HbA1c]); lipid metabolism markers (high-density lipoprotein cholesterol [HDL-c], low-density

Table 3. Association of antibody biomarkers with diseases

Antibody biomarker	AIS	TIA	CVD	DM	Type-1 CKD	Type-2 CKD	Type-3 CKD	EC	CRC
CPSF2-Ab[a]	**	**	-	***	-	-	-	*	****
LGALS9-Ab[b]	****	-	-	****	****	**	-	-	-
PCK1-Ab[b]	****	*	*	****	**	-	-	**	-
SOSTDC1-Ab[a]	****	-	-	*	****	****	****	*	-
CTNND1-Ab[a]	*	*	-	-	****	****	-	-	-
XRCC4-Ab[a]	***	**	-	-	****	****	****	**	**
DIDO1-Ab[b]	***	***	-	-	****	****	****	-	*
MMP1-Ab[b]	****	***	*	**	*	-	-	-	-
AP3D1-Ab[b]	***	***	****	****	****	****	****	****	***
ASXL2-Ab[b]	***	**	****	****	****	**	****	****	**
ATP2B4-Ab[b]	****	****	**	****	****	****	****	**	ND
BMP1-Ab[b]	**	**	****	****	****	****	***	***	ND
KIAA0513-Ab[b]	***	**	****	****	****	****	****	****	****
SC65-Ab[b]	****	**	**	****	****	****	****	****	***
SNX16-Ab[b]	****	**	****	****	****	****	****	****	****
TMEFF1-Ab[b]	***	ND	**	***	****	***	****	****	****
COPE-Ab[b]	****	*	****	****	****	****	****	*	****
LRPAP1-Ab[b]	**	***	*	****	ND	ND	ND	****	****
CLDND1-Ab[a]	****	*	***	**	****	****	****	****	-
DNAJC2-Ab[b]	***	*	**	****	****	*	****	****	*
UBE2E3-Ab[b]	***	*	**	****	****	****	****	****	-
FOXJ2-Ab[a]	****	***	***	***	****	****	****	**	-
SH3BP5-Ab[a]	****	***	****	****	****	****	****	*	-
HSP8-Ab[b]	***	**	*	****	***	*	-	*	*
IFI16-Ab[a]	**	***	*	****	****	****	****	-	-
LIMA1-Ab[a]	**	***	**	****	****	****	****	-	-
RPA1-Ab[b]	****	-	***	****	****	-	-	-	-
RPA2-Ab[b]	****	*	**	****	***	*	-	-	-
PPPIR15A-Ab[b]	****	**	****	****	****	***	***	-	-
FER1L3-Ab[b]	****	-	*	****	***	**	-	-	-
HSPB1-Ab[b]	***	-	**	****	****	**	-	-	-
CCNG2-Ab[a]	***	-	****	****	****	****	***	-	-
DHPS-Ab[b]	***	***	****	****	****	***	-	-	*
TUBB2C-Ab[b]	****	**	***	****	****	**	**	-	ND

Notes: Summary of *p*-values obtained using the Kruskal–Wallis test for comparisons between healthy donors and patients with AIS, TIA, CVD (including acute myocardial infarction and unstable angina pectoris), DM, diabetic kidney disease (Type-1 CKD), nephrosclerosis (Type-2 CKD), glomerulonephritis (Type-3 CKD), EC, and CRC. [a]Peptide antigens. [b]Protein antigens. *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001. "-" indicates no significant difference, whereas "ND" indicates not determined.

Abbreviations: AIS: Acute ischemic stroke; CKD: Chronic kidney disease; CRC: Colorectal cancer; CVD: Cardiovascular disease; DM: Diabetes mellitus; EC: Esophageal cancer; TIA: Transient ischemic attack.

lipoprotein cholesterol [LDL-c], total cholesterol [T-CHO], and triglycerides [TG]); a pancreatic marker (amylase [AMY]); and other blood test data (Table 4).

Since most AABs were selected using sera from patients with atherosclerosis, the levels of many AABs were correlated to more or less degrees with max-IMT, which

Table 4. Spearman's correlation analysis between serum autoantibody levels and clinical parameters in Sawara Hospital cohort

Antibody	Age	BMI	Max- IMT	BP	Smoking period	CRP	WBC	ALP	TTT	ZTT	CHE	ALB	A/G ratio	TP	BS	HbA1c	HDL-c	LDL-c	T-CHO	TG	AMY
CPSF2-Ab[a]	****	-	****	-	*	**	-	-	-	-	*[c]	****[c]	**[c]	*[c]	-	-	-	*[c]	**[c]	-	-
LGALS9-Ab[b]	****	-	**	*	****	*	*	-	*	-	-	-	-	-	*	-	-	-	-	-	**[c]
PCK1-Ab[b]	-	-	-	-	**	-	-	**	***	-	-	-	-	-	-	-	-	-	-	-	-
SOSTDC1-Ab[a]	****	-	****	****	****	-	-	-	-	-	-	-	-	-	-	-	-	*[c]	-	-	-
CTNND1-Ab[a]	****	**[c]	*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
XRCC4-Ab[a]	***	*[c]	-	-	*	-	-	-	-	*	*[c]	-	-	-	-	-	-	*[c]	*[c]	*[c]	-
DIDO1-Ab[b]	****	-	****	***	***	**	**	*	**	-	*[c]	*[c]	-	**[c]	*	-	-	-	-	-	*[c]
MMP1-Ab[b]	*	-	**	*	****	-	-	-	**	-	-	-	-	-	-	-	-	-	-	-	-
AP3D1-Ab[b]	****	-	****	***	***	-	-	-	**	-	-	-	-	-	-	-	-	*[c]	-	-	*[c]
ASXL2-Ab[b]	****	-	***	***	***	-	**	*	**	-	-	-	-	-	-	-	-	-	-	-	-
ATP2B4-Ab[b]	**	-	**	**	***	-	-	*	**	-	*[c]	-	-	-	-	-	-	-	*[c]	-	-
BMP1-Ab[b]	-	-	**	-	****	-	-	-	*	-	-	-	-	*[c]	-	-	-	-	-	-	-
KIAA0513-Ab[b]	****	-	***	-	**	-	-	*	**	-	-	-	-	-	*	-	-	-	-	-	-
SC65-Ab[b]	*	-	**	-	***	-	*	-	**	-	-	-	-	-	-	-	-	-	-	-	-
SNX16-Ab[b]	****	-	***	***	***	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TMEFF1-Ab[b]	-	-	**	**	****	-	-	-	-	-	-	-	-	-	-	-	-	*[c]	-	-	-
COPE-Ab[b]	**	-	**	***	****	-	*	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LRPAP1-Ab[b]	-	-	-	**	****	-	**	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CLDND1-Ab[a]	**	-	-	-	-	-	-	-	**[c]	*[c]	-	-	-	-	-	-	-	-	-	-	-
DNAJC2-Ab[b]	-	-	-	**	****	-	*	-	**	-	-	-	-	-	-	-	-	-	-	-	-
UBE2E3-Ab[b]	****	-	***	**	**	-	*	*	**	-	-	-	-	-	-	-	-	-	-	-	-
FOXJ2-Ab[a]	**	***[c]	-	-	*	-	*	*	-	-	****[c]	***[c]	-	****[c]	-	-	-	***[c]	**[c]	*[c]	*[c]
SH3BP5-Ab[a]	**	-	***	**	***	-	-	*	-	-	-	-	-	-	-	-	-	*[c]	-	-	-
HSP8-Ab[b]	***	-	**	*	****	*	-	*	*	-	-	-	-	-	-	-	-	*[c]	-	-	-
IFI16-Ab[a]	**	-	*	**	****	*	**	-	*	-	-	-	-	-	-	-	-	-	-	-	-
LIMA1-Ab[a]	-	*	-	-	**	-	-	-	-	-	-	-	-	-	-	-	-	-	*	-	*
RPA1-Ab[b]	**	-	*	*	***	-	**	-	*	-	-	-	-	-	-	-	-	-	-	-	-
RPA2-Ab[b]	*	-	*	-	**	-	*	-	**	-	-	-	-	-	-	-	-	-	-	-	-
PPPIR15A-Ab[b]	****	-	***	*	***	-	*	-	*	-	-	-	-	-	-	-	-	-	-	-	-
FER1L3-Ab[b]	****	-	-	-	**	*	-	-	**	-	*[c]	-	-	-	-	-	-	-	-	-	*[c]
HSPB1-Ab[b]	**	-	*	*	*	-	-	**	***	-	-	-	-	-	-	-	-	-	-	-	-
CTNND1-Ab[b]	-	-	*	-	****	-	-	*	***	-	-	-	-	-	-	-	-	-	-	-	-
DHPS-Ab[b]	-	-	-	-	****	-	-	-	***	-	-	-	-	-	-	-	-	-	-	-	-
TUBB2C-Ab[b]	***	-	**	***	****	*	*	**	**	-	-	-	-	-	-	-	-	-	-	-	-

Notes: The table lists *p*-values obtained using Spearman's correlation analysis between autoantibody levels and the subjects' data, including age, BMI, max-IMT, BP, smoking period (years), CRP, WBC, ALP, TTT, ZTT, CHE, ALB, A/G ratio, TP, BS, HbA1c, HDL-c, LDL-c, T-CHO, TG, and AMY. The full version is shown in Table S1. Subjects from the Sawara Hospital cohort include 139 specimens from healthy donors, 228 from patients with acute ischemic stroke, 44 patients with transient ischemic attack, 122 with deep and subcortical white matter hyperintensity, 17 with asymptomatic cerebral infarction, 59 with chronic-phase cerebral infarction, and 56 disease controls. [a]Protein antigens. [b]Peptide antigens. [c]Inverse correlation. *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001. "-" indicates no significant difference.

Abbreviations: A/G: Albumin/globulin; ALB: Albumin; ALP: Alkaline phosphatase; AMY: Amylase; BMI: Body mass index; BP: Blood pressure; BS: Blood sugar; CHE: Cholinesterase; CRP: C-reactive protein; HbA1c: Glycated hemoglobin; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; Max-IMT: Maximum intima–media thickness; T-CHO: Total cholesterol; TG: Triglyceride; TP: Total protein; TTT: Thymol turbidity test; WBC: White blood cell; ZTT: Zinc sulfate turbidity test.

represents arterial stenosis. CPSF2-Abs, SOSTDC1-Abs, DIDO1-Abs, and AP3D1-Abs showed the strongest correlations with max-IMT among the AABs. As expected, atherosclerosis risk factors such as age, BP, smoking history, and liver dysfunction were significantly correlated with the levels of most AABs. Notably, serum levels of PCK-Abs, BMP1-Abs, TMEFF1-Abs, LRPAP1-Abs, DNAJC2-Abs, LIMA1-Abs, CTNND1-Abs, and DHPS-Abs were not associated with age. These AABs may therefore serve as true atherosclerosis markers independent of age. Unexpectedly, the obesity marker (BMI), DM markers such as BS and HbA1c, and lipid metabolism markers, including HDL-c, LDL-c, T-CHO, and TG, were significantly correlated with the levels of only a few AABs. Moreover, LDL-c, T-CHO, and TG showed inverse correlations with some AABs, such as CPSF2-Abs, XRCC4-Abs, and FOXJ2-Abs. Patients with DM and dyslipidemia may be receiving medications that lower the levels of these lipid markers, whereas AAB levels may be less affected by such medications. Alternatively, lipid metabolism abnormalities may not have substantial impact on the progression of atherosclerosis as indicated by AABs.

Almost no significant correlations were observed between AAB levels and other blood test data, including aspartate aminotransferase, alanine amino transferase, lactate dehydrogenase, leucine aminopeptidase, total bilirubin, direct bilirubin, γ-glutamyl transpeptidase, blood urea nitrogen, creatinine, estimated glomerular filtration rate, uric acid, creatine kinase, sodium, potassium, chloride, calcium, inorganic phosphate, iron, red blood cell count, platelet count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, mean platelet volume, procalcitonin, platelet distribution width, prothrombin time, prothrombin percentage, prothrombin time–international normalized ratio, and activated partial thromboplastin time (Table S1). Therefore, most AABs, if not all, do not simply reflect liver or kidney failure, serum ion levels, hemoglobin, or blood coagulation status.

8. The mechanism of autoantibody development

8.1. Mechanism 1: Overexpression of antigenic proteins followed by tissue destruction

Elevated levels of autoantibodies are frequently attributable to elevated expression of antigenic proteins in tissues. Tissue destruction, followed by antigen release, may trigger autoantibody development. However, the simple release of soluble antigens may not be sufficient to increase antibody levels. Autoantibody development has been reported to result from increased autoantigen presentation on apoptotic blebs and bodies, exosomes, and HSP-mediated cross-priming.[60,61] Thus, localization of antigens on the surface of apoptotic blebs and bodies or exosomes may lead to high autoantibody levels.

Anti-p53 autoantibody is a representative tumor marker.[62] In normal cells, the tumor suppressor p53 protein is maintained at very low levels through ubiquitination followed by proteasomal degradation. *MDM2* is one of the target genes of p53, and the induced MDM2 protein plays a central role in p53 ubiquitination and degradation.[63] In cancer cells, when p53 is inactivated by genetic mutations or other factors, MDM2 is no longer induced, and p53 degradation is alleviated, resulting in a marked increase in p53 and its antibodies. Our previous studies also reported that high antibody levels in patients with EC were observed against TROP2, myomegalin, and TRIM21,[5,6,14] which are highly expressed in EC tissue. Likewise, it has been reported that autoantibody levels against RPA2, PDCD11, SERPINE1, DIDO1, and FOXJ2 are increased in patients with atherosclerosis, and their antigenic proteins were highly expressed in atheromatous foci in the arteries.[15,17,19,34]

If antigen protein levels in lesional tissue reflect their serum antibody levels, the reverse is also possible. It is therefore possible to estimate protein expression levels in tissue from serum antibodies without obtaining tissue samples. Thus, serum autoantibody biomarkers are useful and convenient for assessing protein expression levels in lesions.

8.2. Mechanism 2: Antibodies produced by exogenous substances cross-react with self-proteins

Autoantibodies against secretory proteins such as cytokines are unlikely to be induced by antigen presentation following tissue destruction. After synthesis, cytokine proteins are rapidly released into the extracellular fluid through the secretory pathway. Some antibodies produced against exogenous substances that enter the human body through infection or trauma may cross-react with cytokines. Consistently, serum antibody levels against cytokines are empirically low.

In other words, the increase in autoantibodies against secreted cytokines may not result from high expression of these cytokines in diseased tissues. Nevertheless, autoantibody levels against CSF2 and ADIPOQ were elevated in the serum of patients with atherosclerosis and cancer.[35,42] These autoantibodies may bind to antigenic cytokines in the blood and inhibit their activity, potentially promoting or suppressing disease progression. For example, if autoantibodies are produced against a secreted protein that suppresses a particular disease, high autoantibody

levels would be observed in patients with more advanced stages of the disease.

9. Functional meaning of autoantigens

Atherosclerosis antibody markers listed in Table 2 can be divided into several functional groups as follows:

9.1. DNA repair

RPA1, RPA2, XRCC4, and FOXJ2 are involved in the repair of DNA double-strand breaks (DSBs).[64,65] In the rat brain, DSBs are induced by ischemia.[66] In atherosclerotic plaque, cells are exposed to reactive oxygen species, which can trigger extensive oxidative DNA damage.[64,67] RPA1, RPA2, XRCC4, and FOXJ2, which are required for DSB repair,[68-70] may be expressed at high levels. In addition, high expression levels of RPA2 and FOXJ2 proteins were observed in the intima of atherosclerotic plaque.[15,34] This confirms the close relationship between DSB repair and atherosclerosis development.

9.2. BMPs and their related proteins

BMPs belong to the transforming growth factor-β (TGF-β) superfamily. It is well documented that BMP signaling plays important roles in the development of atherosclerosis.[71,72] The expression of BMP2 and BMP4 is elevated in atherosclerotic endothelium.[73,74] BMP1 is a metalloproteinase containing an astacin-like domain and is also known as procollagen C-proteinase.[75] BMP1 activates BMP signaling by degrading the BMP inhibitor chordin.[76] DAN and SOSTDC1 are antagonists of BMPs.[77,78] *DIDO1* is a target gene of BMP and promotes cell attachment, migration, invasion, and apoptosis resistance in melanoma.[79] CPSF proteins interact with Smad via Smicl and potentiate TGF-β/BMP-stimulated, Smad-dependent transcriptional responses.[80,81] Reports indicating that many autoantibodies against BMP-related proteins are elevated in patients with atherosclerosis suggest a key role for BMPs in the progression of atherosclerosis. This also implies that BMP-related proteins, as well as their autoantibodies, may serve as therapeutic and/or preventive targets.

10. Characteristics of antibody biomarkers

10.1. Characteristic 1: Autoantibodies are sensitive and stable biomarkers

To detect early symptoms of disease, many biomarkers have been developed, including enzymes, antigens, antibodies, DNA, and RNA. Among these, proteins such as enzymes, antigens, and antibodies are relatively stable and most frequently used. Enzyme markers are unavailable if the target proteins lack enzymatic activity. Local tissue destruction may cause the release of otherwise intracellular proteins into systemic circulation. When these proteins are released, antibodies are produced against them. Recent technological advances have revealed that most self-proteins can serve as antigens against which autoantibodies are produced. Both antigens and antibodies appear at very low levels and are rapidly degraded after a single episode of tissue destruction. Thus, their levels may be difficult to detect. However, repeated tissue destruction and repeated antigen release during disease progression could lead to a marked increase in autoantibody levels while maintaining low antigen levels.[82] Therefore, antibody markers are considered much more sensitive than antigen markers. Although antibody levels measured using ELISA are highly variable and unstable, the introduction of the AlphaLISA method enables stable and low-background measurements.

10.2. Characteristic 2: Monitoring of disease progression

A key question is how long elevated levels of autoantibodies are maintained. Increased levels of serum anti-p53 are attributable to increased p53 protein expression in tumor cells. After surgical removal of tumor cells, p53-Ab levels decreased to basal levels within 3 months[83,84] and up to 1 year.[85] Thus, antibody markers may be applicable for monitoring when examined on a monthly basis rather than on a daily basis. Measurement of AABs may enable monitoring of whether lifestyle improvements have successfully suppressed atherosclerosis.

10.3. Characteristic 3: Prediction of AIS onset

Most ischemic strokes do not occur suddenly but are preceded by premonitory symptoms during the prodromal stage. When these symptoms occur, abnormalities exist in the blood vessels or brain, and if certain proteins leak from tissue into the blood, antibodies to these proteins are produced. Although antibody levels are initially low, repeated occurrence of premonitory symptoms causes the same antigen (tentatively named "antigen A") to be repeatedly released, and antibodies gradually increase to detectable levels. Immediately after stroke onset, not only antigen A but also many other antigens are released into the blood. Therefore, regardless of how extensively we search for such antigens in blood collected immediately after onset, they primarily reflect the pathological event itself rather than the predictive phenomenon associated with the prodromal stage. In contrast, serum antibodies obtained immediately after stroke onset are not produced against newly released proteins; rather, they are presumed to have been present prior to onset. In other words, autoantibodies specifically detected in serum obtained immediately after stroke onset can serve as onset-predicting biomarkers (Figure 3).

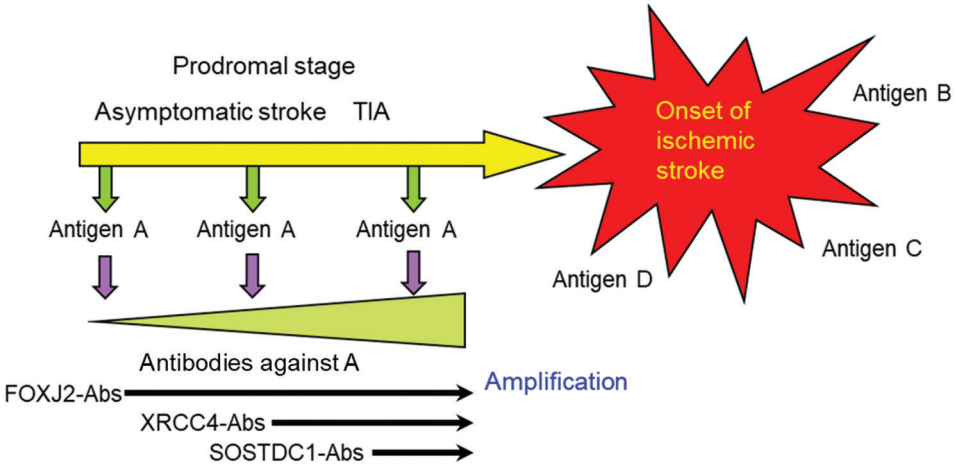

Figure 3. Antigens and antibodies before and after the onset of ischemic stroke. Even at a very early stage of atherosclerosis development, certain proteins, such as the tentatively designated "antigen A," leak from tissues into the blood, leading to the appearance of corresponding antibodies. As atherosclerosis progresses through the prodromal stages, recurrent leakage of antigen A gradually elevates antibody levels to a detectable range. Immediately after stroke onset, not only antigen A but also additional proteins (e.g., antigens B, C, and D) are released into the blood circulation. Only antibodies against antigen A are present and detectable before stroke onset, and therefore can function as onset-predicting biomarkers. The levels of FOXJ2-Abs and XRCC4-Abs were elevated from the prodromal stage (TIA) of acute ischemic stroke, whereas SOSTDC1-Abs were not.
Abbreviations: FOXJ2-Abs: anti-FOXJ2 antibodies; SOSTDC1-Abs: anti-SOSTDC1 antibodies; TIA: transient ischemic attack; XRCC4-Abs: anti-XRCC4 antibodies.

This possibility was confirmed in further studies. A case-cohort study was conducted as part of a public health center-initiated prospective study[86-88] that included approximately 30,000 Japanese subjects aged 40–69 years during the reference period of 1990–1994, with plasma samples stored. Plasma samples, collected at the beginning of the study, were selected from 202 AIS cases that occurred between the reference period and 2008, along with 202 controls matched for age (within 2 years), sex, date of blood collection (within 3 months), time since last meal (within 4 h), and study location (Public Health Center area). The odds ratios (95% confidence intervals) of patients in the third and highest quartiles of KIAA-Ab levels compared with those in the lowest quartile showed a significantly positive association with the risk of developing AIS.[9] Similar findings were observed for DIDO1-Abs, FOXJ2-Abs, CPSF2-Abs, SH3BP5-Abs, LIMA1-Abs, COPE-Abs, KIF20B-Abs, TPM3-Abs, IFI16-Abs, and MMP1-Ab levels.[34,39,42] These results indicate that these AABs are useful for predicting the onset of AIS.

Among the AIS-associated AABs, each AAB was correlated with different patient data, including AIS risk factors such as age, BMI, max-IMT, BP, habitual smoking, inflammation, liver dysfunction, glucose metabolism disorders, and lipid metabolism disorders (Table 4). If positive AABs correlated with different risk factors are identified in each subject, it may be possible not only to predict the onset of AIS but also to infer its cause. Consequently, individuals identified as positive may avoid the onset by modifying the lifestyle habits indicated by positive AABs.

10.4. Characteristic 4: Application to therapy and prevention

As mentioned in the previous section, antibody levels of BMP antagonists such as SOSTDC1 and DAN were elevated in patients with AIS and TIA (Table 3). Given that the BMP family promotes atherosclerosis progression, these antagonist autoantibodies may not simply be increased but may also actively contribute to the development of atherosclerosis and subsequent ischemic stroke. Therefore, in individuals with high levels of such autoantibodies, it may be possible to prevent the onset of ischemic stroke by administering antigen-like drugs.

The peptide hormone adiponectin inhibits atherosclerosis.[89-91] Autoantibody levels are elevated in the sera of patients with myocardial infarction, cerebral infarction, and diabetes.[35] Thus, an increase in serum anti-adiponectin antibodies may decrease adiponectin activity, potentially leading to the progression of atherosclerosis. Therefore, reducing serum anti-adiponectin antibodies may help prevent atherosclerosis progression.

Accordingly, if AABs influence disease progression, they can serve as therapeutic and preventive targets. If autoantibodies inhibit disease progression, artificially prepared antibody drugs can be applied to prevent

progression. Conversely, when autoantibodies accelerate progression, it may be possible to neutralize them by introducing pseudo-antigens or decoy antigens.

11. Prognosis analysis

11.1. Prognosis analysis of AABs

In a study, a cohort of 274 patients with DM underwent a 100-month follow-up after antibody analysis to investigate overall survival. CSF2-Ab–positive patients had a significantly worse prognosis than CSF2-Ab–negative patients.[42] A similar finding was observed for PCSK9-Ab.[51] The difference in overall survival between antibody-positive and antibody-negative patients was initially small but became pronounced after 30–40 months. It is notable that these autoantibodies are capable of predicting prognosis over such a long period.

Some common AABs for atherosclerosis and cancer showed a significant correlation with the prognosis of patients with DM or cancer. For example, the overall survival of anti-CSF2-Abpositive patients with DM was significantly worse than that of antibody-negative patients.[42] The prognosis of anti-JMJD6-Abpositive patients with EC was significantly more favorable than that of antibody-negative patients,[92] whereas antibody-positive patients with CRC had a less favorable prognosis than antibody-negative patients.[46] The extremely high sensitivity of antibody biomarkers may enable prognosis prediction over several years or more.

11.2. Consistent relationship between autoantibody levels and prognosis in patients with gastric cancer

In our previous study, we also investigated cancer-related autoantibody biomarkers. Some autoantibody markers for gastrointestinal cancers showed a correlation with prognosis. For example, anti-fumarate hydratase (FH) antibody levels were higher in patients with gastric cancer than in HDs.[93] Defects in FH and succinate dehydrogenase lead to intracellular accumulation of fumarate and succinate, which inhibit prolyl hydroxylase activity and prevent degradation of hypoxia-inducible factor 1α (HIF1α). Consequently, HIF1α is stabilized under normoxic conditions (pseudohypoxia), leading to increased expression of HIF1-regulated genes such as vascular endothelial growth factor, thereby promoting tumor progression.[94-97] Therefore, high FH expression predicts a better prognosis than low expression. Consistently, high anti-FH antibody expression in patients with gastric cancer was associated with a better prognosis than low expression.[93] This suggests that the antigen–prognosis relationship can be reflected in the antibody–prognosis relationship.

11.3. Estimating functional associations by combining survival analysis of antibody markers

Antibody levels against β-actin (ACTB) and cofilin (CFL1) were elevated in patients with EC.[98] CFL1 is a protein that inhibits actin polymerization. Patients with high ACTB-Ab levels tended to have a slightly worse prognosis than those with low levels (p=0.110), whereas patients with high CFL1-Ab levels tended to have a slightly better prognosis than those with low levels (p=0.535). Cytochalasin D and aplyronine A, which inhibit actin polymerization, were used as anticancer drugs,[99,100] suggesting that a high CFL1/ACTB expression ratio suppresses cancer cell proliferation. Combined survival analysis demonstrated that the CFL1-Ab–positive/ACTB-Ab–negative group had a significantly better prognosis than the CFL1-Ab–negative/ACTB-Ab–positive group (p=0.0368).[98] This suggests that when a functional relationship exists between two antigens, the combination of their antibodies can distinguish prognostic differences more clearly than either antibody alone. Conversely, if the combination of two autoantibodies shows a much larger prognostic difference than each autoantibody alone, it can be inferred that there is a functional relationship between their antigens.

12. Conclusion

In this study, a large number of autoantibodies corresponding to life-threatening atherosclerosis-related diseases were identified. Cancer and autoimmune diseases, for which autoantibodies have traditionally been recognized, are also serious illnesses. Therefore, it is plausible that corresponding autoantibodies exist for any serious disease, not limited to these conditions.

Serum antibody markers are stable, highly sensitive, and exhibit little variability, and blood sampling is minimally invasive and straightforward. Investigating increased autoantibodies may also contribute to elucidating the mechanisms of disease onset and identifying targets for prevention and therapy. The history of autoantibody markers has only just begun, and further developments in autoantibody analysis are expected.

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Conflict of interest

The author declares no conflict of interest.

Author contributions

This is a single-authored article.

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This review paper is based on previously published studies, all of which were conducted in accordance with the relevant institutional review boards and with the Declaration of Helsinki (2013).

Consent for publication

All data included in this review were derived from studies in which participants provided written informed consent.

Availability of data

Not applicable.

Further disclosure

Representative ProtoArray results are publicly available in the Figshare database (https://figshare.com/articles/dataset/Results_of_protein_array_for_atherosclerosis/25906330).

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REVIEW ARTICLE

Computer simulations in left atrial appendage occlusion: Current applications and future potential

Mingmeng Li[1], Yequn Chen[2,3,4], Zemin Cai[5,6], Xiangyuan Ma[1], and Haifeng Wang[1]*

[1]Department of Biomedical Engineering, College of Engineering, Shantou University, Shantou, Guangdong, China

[2]Department of Cardiology, The First Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, China

[3]Guangdong Engineering Research Centre of Human Phenome, Chemistry and Chemical Engineering Guangdong Laboratory, Human Phenome Institute of Shantou University Medical College, Shantou, Guangdong, China

[4]Clinical Research Center, The First Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, China

[5]Department of Electronic Engineering, College of Engineering, Shantou University, Shantou, Guangdong, China

[6]Intelligent Manufacturing Key Laboratory of Ministry of Education, Shantou University, Shantou, China

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***Corresponding author:**
Haifeng Wang
(haifeng.wang@rub.de)

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Abstract

Left atrial appendage (LAA) occlusion (LAAO) prevents thromboembolic stroke in patients with atrial fibrillation, particularly those unsuitable for long-term anticoagulation therapy. However, complex and variable LAA morphology challenges LAAO, including device selection and post-procedural device-related thrombosis. To address these issues, *in silico*/virtual optimization via computational modeling and simulation has been utilized to improve pre-procedural planning, device design, thrombosis prediction, and optimization for LAAO. This review examines the evolving landscape of LAAO, with a focus on computer modeling and simulation. We assess the capabilities, key limitations, and future potential of these computational tools through literature evaluation. These tools demonstrate clinical translatability but face limitations in simulating dynamic physiological interactions. Their broader adoption will drive personalized LAAO strategies, reduce procedural complications, and inform future research aimed at bridging the gap between virtual optimization and real-world clinical outcomes.

Keywords: Left atrial appendage occlusion; Occluders; Atrial fibrillation; Stroke; Computational modeling and simulation; Hemodynamics

1. Introduction

Atrial fibrillation (AF) is a significant risk factor for thromboembolic stroke, with the left atrial appendage (LAA) being a common site for thrombus formation. According

to a report, 90% of intracardiac thrombi found in patients with cardioembolic stroke or transient ischemic attack arise from the LAA.[1] Despite oral anticoagulation (OAC) therapy, many patients remain exposed to a high bleeding risk[2,3] and a poor long-term adherence (approximately one-third discontinue or fail to take their OAC medication[4,5]). This highlights the need for alternative strategies to mitigate stroke risk in these patients.[6]

LAA occlusion (LAAO) has emerged as a promising interventional alternative,[7-10] aimed specifically at reducing thromboembolic stroke risk by mechanically excluding the LAA from the systemic circulation. Clinical studies have demonstrated the efficacy of LAAO for stroke prevention,[11,12] with specific devices such as the Watchman (Boston Scientific, USA) and Amulet (Abbott, USA) proving non-inferior to OAC in reducing stroke risk.[13-15] However, despite these positive outcomes, procedural challenges remain. Anatomical variability of the LAA poses significant difficulties for device selection and deployment, as exemplified by its four predominant morphological types (chicken wing, cactus, windsock, and cauliflower; Figure 1),[16] each introducing unique implant constraints and hemodynamic profiles. Post-procedurally, peri-device leaks (PDLs) remain a frequent concern, occurring in approximately 26% of patients according to a meta-analysis, with larger leaks (>5 mm) associated with a higher risk of thromboembolic events.[17] Device-related thrombus (DRT) is another serious complication, observed in 3–5% of cases, further contributing to stroke risk.[18] Suboptimal implantation depth or device positioning also often increases the incidence of DRT.[19] Despite rapidly evolving treatment strategies, the marked inter-patient variability of LAA anatomy still deprives clinicians of reliable pre-procedural predictors of success.[20] Closing this gap demands pre-procedural planning tools that can personalize device choice and deployment to each unique anatomy, thereby translating technical advances into consistently better clinical outcomes.

Computational modeling and simulation, particularly through techniques such as computational fluid dynamics (CFD) and finite element analysis (FEA), have become important tools across a wide spectrum of cerebro-cardiovascular research and clinical applications. These methods provide critical insights into the biomechanical and hemodynamic behaviors underlying various pathologies, including aneurysms,[21-23], stenosis,[24] stroke,[25,26] and ischemia,[27] as well as their treatments.[28,29] In the context of AF, such technologies are increasingly applied to optimize interventional treatments such as LAAO.[30-36]

A systematic and comprehensive literature search was conducted using PubMed, Web of Science, and Google Scholar, ensuring broad coverage of computational modeling and simulation studies that advance LAAO therapy. By examining their use at key procedural stages—such as pre- and post-procedural hemodynamic assessment to refine planning and lower the risk of DRT, and virtual device implantation to optimize placement—we critically appraised the status of these computational methods, acknowledged their limitations, and outlined their future potential for safer, more personalized LAAO outcomes.

2. Computer modeling in pre- and post-procedural hemodynamic assessment

Computer modeling has become an essential methodology for evaluating hemodynamics in LAA interventions. CFD is the predominant tool for quantifying blood flow characteristics, owing to its ability to resolve spatially and temporally varying hemodynamic parameters. The integration of CFD with advanced imaging modalities such as angiography, transesophageal echocardiography (TEE), and 3D computed tomography (CT) has significantly enriched the morphological and functional assessment of the LAA, providing deeper insights into thrombogenic flow patterns and supporting intervention planning.

CFD enables the quantification of key hemodynamic indicators, including velocity patterns, vorticity, wall shear stress (WSS), and pressure, all of which are critical in evaluating thrombosis risk.[37-39] Studies have employed CFD to compare hemodynamic environments between healthy individuals and patients with AF. For example,

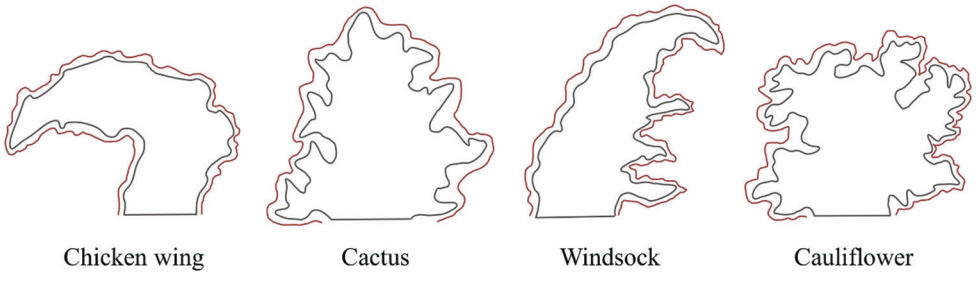

Figure 1. Representative examples of left atrial appendage morphologies

Koizumi *et al.*[37] developed models of a healthy LA and two AF scenarios, one without atrial kick and another with high-frequency wall fibrillation, and demonstrated increased relative residence time (RRT, a metric proposed by Himburg *et al.*[40]) in the upper LAA during AF, indicating regions prone to thrombus formation. Another research examined the four common LAA morphologies (Figure 1) and revealed that velocity and shear strain rate decrease from the ostium to the tip, a trend exacerbated by AF.[41] The cauliflower morphology retained 3.27% of contrast agent under AF conditions, significantly more than the 0.56% in windsock morphologies, suggesting that complex geometry interacts with AF to promote blood stasis.

Recent studies have introduced more refined hemodynamic indices to effectively capture thrombotic risk. Dueñas-Pamplona *et al.*[42] proposed the fourth moment of the blood age distribution (M_4), which effectively filters non-stagnant flow components, offering a more reliable assessment of stasis. In a subsequent study, M_4 improved the identification of "dead volumes," where blood remains stagnant and isolated from circulation, enabling earlier detection and intervention.[43] Corti *et al.*[44] further introduced a novel "age stasis" index by integrating Eulerian (based on continuum flow-field analysis) and Lagrangian (tracking individual red blood cells) perspectives. This metric identifies regions where low flow velocities coincide with "aged" blood components. We noted that the "age of blood" was defined as the residence time of a red-blood-cell particle within the LA; blood was considered "aged" when its residence time is comparable to one complete cardiac cycle. Their results showed that persistent AF cases exhibit up to 27.5% of LA volume with high age stasis, a stark contrast to healthy hearts, offering a dimensionless metric for cross-patient comparison.[44]

CFD also enables the incorporation of morphological features such as LAA shape, volume, ostium dimensions, tortuosity, and lobular complexity into hemodynamic analyses. For example, chicken wing and windsock morphologies, with their larger ostia, often facilitate better blood washout through relatively higher velocities (>4 cm/s) that penetrate deeper into the appendage, reducing stagnation risk.[45] In contrast, cauliflower and cactus types, characterized by more lobes and a high value of tortuosity variation (>30%) associated with a low centerline length variation (<10%), tend to have lower velocities (<4 cm/s), resulting in increased blood stasis.[45] Specific geometric parameters also play critical roles. Wang *et al.*[46] compared stroke and non-stroke patient groups and found that stroke patients had smaller LAA depth and direct length. Interestingly, species-transport and discrete phase models indicated more frequent blood renewal in the stroke group, contradicting traditional assumptions. This paradox may arise from more pronounced morphological variations in stroke patients, underscoring the importance of patient-specific geometry. Moreover, Dueñas-Pamplona *et al.*[43] identified cardiac output and LAA volume as major influencers of dead volume, while pulmonary vein (PV) orientation had minimal effect on stasis in AF.

CFD is equally valuable in evaluating pre- and post-procedural hemodynamics following LAAO. Using patient-specific data, researchers can simulate device implantation scenarios and evaluate post-implantation hemodynamics, which are critical for optimizing device positioning, comparing occluder designs, and predicting thrombotic risks. Alinezhad *et al.*[47] used CT-based CFD to simulate LAA removal and found that hemodynamic changes were morphology-dependent: in a two-lobe LAA, flow rate decreased by 9.15% and vorticity by 7.27%, while in a one-lobe LAA, velocity and vorticity reductions reached 23.33% and 18.6%, respectively. Jia *et al.*[48] reported that post-occlusion flow became more organized, with reduced vortex size and intensity (e.g., peak vortex diameter decreasing from 2.8 cm to 1.5 cm), and a 25% drop in vorticity, collectively lowering thrombotic risk. Both pre- and post-LAAO hemodynamics are highly patient-specific, necessitating individualized CFD-based planning to optimize device selection and placement for effective thromboprophylaxis.

3. Virtual device selection and implantation optimization

Virtual implantation platforms, such as the Virtual Implantation and Device Selection in LAAs (VIDAA),[33] allow clinicians to test different device types, sizes, and landing zones. CFD simulations show that optimal device placement minimizes regions of low velocity and complex flow, reducing endothelial cell activation potential (ECAP)[49]—a combined metric of time-averaged WSS (TAWSS)[50] and oscillatory shear index.[33,51] Comparative studies indicate that "pacifier"-type devices promote organized flow toward the mitral valve and better washout compared to "plug"-type devices, which may produce less uniform flow and higher ECAP.[52] However, even minor PDL can reintroduce stasis, increase ECAP (up to 3.84 Pa^{-1}), and impair washout, emphasizing the need for precise implantation.[52] Therefore, device selection and positioning are crucial.

3.1. The importance of device selection: Watchman versus Amulet

The "pacifier"-type occluder (often called "nipple" type) is characterized by a double-disc design, as exemplified by the Amplatzer Amulet device and LAMax (Shenzhen Salubris Medtech Co., Ltd, China) (Figure 2A). In

contrast, "plug"-type devices are typically single-bodied and designed to occlude the LAA orifice from within the appendage itself, with the Watchman device series being a prominent example (Figure 2B). Figure 2C and D shows the implantation of the pacifier-type and plug-type devices into the LAA, respectively. Commonly used LAAO devices in clinical practice are summarized in Table 1.

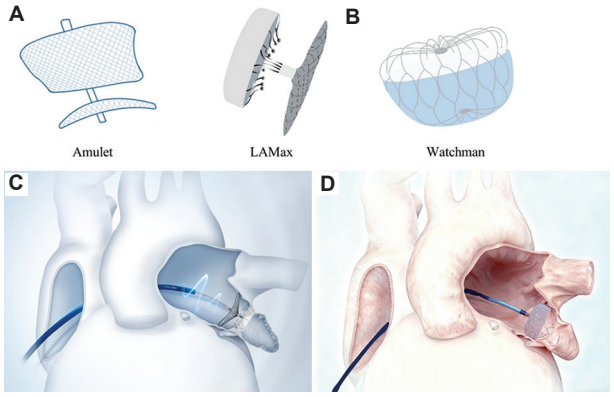

Figure 2. Representative examples of left atrial appendage occlusion devices for (A) "pacifier" type and (B) "plug" type. (C) Pacifier-type implantation. Reproduced with permission from Shenzhen Salubris Medtech Co., Ltd. Copyright © 2025, Shenzhen Salubris Medtech Co., Ltd.[53] (D) Plug-type implantation. Adapted with permission from Shenzhen Salubris Medtech Co., Ltd. using the DOUBAO artificial intelligence image generation tool (ByteDance, China).

Table 1. A summary of commonly used LAAO devices in clinical practice

Device	Features	Marketing approval
Watchman 2.5	Self-expanding nitinol mesh; diameter range: 21–33 mm; precurved delivery sheath: 14 F	CE mark in 2005; FDA approved in 2015
Watchman FLX	Next-generation nitinol mesh (softer) with PET coating; diameter range: 20–35 mm; precurved delivery sheath: 14 F	CE mark in 2019; FDA approved in 2020
Amplatzer Cardiac Plug	Dual-disc nitinol (central waist); diameter range: 16–30 mm; nonsteerable sheath: 9, 10, and 13 F	CE mark in 2008
Amulet	Self-expanding nitinol (pre-mounted); diameter range: 16–34 mm; steerable sheath: 14 F	CE mark in 2013; FDA approved in 2021
Lariat	Suture-based ligation system (pre-tied suture loop); EndoCATH occlusion balloon; 15 mm (diameter) ×12 mm (length)	FDA510(k) clearance in 2006

Abbreviations: CATH: Catheter; CE: *Conformité Européenne*; F: French scale (1 F=0.33 mm); FDA: Food and Drug Administration; LAAO: Left atrial appendage occlusion; PET: Polyethylene terephthalate.

The Watchman 2.5, Boston Scientific's first-generation device, features a self-expanding nitinol framework with fixation hooks and a polyethylene terephthalate membrane. It received the *Conformité Européenne* (CE) mark in 2005 and Food and Drug Administration (FDA) approval in 2015. It is available in diameters ranging from 21 to 33 mm and is delivered via a 14 F guide system. Its next-generation successor, the Watchman FLX, received FDA approval in 2020. This device is offered in five sizes and incorporates several design enhancements, including a closed distal end and two rows of J-shaped anchoring hooks, which reduce device length and perforation risk.

The Amplatzer Cardiac Plug (ACP), the precursor to the Amulet occluder, is constructed from 144 braided nitinol wires forming a distal lobe and a proximal disc, which secures the device at the LAA ostium through axial tension. The second-generation Amulet occluder, approved by the FDA in 2013, introduces a double-sealing design, additional anchor hooks, and a deeper distal lobe compared to its predecessor. Both the ACP and Amulet devices are available in eight sizes and received CE markings in 2008 and 2013, respectively.

The choice between the Watchman and Amulet occluders remains a pivotal decision in LAAO therapy, guided by a growing body of comparative evidence. In the PROTECT-AF[54] and PREVAIL[55] trials, long-term follow-up of patients receiving the Watchman 2.5 device demonstrated that LAAO was associated with reduced risks of hemorrhagic stroke, disabling or fatal stroke, and overall mortality compared to warfarin over a 5-year period. The subsequent PINNACLE FLX trial further confirmed that the next-generation Watchman FLX device exhibits a favorable safety profile and a high rate of successful appendage closure.[56] Although most existing literature pertains to the Watchman 2.5, large-scale clinical evaluations—including a multicenter experience and a global prospective observational study—have also established the safety and efficacy of the ACP and Amulet occluders, respectively.[57,58] A study-level meta-analysis comparing Watchman 2.5 and Amulet found no significant differences in overall safety and efficacy outcomes between the two devices.[59] However, another meta-analysis reported a higher incidence of DRT (3.3% vs. 2.2%) and PDL >5 mm (2.4% vs. 1.0%) in the Watchman group compared to the ACP/Amulet group.[60] The Amulet IDE trial—the largest global randomized controlled trial on LAAO—demonstrated the non-inferiority of the Amulet device to the Watchman 2.5 in terms of both safety and effectiveness at 12 and 18 months.[61] Five-year extended follow-up data suggested sustained superiority of the Amulet device, attributable to lower stroke rates and a reduced need for OAC therapy post-implantation.[62]

Therefore, device selection should not be viewed as a binary choice, but rather as a strategic decision tailored to individual patients' anatomy and risk profile. The Amulet device may offer advantages in certain scenarios, particularly where minimizing DRT and PDL is paramount, while the Watchman FLX represents a proven and continually refined option.

3.2. Virtual implantation optimization

Virtual implantation optimization has been significantly advanced by the development of patient-specific computational models. By integrating patient-specific anatomical models constructed from medical imaging techniques, such as CT and ultrasonography, CFD simulations can replicate blood flow patterns around the LAAO device. This capability allows for the identification of key pro-thrombotic factors, such as stagnant blood flow, prolonged blood residence time, abnormal WSS, and elevated ECAP.

For example, Aguado *et al.*[33] developed the interactive VIDAA platform to perform virtual implantation of LAAO devices on patient-specific geometries. By evaluating variables such as device type, size, and landing zone, VIDAA can quantify important parameters, including residual blood volume, washout efficiency, and thrombogenic indices, like ECAP, helping identify the optimal configuration that minimizes the risk of thrombosis. Using the VIDAA platform, Albors *et al.*[35] compared different device types (Watchman vs. Amulet) and implantation positions (covering vs. not covering the PV ridge) and revealed that coverage of the PV ridge, coupled with the use of the Amulet device, often led to more favorable hemodynamic conditions. These favorable hemodynamic conditions include higher flow velocities and reduced flow recirculation zones, which are associated with a lower risk of DRT.[35] These findings are supported by two additional studies that also reported a reduced DRT risk with PV ridge coverage.[63,64] In a complementary approach, Zhong *et al.*[34] utilized FEA to simulate the virtual implantation of LAAO, showing that deep and/or off-axis device positioning can promote blood stasis, reduce WSS, and increase ECAP, all of which contribute to an elevated DRT risk.

A cardiac CT (CCT)-based computational model (FEops HEARTguide™) has been validated to accurately predict the deformation and wall apposition of both Amplatzer Amulet and Watchman LAA closure devices, with a coefficient of determination (R^2) ≥0.91 and measurement differences ≤5% compared to post-procedural CCT data.[65] Specifically, in predicting Watchman FLX, this model showed an excellent correlation with intraprocedural 3D-TEE measurements, even without knowing the size and position of the implanted device, and no patients had PDL when the model-predicted device size was used.[66] Moreover, virtual reality derived from CCT angiography (CCTA) has also shown promise in LAAO device size prediction, as its measurement of the maximal LAA ostium diameter has a stronger correlation with the implanted device size compared to CCTA and TEE.[67] Heidari *et al.*[68,69] found that virtual reality-based visualization of LAA derived from multi-slice CT enables precise measurement of landing zone dimensions and superior 3D anatomical orientation, which can further support the accurate determination of landing zones for LAAO.

The evolving evidence base underscores that informed device selection, complemented by optimal implantation technique, is critical for maximizing long-term patient outcomes. By leveraging these computational tools, computer simulations facilitate a more personalized and precise approach to LAAO procedure planning, providing clinicians with actionable insights for selecting optimal device types and implantation strategies tailored to individual patient anatomy, ultimately improving procedural outcomes and reducing thrombotic complications. However, published research dedicated to the virtual optimization of LAAO devices remains limited, although progress has been made for double-disc occluders such as the Amplatzer Amulet, where a novel braided model has been developed to simulate the LAAO process with higher fidelity. The braided model offers valuable insights for occluder design refinement and has the potential to enhance procedural success rates.[30] Moving forward, further application of computational modeling is also encouraged to advance the development and optimization of next-generation occluders, aiming to reduce the risk of thrombosis.

4. Simulation-assisted prediction of thrombosis risk

CFD enables the exploration of hemodynamic characteristics within the LAA, thereby assisting in the prediction of thrombosis risk. Yang *et al.*[70] demonstrated that the chicken-wing morphology, despite being the most common, exhibits lower blood flow velocities and TAWSS, along with higher RRT in AF compared to sinus rhythm, indicating an elevated thrombotic risk. They also pointed out that the thrombotic risk increases with the burden of AF. Similarly, Masci *et al.*[71] highlighted that both complex and seemingly simple LAA morphologies can present a high thrombogenic potential, as factors such as ostium diameter, centerline length, flow stagnation, and poor washout significantly contribute to thrombus formation. Furthermore, combined analyses of morphological parameters and CFD-based hemodynamic indices have

shown improved predictive accuracy for transient ischemic attack or cerebrovascular accident history compared to using either approach alone, emphasizing the value of integrating these approaches.[72]

Beyond morphology, PV configuration and LA wall motion are also beneficial for predicting thrombosis. PV configuration and orientation, including number, angles, and alignment with the LAA, significantly influence LA flow. A study of 130 patients demonstrated that the angles between different PVs and the alignment between the LAA and left superior PV determine the flow entry into the LAA, which, in turn, affects the risk of thrombus formation. The total number of particles within the LAA was identified as a key distinguishing parameter between thrombus and non-thrombus groups.[73] Further controlled studies modifying PV orientations have revealed that PV angles alter the position of the main atrial vortex, critically affecting LA flow patterns and LAA washout, which directly modulate the risk of stasis and thrombosis.[74] Regarding LA wall motion, simulations comparing moving versus fixed walls have shown that moving-wall models can more accurately capture hemodynamic indices such as residence time[75] and kinetic energy[38] within the LAA. In contrast, fixed-wall simulations fail to account for physiological contractions, resulting in less reliable risk stratification—particularly in patients with intermediate residence time.[76] Specifically, rigid-wall assumptions were found to overestimate thrombus predictors such as RRT and ECAP in the LAA. Meanwhile, generic or semi-generic moving-wall models, which approximate physiological motion, yielded hemodynamic patterns comparable to those of patient-specific moving-wall simulations, highlighting their potential as practical alternatives when detailed motion data is unavailable.[77]

DRT remains a critical complication post-LAAO, with an overall incidence of approximately 3.9% in the Amulet IDE trial, varying slightly between device types (3.4% for Watchmen and 4.8% for Amulet).[78] Key predictors of DRT include older age, female sex, and AF during the procedure, as identified in the Amulet IDE trial,[78] while other studies have also highlighted hypercoagulability disorders, pericardial effusion, renal insufficiency, deep device implantation (>10 mm from the PV limbus), and non-paroxysmal AF as significant risk factors.[79] Regarding the clinical course of DRT, approximately 28.5% of cases persist, while 17.1% of resolved DRT cases recur. An initial thrombus size >7 mm strongly predicts persistence or recurrence, which is in turn associated with a 2.13-fold increased risk of thromboembolic events.[80]

Computer simulations help assess the impact of different LAAO device configurations (size, type, and position) on hemodynamics, thereby reducing the risk of DRT.[35] Studies indicate that low blood flow velocities (<0.20 m/s) near the device surface, flow stagnation, and recirculation are key hemodynamic factors correlated with DRT.[81] Sensitivity analyses further demonstrate that boundary conditions have a significant impact on prediction accuracy. Incorporating patient-specific mitral valve velocities from echocardiography, generic pressure waves from AF patients at the PVs, and dynamic mesh approaches for LA wall deformation enhances the realism of flow patterns and improves the representation of recirculation and stagnant zones.[82] Moreover, comprehensive assessments that combine CFD with FEA can account for device deformation and interactions with the atrial wall. These integrative assessments have confirmed that DRT cohorts consistently exhibit lower TAWSS, higher oscillatory shear index, and higher ECAP than controls—parameters that closely align with thrombus locations observed *in vivo*.[83] These findings highlight the potential of CFD in predicting DRT risk, offering a basis for improved risk stratification and personalized intervention strategies for LAAO patients.

5. Limitations and future directions

Computational modeling and simulation play a critical role in LAA-related research and clinical practice, enhancing the understanding of flow patterns, facilitating thrombosis risk assessment, and supporting *in silico*/virtual testing of occlusion outcomes. Nevertheless, several key limitations must be acknowledged (Figure 3).

Most studies are constrained by small patient cohorts.[34,37-39,42-44,47,48,70,71,74,76,77,81,82] limiting statistical power and generalizability across diverse LAA morphologies and AF subtypes. Modeling simplifications[33,35,37-39,41-48,52,63,64,70,81] such as rigid wall assumptions, idealized boundary conditions, and Newtonian blood behavior—compromise physiological accuracy, particularly in capturing wall motion, patient-specific flow variations, and non-Newtonian effects in low-shear zones. Key anatomical and physiological factors,[37,43,63,72,74,76] including PV variability and coagulation mechanisms, are often omitted. Moreover, many models rely on generalized rather than patient-derived data,[47,64] reducing clinical translatability.

Future research should prioritize integrating advanced imaging techniques, such as four-dimensional flow magnetic resonance imaging, to enhance both anatomical and dynamic accuracy in simulations. It is also essential to incorporate more realistic physiological models, including fluid-structure interaction (FSI), non-Newtonian blood behavior, and coagulation processes, to improve simulation fidelity. FSI, which considers the interaction between the LAA

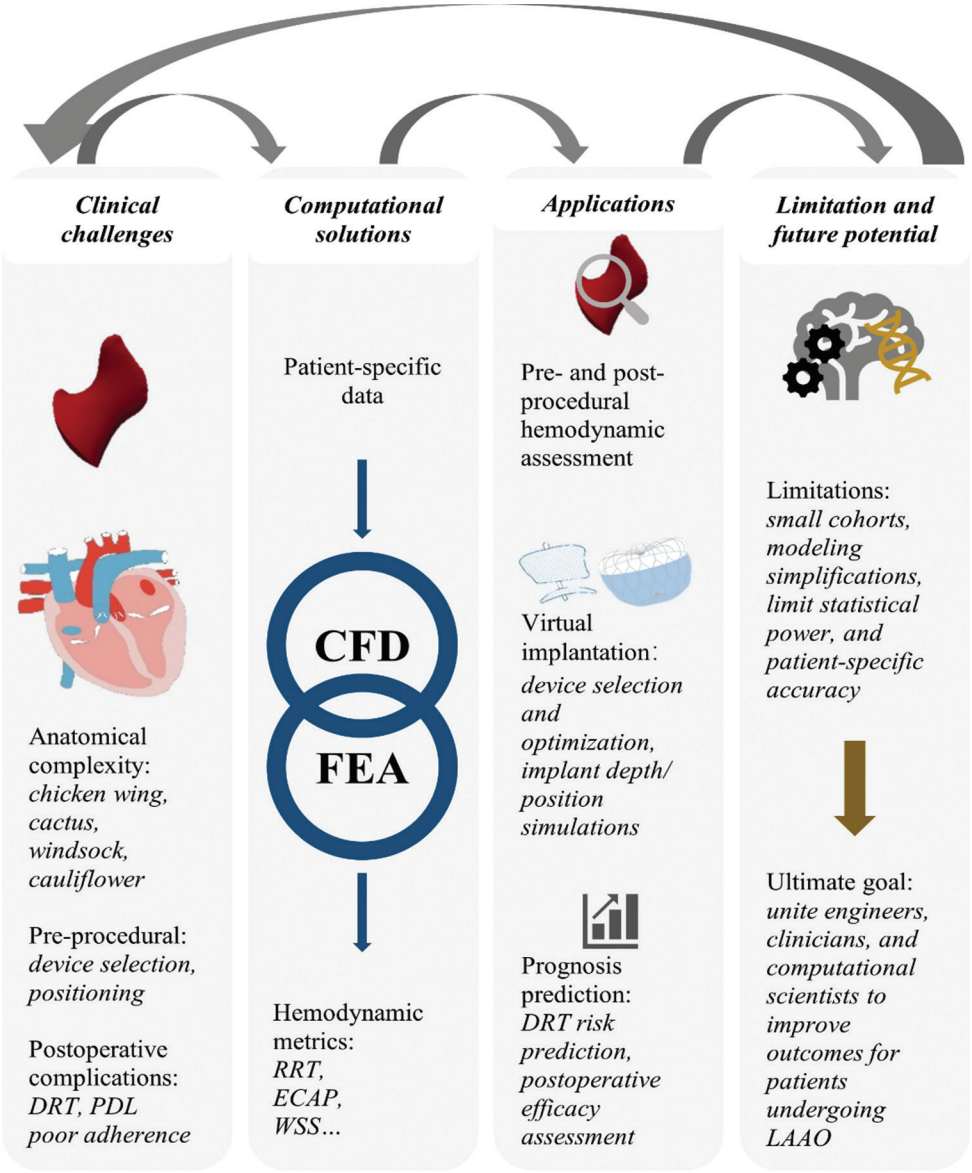

Figure 3. Overview of computational modeling and simulation in advancing LAAO therapy
Abbreviations: CFD: Computational fluid dynamics; DRT: Device-related thrombus; ECAP: Endothelial cell activation potential; FEA: Finite element analysis; LAAO: Left atrial appendage occlusion; PDL: Peri-device leak; RRT: Relative residence time; WSS: Wall shear stress.

wall and blood flow, is closer to the real physiological state than CFD, which typically assumes a rigid wall. Although preliminary work on FSI models has been conducted by several research groups,[84-88] further collaboration is needed to advance their theoretical foundations and clinical applicability. In addition, the development of standardized, multi-parametric risk indices that combine hemodynamic, morphological, and biochemical markers could greatly improve clinical utility. Deep learning methods also hold significant potential for automating image segmentation, accelerating simulation workflows, identifying complex correlations between flow and thrombosis, and enhancing diagnostic accuracy. For example, deep neural networks trained on large-scale CFD datasets can rapidly predict key hemodynamic metrics—such as ECAP and RRT—within minutes from patient-specific LAA geometries.[89-91] Deep learning methods also assist in predicting obstructive coronary artery disease and short-term mortality in patients with acute pulmonary embolism.[92,93] Ultimately, advancing computational techniques is essential for driving the development and optimization of next-generation occluders and reducing the incidence of DRT.

6. Conclusion

LAAO has emerged as an effective interventional alternative to OAC for stroke prevention in patients with AF. However, challenges such as complex LAA anatomy, PDL, and DRT remain significant barriers to optimal outcomes. This review highlights the growing role of computational modeling and simulation, particularly CFD and FEA, in addressing these challenges and advancing toward personalized LAAO therapy.

CFD simulations have enabled detailed assessment of pre- and post-procedural hemodynamics, identifying key thrombogenic factors such as flow stagnation, abnormal WSS, and elevated ECAP. Through patient-specific modeling, researchers have elucidated the impact of LAA morphology, PV configuration, and LA wall motion on thrombosis risk, providing deeper insights into patient stratification and procedural planning. Furthermore, virtual implantation platforms now allow clinicians to simulate device deployment, optimize occluder selection and positioning, and predict complications such as DRT before the actual procedure.

Despite these advancements, current computational models face several limitations, including small sample sizes, simplified boundary conditions, and the omission of key physiological processes such as coagulation. Future efforts should focus on integrating advanced imaging, adopting more physiological modeling approaches, and developing multi-parametric risk indices. Deep learning methods show particular promise in accelerating simulation workflows and improving predictive accuracy.

In conclusion, computational modeling and simulation are transforming LAAO from a one-size-fits-all procedure to a personalized, precision-based intervention. Continued collaboration between engineers, clinicians, and computational scientists will be essential to refine these tools, validate their clinical utility, and ultimately improve outcomes for patients undergoing LAAO.

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Conflict of interest

Haifeng Wang is the Youth Editorial Board Member of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Haifeng Wang, Yequn Chen
Visualization: Mingmeng Li
Writing – original draft: Mingmeng Li
Writing – review & editing: All authors

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Consent for publication

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Availability of data

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ACCSCIENCE PUBLISHING

Brain & Heart

REVIEW ARTICLE

Risk stratification in takotsubo syndrome and its atypical association with diabetes mellitus: A review of current evidence

Javeria Taj[1], Moiz Shah Khan[2], Hermann Yokolo[3]*, Amer Hammad[4], Haris Muhammad[5], Aparna Iyer[6], Oghenetejir Gbegbaje[4], Syeda Hafsa Qadri[7], and Hafeez Hassan Virk[8]

[1]Department of Internal Medicine, Dow Medical College, Dow University of Health Sciences, Karachi, Sindh, Pakistan

[2]Department of Internal Medicine, Ziauddin University, Karachi, Pakistan

[3]Department of Research, Medical Research Circle (MedReC), Goma, North Kivu, Democratic Republic of the Congo

[4]Department of Internal Medicine, Englewood Medical Center, Englewood, New Jersey, United States of America

[5]Department of Cardiology, Newark Beth Israel Medical Center, Newark, New Jersey, United States of America

[6]Department of Internal Medicine, Maimonides Medical Center, New York, United States of America

[7]Department of Internal Medicine, Dow University of Health Sciences, Karachi, Sindh, Pakistan

[8]Department of Cardiology, Adena Greenfield Medical Center, Chillicothe, Ohio, United States of America

***Corresponding author:**
Hermann Yokolo
(hermannyokolo40@outlook.com)

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Abstract

Takotsubo syndrome (TTS), also known as broken heart syndrome, is an acute cardiac condition with a poorly understood pathophysiology due to its relative rarity. Once considered benign, it is now recognized as a serious disorder with severe complications and a mortality rate comparable to or exceeding that of acute coronary syndrome. This narrative review aims to summarize current knowledge on the prognostic factors associated with TTS, with a particular focus on its relationship with diabetes mellitus (DM). A thorough analysis of 57 relevant studies, selected from over 98,000 articles retrieved from PubMed and Google Scholar, was conducted based on strict inclusion criteria. The findings indicate that advanced age, female sex, pre-existing cardiovascular diseases, and systemic disorders significantly influence the prognosis and mortality of patients with the syndrome. DM plays a paradoxical role, being associated with increased long-term mortality risk while potentially providing a protective effect during the acute phase of the syndrome, possibly by modulating stress responses involved in its onset. Therefore, a deeper understanding of the prognostic implications of TTS and its interaction with diabetes is crucial for developing appropriate risk stratification tools and improving clinical management of patients.

Keywords: Takotsubo syndrome; Atypical association; Diabetes mellitus; Current evidence; Broken-heart syndrome

1. Introduction

Takotsubo syndrome (TTS), also known as "broken-heart syndrome" or "stress cardiomyopathy," is a relatively rare acute cardiac condition with symptoms that mimic acute coronary syndrome (ACS) and has an estimated prevalence of approximately 2% among patients suspected of having ACS.[1] Recent studies indicate that TTS is not restricted to a single ethnicity, contrary to earlier assumptions, and may be more frequently observed in White European populations than in Japanese Asians.[2]

TTS is characterized by transient left ventricular (LV) systolic and diastolic dysfunction, often preceded by emotional or physical stressors, with apical ballooning in the absence of coronary artery disease or occlusion, producing a shape resembling a Japanese octopus fishing pot, after which it was named.[3] According to the American Heart Association, TTS is considered a primary and acquired cardiomyopathy.[4]

Owing to the scarcity of cases, the exact pathophysiology of TTS is poorly understood, with several well-documented and clinically supportive theories suggesting that a catecholamine surge and increased sympathetic nervous system (SNS) activation are the primary driving forces underlying symptom generation.[5]

Although TTS was previously considered benign, recent evidence indicates that it carries a mortality risk comparable to ACS and may be associated with multiple complications, including ventricular thrombus formation, arrhythmia, and cardiogenic shock.[6-8] Furthermore, emerging evidence suggests that TTS may be associated with diabetes mellitus (DM) type 2, with some studies indicating that DM in TTS patients could either increase long-term mortality or paradoxically be cardioprotective.[9,10]

This narrative review aims to synthesize the currently available literature to clarify the prognostic features of TTS and its relationship with diabetes.

2. Methodology

In this review, we conducted an extensive literature search using PubMed and Google Scholar, limited to articles published in the English language between January 1990 and June 2025. The following medical subject headings (MeSH) terms were used: "takotsubo syndrome" OR "takotsubo cardiomyopathy" OR "stress cardiomyopathy" OR "broken heart syndrome" AND "type 2 diabetes mellitus" OR "diabetes mellitus, type 2" OR "non-insulin-dependent diabetes" AND "prognosis" OR "risk factors" OR "mortality."

Eligible article types included editorials, commentaries, prospective cohort studies, retrospective and cross-sectional studies, meta-analyses, and systematic reviews relevant to the topic.

Titles, abstracts, and conclusions were initially assessed to determine the relevance of the retrieved articles. Inclusion criteria were articles published in English or with an English translation. Exclusion criteria were articles that were not published in English or did not have an English translation. After full-text screening of relevant articles and application of the inclusion and exclusion criteria, a total of 57 articles were selected out of 98,431 search results for inclusion in this narrative review (Tables 1 and 2).

3. Pathophysiology

The pathophysiology of TTS is multifactorial and involves several main hypotheses, including catecholamine surge, sympathetic overactivation, coronary vasospasm and microvascular dysfunction, hormonal and endothelial factors, systemic inflammation, and neuropsychological dysregulation.[21]

3.1. Catecholaminergic hypothesis and sympathetic nervous system activation

The most widely accepted hypothesis involves excessive stimulation of the SNS in response to emotional or physical stress, leading to a massive release of catecholamines.[22] This surge results in an abnormal cardiac response. The locus coeruleus, which releases norepinephrine and activates the hypothalamic–pituitary–adrenal axis, plays a central role in this cascade. The adrenal glands release norepinephrine and epinephrine, thereby increasing plasma catecholamine concentrations.[23]

The ventricular apex, rich in β-adrenergic receptors, is particularly vulnerable to this activation, which explains the characteristic apical ballooning of TTS. At high concentrations, catecholamines induce a shift in the

Table 1. Summary of search methodology

Items	Specifications
Date of search	June 4, 2025
Databases used	PubMed and Google Scholar
Searched terms	"Takotsubo syndrome" OR "takotsubo cardiomyopathy" OR "stress cardiomyopathy" OR "broken heart syndrome" AND "type 2 diabetes mellitus" OR "diabetes mellitus, type 2" OR "non-insulin-dependent diabetes" AND "prognosis" OR "risk factors" OR "mortality"
Timeframe	January 1990 to June 2025
Inclusion and exclusion criteria	(i) Inclusion criteria: Articles that were published in English or with an English translation (ii) Exclusion criteria: Articles that were not published in English or did not have an English translation

Table 2. Search summary

Year	Study/Author	Strengths	Limitations
2003	Burgdorf *et al.*[11]	Demonstrates reduced norepinephrine release in diabetic hearts; supports the protective role of diabetes in TTS	Experimental study, not specific to TTS
2008	Lyon *et al.*[12]	Introduced stimulus trafficking hypothesis; strong pathophysiologic basis	Mechanistic, lacking large clinical data
2010	Kuo *et al.*[13]	Highlights the role of reduced estrogen in postmenopausal women	Focused on gender roles; no interventional data
2015	Templin *et al.*[6]	A large multicenter prospective study showing severe outcomes in TTS	Limited to a European population
2016	Stiermaier *et al.*[14]	Multicenter registry (GEIST); evaluates diabetes impact on outcomes	Registry bias possible; observational design
2016	Bill *et al.*[10]	Suggests "diabetes paradox"—protective short-term, harmful long-term	Small cohort; observational
2018	Ghadri *et al.*[15]	Large prospective trial on long-term prognosis by gender	Demographic limitations
2018	Almendro-Delia *et al.*[16]	Links cardiogenic shock with mortality in TTS from the RETAKO registry	Limited follow-up duration
2020	Cammann *et al.*[17]	Age-stratified outcomes; gender/age interactions	*Post hoc* analysis
2021	Lu *et al.*[18]	Systematic review identifying prognostic factors in TTS	Dependent on the quality of the included studies
2022	Singh *et al.*[19]	Comprehensive review of pathophysiology and emerging concepts	Narrative format; no new data
2023	Núñez-Gil *et al.*[20]	Assesses the influence of smoking in the international TTS cohort	Focus limited to smoking

Abbreviations: GEIST: German–Italian–Spanish takotsubo registry; RETAKO: Registry on takotsubo syndrome; TTS: Takotsubo syndrome.

coupling of β_2 receptors from the stimulatory guanine nucleotide-binding protein to the inhibitory guanine nucleotide-binding protein, causing negative inotropy and LV dysfunction.[12]

3.2. Calcium dysregulation and oxidative stress

Prolonged activation of adrenergic receptors can alter key proteins involved in calcium regulation, particularly sarcoplasmic/endoplasmic reticulum Ca^{2+}–ATPase and phospholamban, thereby disrupting intracellular calcium homeostasis. This alteration compromises myocardial energy balance and promotes myocardial hypoxia and cellular damage.[24]

3.3. Neuropsychological dysregulation and brain-heart connections

TTS is often triggered by intense psychological stress, particularly in individuals with anxiety or depressive disorders, and has been associated with high levels of miR-16 and miR-26a. Functional changes observed in the amygdala and hippocampus—brain regions involved in the stress response—suggest a dysregulation of autonomic control. This imbalance could lead to cardiac damage similar to that observed after neurological insults.[19,25]

3.4. Microvascular dysfunction, coronary vasospasm, and hormonal role

According to Wittstein,[26] TTS results from microvascular dysfunction associated with increased sympathetic activity. Postmenopausal women and depressed patients appear particularly vulnerable due to impaired microcirculation and reduced vasomotor tone.[13] Estrogen deficiency, known for its cardioprotective properties, may promote vasospasm and endothelial dysfunction, thereby contributing to the increased susceptibility to developing TTS and other sequelae, such as coronary artery dissection leading to myocardial infarction.[27,28]

3.5. Systemic inflammation and immunity

Inflammation plays a crucial role in TTS pathophysiology. Cardiac magnetic resonance imaging often shows myocardial edema and characteristic gadolinium enhancement patterns, distinct from other cardiomyopathies.[29] Chronic inflammation could create a vulnerable environment for the development of the syndrome, as suggested by associations with autoimmune diseases, such as systemic lupus erythematosus and persistent immune activation.[17]

4. Prognostic factors

The prognosis for TTS has traditionally been considered to be favorable, with mortality rates comparable to those of the general population and full recovery of cardiac function. However, recent research has called this notion into question, raising the possibility that TTS patients may have a greater long-term mortality rate than the general population.[6,30] According to recent research, the underlying cause of TTS has a significant impact on the condition's prognosis.

There are two types of TTS: primary, which is brought on by psychological or emotional stress, and secondary, which is brought on by physical stressors such as trauma, stroke, or serious illness. Compared with the primary type,

secondary TTS is typically linked to significantly higher rates of morbidity and mortality.[31,32]

Since the reported rate of relapses varies between 1.8% and 10%,[33] it is critical to determine the underlying cause of TTS and take a trigger-based prognosis into account (Figure 1). Each important clinical variable is discussed in Table 3.

4.1. Gender

In the context of TTS, men typically have worse outcomes than women. This discrepancy is likely associated with the fact that men are more likely to experience acute critical events, which are linked to higher blood catecholamine levels and, ultimately, higher inpatient mortality.[27]

Based on results from a large prospective trial, Ghadri *et al.*[15] indicated that male patients had a significantly higher risk of all-cause mortality over a 5-year follow-up period than female patients. Through a number of mechanisms, estrogen in women has protective effects on the sympathetic nervous system and coronary circulation.

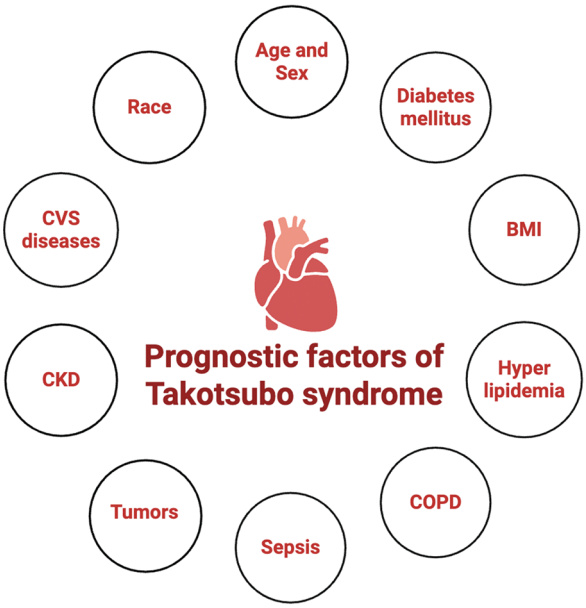

Figure 1. Prognostic factors associated with takotsubo syndrome. This figure illustrates the key prognostic factors that influence clinical outcomes in patients with takotsubo syndrome. These include demographic characteristics (e.g., age and sex), cardiovascular comorbidities (e.g., hypertension and coronary artery disease), systemic conditions (e.g., neurological and psychiatric disorders), and paradoxical factors, such as diabetes mellitus, which may have both protective and detrimental effects depending on the disease phase. Understanding these variables is essential for accurate risk stratification and effective clinical management. Created with BioRender. Javeria Taj. (2025). https://app. biorender.com/illustrations/68596bc1383b10b33dac9d43.
Abbreviations: BMI: Body mass index; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CVS: Cardiovascular.

Men may be more vulnerable to severe TTS outcomes due to their decreased estrogen levels. In postmenopausal women, an increased risk of developing TTS has been associated with estrogen insufficiency. In addition, animal studies suggest that estradiol supplementation can attenuate stress-induced cardiac dysfunction.[27]

4.2. Age

Postmenopausal women are more likely to develop TTS due to decreased estrogen levels.[50] Although the majority of patients are between the ages of 53 and 76, younger individuals, including children, may also be affected. In addition to having a higher risk of acute complications, including cardiogenic shock and the need for critical care, younger patients frequently exhibit identifiable emotional or neurological triggers.[26] Conversely, older patients, particularly women, have higher in-hospital and long-term mortality rates, which are likely associated with cardiovascular risk factors and comorbidities. It has been demonstrated that age predicts in-hospital mortality for women but not for men.[17]

4.3. Race

Due to conflicting results across studies, the effect of race on the prognosis of TTS remains uncertain. Several studies report that African American patients experience worse in-hospital outcomes, such as prolonged hospital stays and higher rates of mechanical ventilation and respiratory failure.[34] Other extensive investigations, however, have found that African American patients have a lower incidence of cardiogenic shock and reduced use of mechanical circulatory support, with no significant difference in mortality compared with white patients. White patients have also been shown to experience emotional triggers more frequently.[35]

Although some studies suggest that race may influence secondary TTS, other studies have reported no correlation after adjustment for demographics and comorbidities. Differences in study design, bias corrections, and disparate racial classifications across studies may account for these discrepancies.

4.4. Cardiovascular diseases

TTS prognosis is significantly influenced by a number of cardiovascular factors. A greater risk of heart failure, thromboembolic events, and in-hospital mortality is linked to atrial fibrillation,[36] a prevalent arrhythmia in TTS. Worse outcomes are also predicted by ventricular arrhythmias, especially ventricular fibrillation, due to catecholamine surges and disruptions in repolarization.[37] Male sex, physical stressors, and a low ejection fraction are frequently linked to cardiogenic shock, another serious

Table 3. Prognostic factors with references

Prognostic factors	Associated outcomes	Level of evidence	Coherence across studies	Direction of effect	References
Gender	Males have worse outcomes (higher in-hospital and long-term mortality)	Observational cohort	Consistent	↑ Risk	Ghadri *et al.*[15]
Age	Older patients, especially women, have higher long-term mortality; younger patients experience more acute events	Observational/Clinical trial	Consistent	↑ Risk in older patients	Wittstein;[26] Cammann *et al.*[17]
Race	Mixed results: African Americans have worse in-hospital outcomes; Whites have more emotional triggers	Observational/ Retrospective cohort	Inconsistent	↑ Risk (AA)	Dias *et al.*;[34] Zaghlol *et al.*[35]
Cardiovascular disease	Atrial fibrillation, ventricular arrhythmias, and cardiogenic shock worsen outcomes	Observational/Review	Consistent	↑ Risk	Almendro-Delia *et al.*;[16] Hammad *et al.*;[36] Möller *et al.*[37]
CKD	Increased hospital complications and long-term mortality	Observational cohort	Consistent	↑ Risk	Ando *et al.*;[38] Santoro *et al.*[39]
Malignancy	Poor in-hospital and long-term outcomes	Retrospective observational	Consistent	↑ Risk	Girardey *et al.*;[40] Joy *et al.*[41]
Sepsis	Higher in-hospital mortality and severe presentation	Case reports/ Retrospective	Limited	↑ Risk	Wang and Wen;[42] Napierkowski *et al.*[43]
COPD	Higher risk of respiratory failure and cardiogenic shock	Retrospective cohort	Consistent	↑ Risk	Li *et al.*;[44] Kato *et al.*[45]
Anemia	Worsens long-term and in-hospital outcomes	Observational cohort	Consistent	↑ Risk	Lu *et al.*[46]
BMI and hyperlipidemia	Obesity paradox: Hyperlipidemia may improve in-hospital outcomes	Retrospective observational	Variable	↓ or↑depending on the study	Desai *et al.*;[47] Li *et al.*[48]
Diabetes mellitus	Paradoxical: Lowers short-term complications but increases long-term mortality	Cohort/Observational/ Guideline	Variable	↑ Long-term risk; ↓ short-term complications	Stiermaier *et al.*;[9] Bill *et al.*;[10] Madias[49]

Abbreviations: BMI: Body mass index; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease.

complication that has been linked to increased mortality.[16] The prognosis can deteriorate due to life-threatening arrhythmias such as torsades de pointes caused by prolongation of the QT interval.[51]

Both short- and long-term mortality are influenced by LV dysfunction, and the risk is higher in older patients and those with an LV ejection fraction. Outflow tract obstruction does not affect overall mortality, but it may increase the risk of heart failure and hypotension in TTS, particularly among older women.[52]

4.5. Chronic kidney disease (CKD)

CKD is a known risk factor for takotsubo cardiomyopathy. Numerous studies have demonstrated that longer hospital stays and more in-hospital complications, including acute renal injury, are linked to decreased kidney function, specifically lower estimated glomerular filtration rate, in the context of TTS.[38] The influence of CKD on in-hospital mortality, however, has been inconsistently reported, with some studies showing no meaningful correlation.[53] Patients with lower estimated glomerular filtration rate levels had higher mortality rates and more cardiovascular events. Although a single small study suggests that CKD is associated with reduced long-term mortality, the majority of the evidence suggests that CKD is a negative prognostic factor for TTS.[39]

4.6. Malignancy

In individuals with TTS, malignancy is frequently documented and is highly correlated with poorer outcomes.[40] Unfavorable clinical progression may be associated with cancer-related processes, such as systemic inflammation and neurohormonal activation. Cancer-related pain and chemotherapy have also been identified as triggers of TTS.[54,55] In-hospital complications and death are increased among patients with malignancy, especially those with solid tumors, hematologic malignancies, or metastatic illness.[41] Extensive follow-up research and meta-analyses indicate that TTS patients with underlying cancer have a markedly higher mortality rate.

4.7. Sepsis

A proportion of TTS cases, especially those presenting with secondary manifestations, have been reported to

be precipitated by sepsis.[42] Using multivariable analysis, several studies have shown that sepsis considerably increases the risk of in-hospital death in TTS. Higher rates of organ dysfunction and more severe clinical manifestations are associated with sepsis-related TTS. These findings highlight the crucial need for early diagnosis and treatment of sepsis in TTS patients.[43]

4.8. Chronic obstructive pulmonary disease (COPD)

Most TTS individuals have been found to have COPD, which is known to function as a physiological stressor that can trigger the onset of TTS.[56] Patients with coexisting COPD have shown a higher risk of respiratory complications and cardiogenic shock during hospitalization. The inpatient mortality rate is higher in this subgroup.[44] Furthermore, TTS associated with an acute pulmonary event is associated with a higher long-term mortality rate than stable chronic lung illness.[45] In addition, smoking, a major cause of COPD, has well-established cardiovascular hazards that may further exacerbate poor outcomes.[20]

4.9. Hyperlipidemia and body mass index

Patients with TTS are often obese, which is associated with an increased risk of in-hospital complications, such as myocardial infarction, cardiac arrest, and cardiogenic shock.[47] A phenomenon known as the "obesity paradox" has been observed. In addition, individuals with higher body mass index may have better long-term outcomes than those with lower body mass index.[57]

Hyperlipidemia is also common in TTS. Several studies have reported better in-hospital outcomes for patients with hyperlipidemia, likely due to the protective benefit of statins and higher overall nutritional status, but other data indicate no clear association with mortality.[48]

4.10. Anemia

A significant proportion of TTS patients suffer from anemia, which has been associated with worse clinical outcomes[46] and is linked to higher incidences of complications, such as organ dysfunction and ventricular arrhythmias.[46] Several studies highlight its role in predicting long-term mortality. In addition, prolonged hospitalization in TTS cases has been linked to anemia.[58] These findings highlight the crucial need to determine the prognosis and manage patient risk.

4.11. Association with DM

Various studies report varying incidences of DM in TTS patients, with a reported prevalence between 1.6% and 21.1%.[10] DM is a recognized risk factor for cardiovascular disease, but its prognostic role in TTS remains controversial.[14] Several studies suggest higher long-term mortality in diabetic patients, whereas others report a lower incidence of TTS among diabetic patients, indicating a possible complex pathophysiological interaction.[10,18] Núñez-Gil *et al*.[20] specifically demonstrated that diabetes was associated with a significantly increased risk of long-term death. These discrepancies may be attributed to methodological differences, particularly in follow-up duration and assessment criteria.

In a large multicenter study, diabetic patients with TTS presented with more severe heart failure and pulmonary edema, mainly due to typical apical ballooning causing impaired systolic function. However, diabetes did not significantly influence short-term outcomes, although it was associated with increased long-term mortality. This suggests that prognosis in patients with TTS may be influenced more by the chronic consequences of diabetes than by the acute episode itself.[59]

Conversely, several studies support a potential protective effect of diabetes in TTS. According to Madias,[49] diabetic autonomic neuropathy could reduce the excessive adrenergic response responsible for the myocardial dysfunction observed in TTS. Indeed, an experimental study showed that stimulation-induced cardiac norepinephrine release was decreased by 25% in diabetic patients compared with non-diabetic patients, whereas basal release remained comparable. This reduction, independent of cardiac function and blood pressure, could mitigate stress-induced myocardial damage and explain the lower prevalence of TTS in diabetic patients.[11]

An analysis of 33,894 patients with TTS confirmed this trend, reporting a lower prevalence of diabetes than in the general population (16.8% vs. 26.9%, according to the National Health and Nutrition Examination Survey). This finding reinforces the idea that diabetes may modulate susceptibility to TTS, likely due to adrenergic desensitization related to autonomic neuropathy. However, when TTS occurs in diabetic patients, long-term cardiovascular complications remain more frequent.[49]

In summary, diabetes appears to exert opposing effects depending on the timing of follow-up: A short-term protective effect through reduced catecholaminergic hyperstimulation, but a long-term detrimental effect due to the progression of metabolic and vascular complications. Thus, diabetes should be considered a mixed prognostic factor, requiring prolonged monitoring and individualized management after a takotsubo episode.

5. Management

Following the guidelines for ACS and heart failure, TTS is diagnosed when coronary artery disease has been ruled out. Cardiac echocardiography and cardiac magnetic

resonance imaging aid in excluding diseases such as myocarditis or LV outflow tract obstruction, and in determining underlying reasons.[60] Medications frequently used in heart failure and cardiac care are commonly employed to treat TTS. Beta-blockers are widely used and may mitigate the effects of catecholamine surges. While some studies link pre-admission use to a greater incidence of complications, others show no significant advantage in mortality or recurrence.[61] Due to their impact on vascular function and sympathetic activity, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are also often prescribed. These medications have been linked to lower long-term cardiac mortality and recurrence rates. Patients with heart failure and systolic dysfunction typically receive both classes as part of their treatment.[62]

6. Conclusion

Complex processes, such as catecholamine surge, sympathetic overactivation, and microvascular dysfunction, contribute to TTS. Patients' age, gender, cardiovascular comorbidities, and systemic disorders all influence prognosis. Diabetes has a paradoxical role: autonomic neuropathy in diabetes may attenuate short-term events and acute catecholamine effects; however, diabetes is linked to more severe cardiac impairment, higher rates of pulmonary edema, and worse long-term mortality in patients with TTS. This demonstrates the dual impact of diabetes, with protective mechanisms coexisting alongside long-term consequences that exacerbate outcomes. To improve patient risk classification and treatment, a thorough understanding of these prognostic factors is crucial, particularly the complex function of diabetes.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Moiz Shah Khan, Javeria Taj
Visualization: Javeria Taj
Writing–original draft: Haris Muhammad, Aparna Iyer, Amer Hammad, Oghenetejir Gbegbaje, Syeda Hafsa Qadri
Writing–review & editing: Haris Muhammad, Hafeez Hassan Virk, Hermann Yokolo

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Impact of July resident turnover on inpatient outcomes in patients with congestive heart failure and concomitant sepsis: Analysis of the national inpatient sample

Oghenetejiri Gbegbaje[1], Gabriel Alugba[1], Haris Muhammad[2], Favour Nelson[3], Chidubem Ezenna[4], Aparna Iyer[1], Vicky Kumar[5]*, Dipal R. Patel[1], and Sidni Fullerton[1]

[1]Department of Internal Medicine, Englewood Hospital and Medical Center, Englewood, New Jersey, United States

[2]Department of Cardiovascular Medicine, Newark Beth Israel Medical Center, Newark, New Jersey, United States

[3]Department of Internal Medicine, Geisinger Medical Center, Danville, Pennsylvania, United States

[4]Department of Internal Medicine, Baystate Medical Center, Springfield, Massachusetts, United States

[5]Department of Critical Care, George Washington University, Washington, District of Columbia, United States

***Corresponding author:**
Vicky Kumar
(dr.vickykumar08@gmail.com)

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Abstract

The notion of a "July effect," suggesting that the influx of new residents in teaching hospitals every July (JU) may adversely affect patient care and outcomes, remains debatable. This study evaluated the impact of resident turnover in JU on patients admitted for congestive heart failure (CHF) and concomitant sepsis. This retrospective cohort study utilized data from the 2016 to 2020 National Inpatient Sample. Patients with CHF and concomitant sepsis hospitalized at teaching hospitals, as determined by International Classification of Diseases, 10th Revision (ICD-10) codes, were included. Univariate and multivariate logistic regression analyses were performed to estimate in-hospital mortality and secondary outcomes after adjustment for confounders, including cardiac arrest (CA), cardiogenic shock, non-ST segment elevation myocardial infarction, respiratory failure (RF), use of cardiac and respiratory devices, and healthcare resource utilization metrics such as length of stay (LOS) and total hospitalization charges (TOTCHG). Patients were classified according to the month of admission as JU or other months (OM) to investigate the potential impact of the "July effect" on patient outcomes. The study included 281,874 patients, of which 8% were in the JU group and 92% in the OM group. The mean age was 71 ± 13 years, with a slight male predominance (52% vs 48%), and most patients were White (70%). A total of 34,974 in-hospital deaths occurred, with no significant difference between the JU and OM groups (odds ratio [OR] = 0.95; 95% confidence interval [CI] = 0.85–1.06; p=0.329). Similarly, no significant differences were observed in CA (OR = 0.88; 95% CI = 0.70–1.11; p=0.282), RF (OR = 0.98; 95% CI = 0.90–1.06; p=0.597), ventilator use (OR = 0.99; 95% CI = 0.77–1.25; p=0.879), LOS (11.3 vs. 11.3), and TOTCHG (USD 136,377 vs. USD 136,181). However, lower rates of acute kidney injury were observed in the JU group compared with the OM group (OR 0.90; 95% CI, 0.84–0.98, p=0.011). This study demonstrates that the "July effect" does not significantly influence

in-hospital outcomes in patients with CHF and concomitant sepsis. While mortality and major clinical outcomes were comparable across groups, lower rates of acute kidney injury were observed in patients admitted in JU. Further research is needed to understand the complex interplay between healthcare resident turnover and patient outcomes.

Keywords: Congestive heart failure; Concomitant sepsis; July effect; July phenomenon; Inpatient outcomes; National inpatient sample; International classification of diseases 10th revision codes

1. Introduction

The "July effect" refers to a phenomenon observed in teaching hospitals, where increases in medical errors, complications, and mortality rates have been reported in July (JU). Every year, teaching hospitals undergo a turnover period among house staff when experienced trainees depart and are replaced by a new group of trainees to maintain continuity of care. This annual changeover typically occurs in JU and affects more than 100,000 trainees in the United States[1] and approximately 32,000 in Europe.[2]

Because routine hospital operations are disrupted and institutional knowledge and experience are loss during staff turnover, this period is thought to increase the risk of medical errors and adverse patient outcomes. Given the challenges of understanding and acclimatizing to the healthcare system and the complexities of delivering acute care as new trainees acclimate, there have been suggestions that outcomes may be poorer in JU than later in the academic year.[3] As a result, this transition period has been called the "August killing season" in the United Kingdom and the "July phenomenon" or "July effect" in the United States.[4,5] Prior investigations have evaluated the possibility of such an association with conflicting results.[6-11] Several studies have demonstrated poor outcomes, whereas others have found no evidence supporting the JU effect.[6,9-12]

The inexperience of new trainees may be offset by increased supervision from senior clinicians during this transitional period, potentially resulting in comparable, if not improved, patient outcomes. Despite multiple studies examining the impact of JU admission on patient outcomes, data remain limited for patients with congestive heart failure (CHF), particularly those with concomitant sepsis. Therefore, this study aims to determine whether patients admitted during the early academic year experience higher rates of complications, mortality, or non-routine discharge during hospitalization for CHF with concomitant sepsis. Non-routine discharge was defined according to National Inpatient Sample (NIS) conventions and included discharge to skilled nursing facilities, long-term acute care hospitals, rehabilitation facilities, home health services, hospice, or discharge against medical advice.

2. Methods

2.1. Study design and database description

We conducted a retrospective cohort study of adult patients hospitalized between 2016 and 2020 with CHF and concomitant sepsis in acute care hospitals across the United States. Patients were identified from the NIS database. The NIS contains discharge data from a 20% stratified sample of all hospitals and is part of the Healthcare Quality and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality. Each discharge record includes patient demographics, primary payer, hospital characteristics, principal diagnosis, secondary diagnosis, and procedural codes. These data are publicly available through the HCUP-NIS database; therefore, institutional review board approval was not required.

Using the NIS data from 2016 to 2020, a retrospective cohort of patients with CHF and concomitant sepsis admitted to teaching hospitals was constructed using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM). Patients were included if both CHF and sepsis ICD-10-CM codes were present within the same hospitalization. The NIS does not consistently capture present-on-admission indicators for all years; therefore, sepsis could not be definitively classified as either present on admission versus hospital-acquired. Patients were classified according to month of admission as JU or other months (OM) to investigate the potential impact of the JU effect on patient outcomes.

Patient admissions to non-teaching hospitals were excluded. In the NIS database, hospitals are classified as teaching hospitals if they have one or more Accreditation Council for Graduate Medical Education-approved residency programs, are members of the Council of Teaching Hospitals, or have a ratio of full-time equivalent interns and residents to beds of 0.25 or higher. In urban teaching hospitals, CHF and sepsis patients were evaluated

for differences in baseline and in-hospital characteristics between those admitted in JU and OM of the year. The burden of comorbid disease was identified using the Charlson comorbidity index.

This study aimed to compare in-hospital mortality among CHF and sepsis admissions in teaching hospitals in JU versus OM of the same calendar year. Secondary outcomes included rates of cardiac arrest (CA), cardiogenic shock (CS), respiratory failure (RF), non-ST-segment elevation myocardial infarction (NSTEMI), and acute kidney injury (AKI), as well as use of cardiac and respiratory devices. Cardiac device utilization included ICD-10 Procedure Coding System (ICD-10-PCS) codes for intra-aortic balloon pump placement, temporary mechanical circulatory support (e.g., Impella), and temporary pacemaker insertion, while respiratory device utilization included codes for invasive mechanical ventilation, non-invasive ventilation, and tracheostomy. We also evaluated healthcare resource utilization measures, such as length of stay (LOS) and total hospitalization charges (TOTCHG).

The NIS does not provide detailed information on specific medical therapies administered (e.g., pharmacologic treatments or fluid/vasopressor management). Only major procedures identifiable through ICD-10-PCS codes—such as mechanical ventilation, non-invasive ventilation, renal replacement therapy, and temporary mechanical circulatory support—were included in the analysis.

2.2. Statistical analysis

Statistical analysis was performed using STATA version 18 (StataCorp, Texas, USA). All analyses incorporated the NIS stratified and clustered sampling design and discharge weights using the svy survey commands to obtain nationally representative estimates and correct variance calculations. Univariate logistic regression analysis was used to calculate unadjusted odds ratios (ORs) for primary and secondary outcomes. Multivariate logistic regression analysis was performed to adjust for potential confounders. Chi-square tests and Student's *t*-tests were used to compare categorical and continuous variables, and a $p<0.05$ was defined as the threshold for statistical significance.

3. Results

3.1. Patient characteristics

During the study period, from January 1, 2016, to December 31, 2020, 281,874 patients with CHF and sepsis met the inclusion criteria. Among these, 22,549 (8%) were admitted in JU, and 259,324 (92%) were admitted in OM of the year. Patients admitted during JU and OM had comparable median age (71.6 vs. 71.9), racial distribution, with the population being predominantly White (68.8% vs. 69.9%), and median income distribution (Table 1). Compared with OM admissions, patients admitted in JU had higher rates of comorbidities, including dyslipidemia, obesity, and liver disease. Conversely, OM admissions had higher rates of electrolyte abnormalities and anemia compared with JU admissions. Although these differences were statistically significant, the absolute differences were small (Table 1).

3.2. In-hospital mortality based on the month of admission

A total of 34,974 in-hospital deaths occurred during the study period. Based on Table 2, the mortality rate in JU was 11.24%, compared with 12.49% in OM. In unadjusted comparisons, in-hospital mortality was higher in patients admitted in OM than in JU (OR = 0.88; 95% confidence interval [CI] = 0.81–0.97, p=0.013).

In a multivariate analysis adjusting for demographics, comorbidities, hospital characteristics, cardiac and non-cardiac procedures, and in-hospital clinical events, JU admission was not independently associated with in-hospital mortality compared with OM admissions (adjusted OR = 0.95; 95% CI = 0.85–1.06; p=0.329) (Table 3).

3.3. Secondary outcomes

No statistically significant differences were observed in the rates of CA, CS, RF, NSTEMI, or use of cardiac and respiratory devices (Table 2). However, compared with OM admissions, patients admitted in JU had lower rates of AKI (adjusted OR = 0.90; 95% CI = 0.84–0.98; p=0.011) (Table 3). The median LOS for patients admitted during JU and OM is presented in Table 4. There was no significant difference in LOS between the groups. Median total hospitalization charges were also similar, with TOTCHG of 136,377 (JU) versus 136,182 (OM).

4. Discussion

The findings of our study, involving a cohort of 281,874 patients, provide a comprehensive analysis of the impact of JU resident turnover on inpatient outcomes in patients with CHF and concomitant sepsis. The study population was predominantly elderly, with a mean age of 71. Notably, despite higher rates of comorbidities, including dyslipidemia, obesity, and liver disease in JU patients, the in-hospital mortality rate was not higher compared with OM. Further analysis of specific clinical outcomes also revealed no significant differences. However, there was a notable difference in the rates of AKI between the JU and OM groups. This observation may warrant further investigation into the specific factors

Table 1. Characteristics of hospitals and patients

Patient characteristics	Admission month		*p*-value
	July	Other months	
No. of patients (%)	22,549 (8)	259,324 (92)	-
No. of female patients (%)	10598 (47)	71,708 (48)	0.0455
Race/ethnicity (%)			
White	68.8	69.9	0.3846
Black	16	15.7	
Hispanic	8.5	8.3	
Asian or Pacific Islander	3.4	3.1	
Native American	0.9	0.7	
Other	2.3	2.4	
Median age (years)	71.6±13.55	71.9±13.42	-
Charlson comorbidity index score (%)			
0	0	0	-
1	7.4	7.2	
2	14.7	14	
>3	77.9	78.8	
Median annual income of patient ZIP code (%)			
USD 1–38,999	28.3	28.2	0.7832
USD 39,000–47999	25.3	25	
USD 48,000–62,900	24.9	25.6	
>USD 63,000	21.5	21.2	
Insurance type (%)			
Medicaid	77.7	77.7	0.7953
Medicare	9.6	9.4	
Private	10.9	11.3	
Uninsured	1.7	1.6	
Hospital region (%)			
Northeast	22.4	21.3	0.2780
Midwest	24	23.9	
South	32.6	33.6	
West	20.6	21.1	
Hospital bed size (%)			
Small	22.8	23.2	0.8348
Medium	29.3	29.1	
Large	47.9	47.7	
Urban location			
Urban	NA	NA	NA
Rural	NA	NA	NA
Teaching hospital			
Yes	NA	NA	NA
No	NA	NA	NA
Cardiovascular comorbidities (%)			
Dyslipidemia	10.8	9.6	0.0058
History of percutaneous coronary intervention	0.6	0.7	0.2690
History of coronary artery bypass grafting	8.1	8.1	0.9960
History of pacemaker placement	5.6	5.6	0.9424
Coronary artery disease	11.9	0.94	0.0805
History of stroke	2.6	2.7	0.8737
Hypertension	5.5	5.4	0.8274
Peripheral vascular disease	4.7	4.7	0.8512
Diabetes	9.5	9.1	0.4879
Heart failure			
Obesity	24.5	23.3	0.0498
Smoking	20.9	21.4	0.3899
Atrial fibrillation	45	46.3	0.0907
Non-cardiovascular comorbidities (%)			
Liver disease	13.6	12.6	0.0366
Electrolyte abnormalities	61.2	63.4	0.0021
Maintenance hemodialysis	6.7	6.1	0.1108
Oxygen dependence	6.2	6.3	0.8330
Anemia	45.8	47.6	0.0181
Chronic obstructive pulmonary disease	28.9	29.3	0.6335
Hyperthyroidism	0.5	0.6	0.5287
Depression	13.2	12.9	0.6225
Obstructive sleep apnea	13.6	13.7	0.8474

Abbreviation: NA: Not available.

or practices during the JU turnover that could contribute to a potential protective effect against AKI in this patient population. AKI was identified using ICD-10-CM codes. The lower AKI incidence in JU may reflect minor differences in case mix, more conservative early-year trainee management, seasonal variation, or unmeasured confounding. These hypotheses are speculative and warrant further investigation. Overall, these results suggest a general equivalence in the management and outcomes of patients with CHF and concomitant sepsis, irrespective of the timing of resident turnover.

Numerous studies in recent years have examined the impact of new residents and fellows on patient outcomes, including differences in mortality, morbidity, and

Table 2. Unadjusted clinical outcomes among patients by month of admission

Clinical outcome	Admission month		Unadjusted odds ratio (95% confidence interval)	*p*-value
	July	Other months		
In-hospital mortality	11.2	12.5	0.88 (0.81–0.97)	0.013
Cardiac arrest	2.4	3.0	0.81 (0.67–0.98)	0.029
Cardiogenic shock	3.4	3.5	0.97 (0.82–1.14)	0.722
Respiratory failure	29.8	31.8	0.91 (0.86–0.98)	0.008
Mechanical ventilation	2.0	2.7	0.92 (0.74–1.13)	0.411
Non-ST-segment elevation myocardial infarction	5.85	6.49	0.89 (0.79–1.02)	0.091
Acute kidney injury	57.26	59.48	0.91 (0.86–0.97)	0.003
Use of cardiac devices	0.19	0.28	0.69 (0.35–1.36)	0.281

Table 3. Multivariate regression analysis of in-hospital mortality and other outcomes (July versus other months)

Clinical outcome	Odds ratio	95% confidence interval		*p*-value
		Lower limit	Upper limit	
In-hospital mortality	0.95	0.85	1.06	0.329
Cardiac arrest	0.88	0.70	1.11	0.282
Cardiogenic shock	1.03	0.84	1.28	0.762
Respiratory failure	0.98	0.90	1.06	0.597
Mechanical ventilation	0.97	0.77	1.25	0.879
Non-ST-segment elevation myocardial infarction	0.91	0.78	1.06	0.220
Acute kidney injury	0.90	0.84	0.98	0.011
Use of cardiac devices	0.74	0.34	1.61	0.446

Table 4. Healthcare resource utilization

Healthcare resource utilization	Admission month	
	July	Other months
Length of stay (days)	11.3±13.4	11.3±11.6
Total hospital charges (USD)	136,377±231,276	136,182±194,421

readmission rates. Some researchers advocate shifting the focus from the JU effect hypothesis to reassessing system-level factors that may influence patient care consistently over time.[13] It is crucial to highlight the distinct treatment approaches for CHF and sepsis, as they pose challenges in patient management. While CHF patients typically receive fluid restriction, septic patients require fluid administration. Despite sharing similar presentations, such as hypotension and AKI, the differing treatment strategies can lead to complexities in patient care. Nevertheless, our findings did not demonstrate significant differences in mortality between JU admission and OM patients, suggesting that while challenges in treatment differentiation exist, overall patient outcomes remain comparable.

When comparing the findings from our study to existing literature, it is noteworthy that studies such as the one by Young *et al.*[3] reported an increased in-hospital mortality. They systematically reviewed 39 studies encompassing various medical specialties and found an increase in mortality and a decrease in hospital efficiency attributed to changeovers occurring at the end of the academic years. A study examining all United States death certificates from 1979 to 2006, focusing on medication errors, found that fatal medication errors increased by 10% in JU compared with OMs.[7] An 18-year study of 1,312,006 hospitalizations for acute myocardial infarction admitted to urban teaching hospitals or non-teaching hospitals in May and JU showed that JU acute myocardial infarction admissions had lower in-hospital mortality than May admissions.[14] Other studies, especially in the surgical literature, reported no significant impact on outcomes.[10,15,16]

In our study, the absence of the JU effect in patients admitted with CHF and concomitant sepsis could be attributed to several factors. In teaching hospitals, a typical resident teaching team structure comprises junior/1st-year residents, senior residents, and supervising attendings, establishing multiple layers of oversight throughout the year. This structure may mitigate lapses in critical patient information, ensuring thorough and heightened attention to patients regardless of the complexity of their medical presentation. In addition, the heightened vigilance observed in new residents may contribute to more meticulous monitoring, potentially facilitating early interventions. Teaching hospitals have implemented various strategies, such as robust orientation programs and enhanced supervision, to mitigate the potential impact of the JU effect. These initiatives aim to ensure a seamless transition of care and maintain high standards of patient safety. Like any non-medical corporate organization, hospitals undergo human resource turnover.[3] This turnover, whether through staff departures or new additions,

necessitates adjustments and often an orientation process for newcomers to familiarize themselves with the work system. The effectiveness of these system factors is crucial in facilitating the smooth acclimatization of new staff members.

Teaching hospitals likely include non-teaching physicians and other standardized care team members, who remain consistent across academic years. Such multidisciplinary systems decrease dependence on house staff and facilitate smoother transitions in care, likely mitigating the "July effect." Academic curricula may also be structured to provide more intensive supervision at the beginning of training, facilitating a gradual transition from direct supervision to routinely scheduled oversight with increasing autonomy by the end of the training period.[17,18] Not all trainees at a given level possess the same skills. Increasing emphasis on graded responsibilities, in which autonomy is tailored to competency, may help ensure that individual residents are entrusted with a level of responsibility appropriate for their skill level.[19-21] Developing changeover systems informed by human factor principles, such as avoiding cognitive overload and fatigue, may also have benefits. For example, reducing initial trainee workload (e.g., lower admission caps or panel sizes) and enhancing supervision, or increasing the use of multidisciplinary teams, can improve patient care.[22,23]

While our study benefits from utilizing the extensive NIS database and its standardized survey methodology, there are notable limitations. The NIS does not contain physiologic severity indicators, such as laboratory values, vasopressor use, or intensive care unit (ICU) admission status. Although we adjusted for available severity-related diagnoses and procedures (e.g., CA, RF, mechanical ventilation), residual confounding due to unmeasured illness severity cannot be excluded. Primarily, the administrative nature of the database restricts access to detailed clinical information, relying instead on ICD-10 coding diagnoses. Moreover, the dataset lacks information on these patients' treatments and the treatment team involved. In addition, our observations are confined to hospitalizations, limiting our ability to extrapolate our findings to post-hospitalized patients. This absence of post-discharge data restricts our ability to evaluate long-term outcomes such as 30-day mortality, readmission patterns, or outpatient management quality, all of which may be sensitive to variations in trainee experience. The lack of granular temporal data, such as time to intervention, escalation of care, or delays in diagnostic testing, also prevents us from understanding whether more subtle workflow inefficiencies occur during trainee turnover months despite equivalent major clinical outcomes.

Another limitation is that the NIS does not capture the internal structure, culture, or supervision intensity of individual teaching hospitals, all of which may differ substantially across institutions and influence how resident turnover affects care delivery. For example, some academic centers employ robust orientation curricula, simulation-based skill refreshers, and tiered supervision systems during JU, while others may rely more heavily on informal transition processes. Without this contextual detail, our findings represent an average effect across diverse institutions and may not reflect local variability. Similarly, differences in staffing patterns, nursing ratios, hospitalist involvement, and the availability of multidisciplinary support teams—factors known to influence patient outcomes—are not available in the NIS. The inability to separate initial trainee encounters from care delivered primarily by experienced staff further limits our interpretation of whether residents played a direct role in the observed outcomes, or whether attending-driven decision-making buffered any potential adverse effects.

Finally, our analysis focused only on JU versus all OMs to evaluate the classical "July effect." Future studies may explore early-academic-year gradients (e.g., July–September) to determine whether progressive changes in trainee experience influence outcomes. It is possible that any adverse effects associated with inexperience are not confined strictly to JU but may extend into later summer months as trainees assume increasing responsibilities with gradually decreasing supervision. Exploring these gradients may help clarify whether there is a stepwise improvement in outcomes as residents progress through the early stages of their training cycle. In addition, future investigations could evaluate whether certain subgroups—such as patients requiring ICU-level interventions, those with extreme physiologic derangements, or those treated in resource-limited teaching hospitals—experience differential outcomes during resident transition periods. Such analyses would provide a more nuanced understanding of how institutional characteristics, patient complexity, and trainee readiness interact.

Prospective studies incorporating detailed clinical variables, real-time workload metrics, and assessments of supervision intensity would be particularly valuable in identifying whether subtle care variations occur even in the absence of measurable differences in outcomes. Ultimately, expanding the focus beyond binary month comparisons may help illuminate additional aspects of the trainee transition period that large administrative datasets alone cannot capture. Furthermore, evaluating how institutional policies, resident onboarding structures, and multidisciplinary coordination evolve throughout the

academic year may offer additional insight into factors that protect against adverse outcomes. Understanding these elements could help refine transition protocols and strengthen system-level safeguards, ultimately ensuring that patient safety remains consistent regardless of trainee experience or timing within the academic cycle.

5. Conclusion

In this large, nationally representative cohort study evaluating the impact of JU resident turnover on clinical outcomes among patients hospitalized with CHF and concomitant sepsis, we found no evidence to support the presence of a clinically meaningful "July effect." After adjusting for demographic factors, comorbidity burden, hospital characteristics, and relevant in-hospital events, JU admission was not independently associated with increased mortality, major complications, or healthcare resource utilization. These findings are particularly important given the vulnerability of this dual-diagnosis population, for whom the competing management demands of fluid-sensitive heart failure and fluid-requiring sepsis create substantial clinical complexity even under ideal conditions.

Importantly, the absence of an observed JU effect in this high-risk subgroup suggests that modern teaching hospitals may have developed sufficiently robust systems of supervision, structured transition frameworks, and team-based care models to minimize the impact of trainee inexperience during turnover periods. Contemporary residency programs emphasize graded autonomy, standardized onboarding, and multi-layered oversight, all of which may mitigate the theoretical risks historically associated with the early academic year. Furthermore, the involvement of interprofessional staff—nurse practitioners, physician assistants, hospitalists, pharmacists, and nursing teams—creates additional layers of continuity that help ensure stable patient care irrespective of resident experience level. Our findings support the evolving perspective that system-level resilience, rather than individual trainee experience alone, plays a pivotal role in maintaining consistent inpatient outcomes.

The unexpected finding of lower rates of AKI in patients admitted in JU warrants further exploration. While this observation may reflect seasonal variation, shifts in case mix, or unmeasured confounding, it also raises the possibility that heightened caution, increased supervision, or more conservative management patterns early in the academic year may contribute to differences in clinical decision-making behaviors. Although speculative, this finding emphasizes the need for future studies to evaluate not only outcomes but also the mechanisms of care delivery across academic transitions. Incorporating granular physiologic data, medication records, and ICU-level data into future investigations may clarify whether such patterns reflect differences in clinical practice or inherent patient characteristics.

Overall, our findings add to a growing body of evidence suggesting that the JU effect may be less pronounced—or altogether absent—in many modern clinical contexts, especially when care processes are supported by standardized pathways, institutional checks, and rigorous training structures. For patients, clinicians, and policymakers, these findings provide reassurance that seeking care in JU at teaching hospitals does not appear to compromise safety, even for medically complex conditions such as CHF with concomitant sepsis. This is an important public health message, as delayed care-seeking behaviors based on misconceptions about trainee turnover could lead to preventable morbidity.

Nevertheless, the study highlights the need for continued monitoring of transition periods in medical education. The persistence of conflicting findings in prior literature suggests that the JU effect may be context-dependent, varying by specialty, procedure type, institutional support systems, and patient acuity. Understanding these nuances is essential for designing targeted interventions that sustain safe care delivery throughout the academic year. Future research using prospective designs, advanced risk-adjustment methods, and detailed clinical parameters is warranted to better characterize these contextual factors and further refine the understanding of academic-year transitions.

Our analysis of more than 280,000 hospitalizations demonstrates that JU resident turnover does not adversely impact inpatient outcomes among CHF patients with concomitant sepsis. The stability of clinical outcomes across the academic calendar underscores the effectiveness of modern supervisory frameworks and institutional safeguards within teaching hospitals. Thus, patients can be reassured that accessing care in JU is safe, and healthcare systems should continue to optimize training and transition processes to maintain high-quality care independent of trainee turnover timing.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Oghenetejiri Gbegbaje
Data curation: Oghenetejiri Gbegbaje, Haris Muhammad, Chidubem Ezenna, Gabriel Alugba
Formal analysis: Oghenetejiri Gbegbaje
Investigation: Oghenetejiri Gbegbaje
Methodology: Haris Muhammad
Writing–original draft: Oghenetejiri Gbegbaje, Gabriel Alugba, Favour Nelson, Vicky Kumar, Aparna Iyer, Sidni Fullerton
Writing–review & editing: Oghenetejiri Gbegbaje, Vicky Kumar, Dipal R. Patel, Haris Muhammad

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Global burden of ischemic stroke and attributable risk factors from 1990 to 2021: Insights from the Global Burden of Disease study

Xi Peng†, Le Li†, Sheng Su, Zhenhao Zhang, Yulong Xiong, Likun Zhou, Jing Luo, Shengsong Zhu, Zhuxin Zhang, Lihui Zheng*, and Yan Yao*

Arrhythmia Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

Abstract

Ischemic stroke remains a major contributor to population-level health loss, yet contemporary patterns vary widely across locations and over time. Hence, evidence integrating mortality and disability, and benchmarking prevention potential, is still needed. We characterized the ischemic stroke burden using the Global Burden of Disease 2021 estimates for 1990–2021, reporting prevalence, incidence, and disability-adjusted life years (DALYs) per 100,000 persons. The share of DALYs associated with individual risk factors was derived as population-attributable fractions. For 2021, per 100,000 persons, the global age-standardized prevalence, incidence, and DALY rates for ischemic stroke were 819.5 (95% uncertainty interval [UI]: 760.3–878.7), 92.4 (95% UI: 79.8–105.8), and 837.4 (95% UI: 763.7–905.0). From 1990 to 2021, the prevalence decreased by 3.5% (95% UI: −5.1% to −2.1%), incidence decreased by 15.8% (95% UI: −18.8% to −13.3%), and DALYs decreased by 34.9% (95% UI: −39.5% to −30.0%). Patterns differed substantially across sexes, sociodemographic index (SDI), and geographies. DALY rate attribution was dominated by systolic blood pressure (58.38%), followed by low-density lipoprotein cholesterol (29.82%) and fasting plasma glucose (17.58%). Ischemic stroke incidence shifted from high-SDI regions to middle- and low-SDI regions from 1990 to 2021. Despite declining age-standardized rates, absolute numbers increased due to population growth, aging, and improved screening capabilities.

Keywords: Ischemic stroke; Prevalence; Incidence; Disability adjusted life years; Epidemiology

†*These authors contributed equally to this work.*

***Corresponding authors:**
Lihui Zheng
(zhenglihui@263.net)
Yan Yao
(ianyao@263.net.cn)

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1. Introduction

Ischemic stroke is a leading contributor to population-level health loss, producing substantial mortality and long-term disability worldwide.[1] Care has advanced in recent decades—spanning earlier detection, acute therapies, and better control of vascular risks such as hypertension, dyslipidemia, and diabetes.[2] These trends highlight the effectiveness of public health interventions and medical advancements in reducing the global incidence and burden of ischemic stroke. Rising levels of population aging,

unhealthy behaviors, and environmental change argue for updated epidemiologic estimates of ischemic stroke. This update can facilitate the design of effective public health strategies and the optimization of medical resource allocation, ultimately reducing the disease's burden.[3]

This study aims to utilize data from the Global Burden of Disease (GBD) study to conduct a detailed analysis of the global trends in prevalence, incidence, and disability-adjusted life years (DALYs) for ischemic stroke from 1990 to 2021. By examining these trends, we seek to elucidate the impact of past and ongoing public health efforts and identify areas requiring further attention to alleviate the global burden of ischemic stroke.

2. Data and methodology

2.1. Overview of the GBD study

GBD 2021 offers standardized estimates of mortality, incidence, prevalence, years of life lost, years lived with disability, DALYs for 371 diseases and injuries, 288 causes of death, and 88 risk factors across 204 countries/territories.[4-7] This analysis uses recent epidemiologic inputs and standardized methods. Age-standardized rates (ASRs) per 100,000 were derived using the GBD reference population. Here, we report 95% uncertainty intervals (95% UIs) to reflect measurement, sampling, and modeling uncertainties, following the Guidelines for Accurate and Transparent Health Estimates Reporting.[8] Data were retrieved through the GBD "Results" tool and aggregated and de-identified; therefore, no institutional review or individual consent was required. All data are publicly accessible through the Global Health Data Exchange (http://ghdx.healthdata.org/gbd-results-tool).

2.2. Case definition and data sources

In GBD 2021, ischemic stroke is defined as acute neurologic dysfunction due to ischemia, typically arising from thrombosis or embolic events and resulting in focal infarction of the brain, spinal cord, or retina.[5] International Classification of Diseases (ICD) codes used for case identification included ICD-10: I63–I63.9, I65–I66.9, I67.2–I67.3, I67.5–I67.6, and I69.3 and ICD-9: 433–435.9, 437.0–437.1, and 437.5–437.8. The reference case was a first-ever, subtype-specific stroke, and included subjects who did not survive before hospital admission. Adjustments were made for sources using alternate definitions, such as those including first and recurrent strokes, those reporting only combined subtype estimates, and those including only stroke cases surviving to hospital admission.[5] Literature review data and inpatient hospital data were utilized to generate estimates of the ischemic stroke burden. Specifically, GBD 2021 conducted a systematic review of PubMed using terms such as "ischemic stroke," "ischemic stroke," "incidence," "prevalence," "excess mortality," "case fatality," and "mortality ratio." Hospital series were corrected for repeat admissions and primary-to-any diagnosis mapping using claims-based factors derived from the United States of America, Poland, Taiwan, and New Zealand.[5] Vital registration and verbal autopsy data were used to model deaths.[7]

2.3. Estimation of the disease burden of ischemic stroke

We applied the Cause of Death Ensemble modeling (CODEm) framework to estimate deaths from ischemic stroke. CODEm combines geospatial structure with covariates to generate location–year death estimates for 1990–2021.[7] Mortality inputs with non-specific/ill-defined codes were redistributed before deriving stroke-specific mortality rates. The Disease Modeling with Meta-Regression 2.1 model was then used to estimate the non-fatal burden of ischemic stroke, and, as a Bayesian geospatial meta-regression, it links disease parameters and covariates to produce consistent estimates of prevalence and incidence.[5]

2.4. Attributable risk factors

GBD 2021 quantifies risk contributions by contrasting observed exposure distributions with a theoretical minimum risk exposure level. For ischemic stroke, we evaluated the burden linked to 23 risks, including high systolic blood pressure, high low-density lipoprotein (LDL) cholesterol, high fasting plasma glucose, ambient particulate matter pollution, smoking, high sodium intake, impaired kidney function, household air pollution from solid fuels, lead exposure, high body mass index, alcohol use, low temperature, low physical activity, diet low in whole grains, second-hand smoke, diet low in fruits, diet low in vegetables, diet low in fiber, high temperature, diet high in processed meat, diet high in sugar-sweetened beverages, diet high in red meat, and diet low in polyunsaturated fatty acids (as available in GBD 2021).[6] We calculated population attributable fractions for DALYs. Attributable DALYs reflect how much disease burden would decline with a change from current exposure to a counterfactual exposure distribution. Values were obtained by multiplying outcome-specific DALYs by the population attributable fraction, which denotes the proportion reducible at the counterfactual level.

2.5. Statistical analysis

We described ischemic stroke burden using point prevalence, annual incident cases, DALYs, and their ASRs. To quantify trend magnitude and direction, we

computed percentage changes in ASRs from 1990 to 2021. Comparisons were made by sex, age range, and sociodemographic index (SDI) strata. SDI is a composite indicator combining lag-distributed income per capita, mean years of schooling among people aged ≥15 years, and fertility among women <25 years. In GBD 2021, locations were grouped into five SDI categories—low, low–middle, middle, high–middle, and high—with values scaled 0–1 as a proxy for development level. We used ordinary least-squares regression and generalized additive models to explore linear and non-linear associations of SDI with ASRs. All analyses were conducted in R (version 4.3.0).

3. Results

3.1. Global level

In 2021, ischemic stroke affected an estimated 69.9 million people (95% UI: 64.8 to 75.0) worldwide. The global age-standardized prevalence was 819.5 per 100,000 (95% UI: 760.3 to 878.7), a 3.5% decline since 1990 (95%UI: −5.1% to −2.1%). Concurrently, ischemic stroke accounted for 7.8 million (95% UI: 6.7 to 8.9) incident cases, with an age-standardized incidence rate of 92.4 per 100,000 (95% UI: 79.8 to 105.8), which showed a more significant reduction from 1990 to 2021 (−15.8%; 95% UI: −18.8% to −13.3%). Global attributable DALYs from ischemic stroke were 70.4 million in 2021 (95% UI: 64.3 to 76.0), with an ASR of 837.4 per 100,000 (95% UI: 763.7 to 905.0). This measure showed a substantial decrease from 1990 to 2021 (−34.9%; 95% UI: −39.5% to −30.0%) (Tables S1-S3 and Figure 1).

3.2. Regional level

Based on SDI, middle-SDI regions had the highest age-standardized prevalence, incidence, and DALY rates in 2021, whereas low-SDI regions had the lowest; high-SDI regions showed the largest improvements (Tables S1-S3). The number of prevalent cases of ischemic stroke increased from 34.7 million (95% UI: 32.2 to 37.2) in 1990 to 69.9 million (95% UI: 64.8 to 75.0) in 2021. In 1990, the regions with the highest numbers of prevalent cases were East Asia (6.9 million, 95% UI: 6.2 to 7.6), Western Europe (4.6 million, 95% UI: 4.3 to 4.8), and South Asia (3.4 million, 95% UI: 3.0 to 3.8). By 2021, the highest numbers of prevalent cases were found in East Asia (21.5 million; 95% UI: 19.3 to 23.7), South Asia (7.8 million; 95% UI: 7.0 to 8.6), and Western Europe (5.5 million; 95% UI: 5.3 to 5.8) (Table S1 and Figure S1). Incident cases rose from 4.2 million (95% UI: 3.5 to 4.9) in 1990 to 7.8 million (95% UI: 6.7 to 8.9) in 2021, with East, South, and Southeast Asia contributing the largest 2021 tallies (Table S2 and Figure S2). In addition, the number of DALYs due to ischemic stroke increased from 46.2 million (95% UI: 43.0 to 49.4) in 1990 to 70.4 million (95% UI: 64.3 to 76.0) in 2021, with the highest DALY counts recorded in East Asia, South Asia, and Southeast Asia (Table S3 and Figure S3).

Across regions in 2021, age-standardized prevalence per 100,000 was highest in Southern Sub-Saharan Africa (1,122; 95% UI: 1,019.9 to 1,224.9), Western Sub-Saharan Africa (1,046; 95% UI: 977.7 to 1,112.6), and East Asia (1,018; 95% UI: 920.0 to 1,120.1), the lowest values were in South Asia (497.7; 95% UI: 445.7 to 549.0), Andean Latin America (515.1; 95% UI: 490.6 to 539.0), and Central Latin America (552.6; 95% UI: 516.9 to 591.3). In terms of incidence rates, the regions with the highest ASRs per 100,000 individuals were Eastern Europe (142.6; 95% UI: 122.1 to 164.7), East Asia (134.8; 95% UI: 112.6 to 158.4), and Central Asia (132.9; 95% UI: 118.2 to 148.1), while the lowest incidence rates were found in Australasia (52.8; 95% UI: 47.3 to 58.5), Central Latin America (52; 95% UI: 45.1 to 58.8), and Andean Latin America (46.3; 95% UI: 40.6 to 52.4). In addition, the regions with the highest age-standardized DALY rates of ischemic stroke per 100,000 individuals were Eastern Europe (1,601.2; 95% UI: 1,483.5 to 1,723.1), Central Asia (1,356.1; 95% UI: 1,234.2 to 1,474.8), and North Africa and the Middle East (1,329.4; 95% UI: 1,165.6 to 1,483.0), whereas the regions with the lowest DALY rates were Andean Latin America (320.1; 95% UI: 270.1 to 375.3), Western Europe (297.7; 95% UI: 262.8 to 327.9), and Australasia (249.5; 95% UI: 216.5 to 278.2) (Table S1-S3).

Between 1990 and 2021, ischemic stroke ASR rose solely in East Asia (31.5%; 95% UI: 27.4 to 35.7) and declined most in tropical Latin America (−28.7%; 95% UI: −31.5 to −26.0), Southern Latin America (−25.5%; 95% UI: −27.8 to −23.1), and high-income Asia Pacific (−24.7%; 95% UI: −27.5 to −21.1). For incidence, the largest increase was again in East Asia (33.0%; 95% UI: 25.7 to 40.3), with the largest decreases in high-income Asia Pacific (−46.6%; 95% UI: −50.6 to −42.2), Western Europe (−45.1%; 95% UI: −48.1 to −42.1), and tropical Latin America (−44.3%; 95% UI: −47.4 to −41.2). For age-standardized DALY rates, the largest increase was found in Southern Sub-Saharan Africa (17.1%; 95% UI: 6.5 to 34.7). The greatest decreases were observed in Western Europe (−69.1%; 95% UI: −70.9 to −67.5), high-income Asia Pacific (−68.0%; 95% UI: −70.4 to −65.8), and Australasia (−65.1%, 95% UI: −67.4 to −62.8) (Tables S1-S3 and Figures S4-S6).

3.3. National level

The 2021 national ASR prevalence ranged from 312.3 to 1,603.9 per 100,000; Ghana (1,603.9; 95%

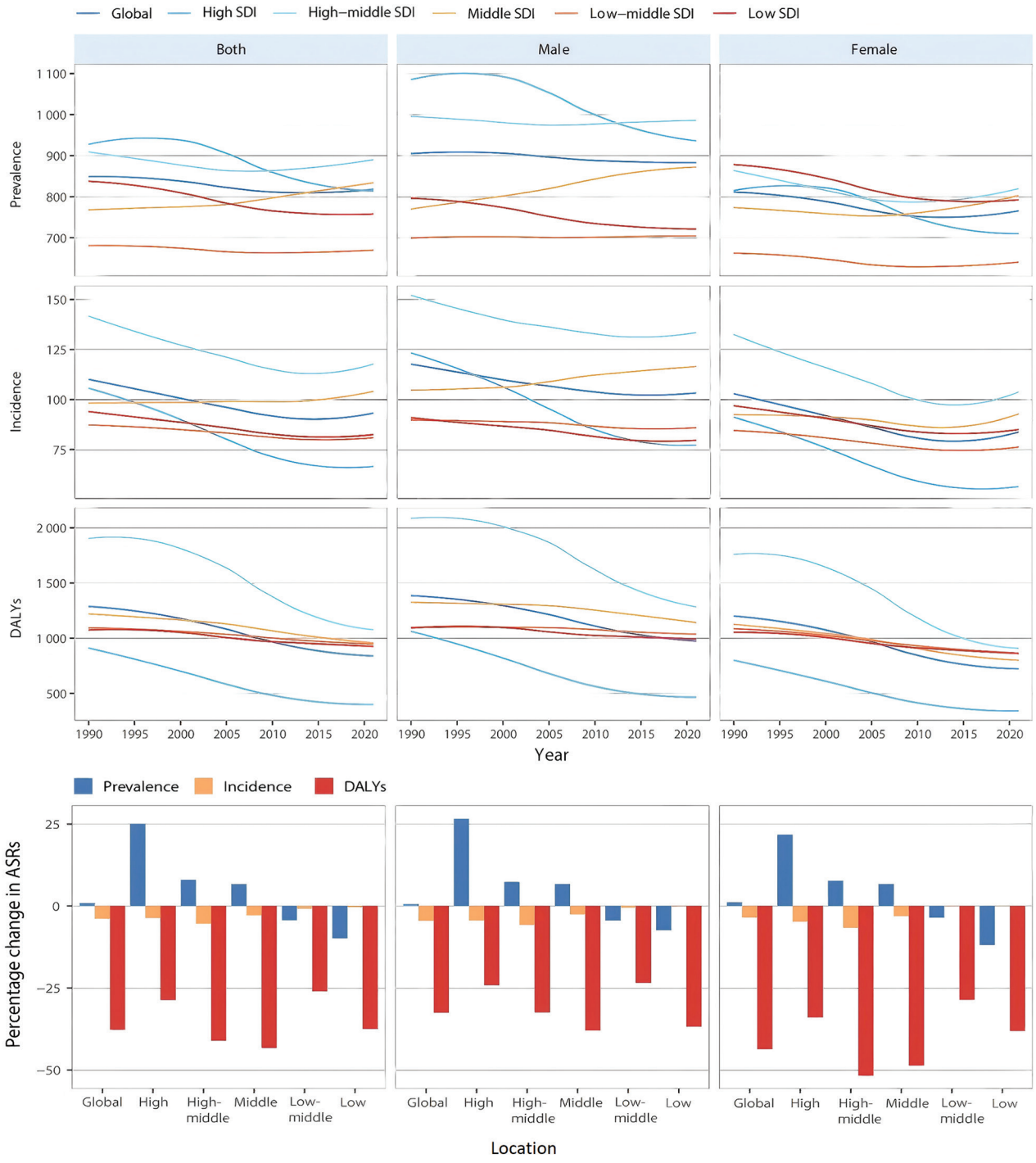

Figure 1. Temporal trends of age-standardized incidence rate, age-standardized prevalence rate, and age-standardized disability-adjusted life year (DALY) rate for the global burden of ischemic stroke, as well as by sociodemographic index, from 1990 to 2021. Percent changes in these age-standardized rates (ASRs) globally and by sociodemographic index (SDI) category from 1990 to 2021 are also presented.

UI: 1,542.0–1,675.7), Sao Tome and Principe (1,422.2; 95% UI: 1,361.8–1,485.1), and Nauru (1,369.0; 95% UI: 1,315.8–1,425.0) recorded the top values. Conversely, the lowest rates were found in Cyprus (312.3; 95% UI: 288.4 to 346.1), Malta (383.7; 95% UI: 363.2 to 403.8), and Ireland (392.9; 95% UI: 370.5 to 414.8) (Table S1 and Figure 2). From 1990 to 2021, Portugal (−58.3%; 95% UI: −61.4% to −54.8%), Singapore (−51.6%; 95% UI: −53.7% to

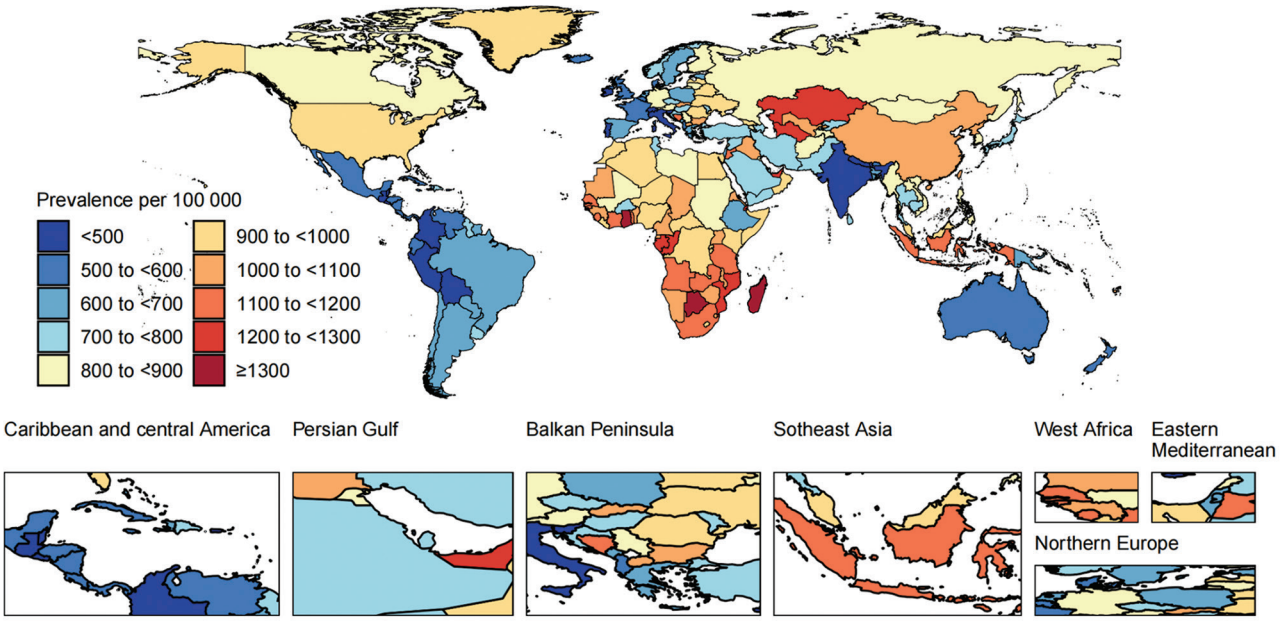

Figure 2. Age-standardized point prevalence rate of ischemic stroke per 100,000 population in 2021, by country and territory

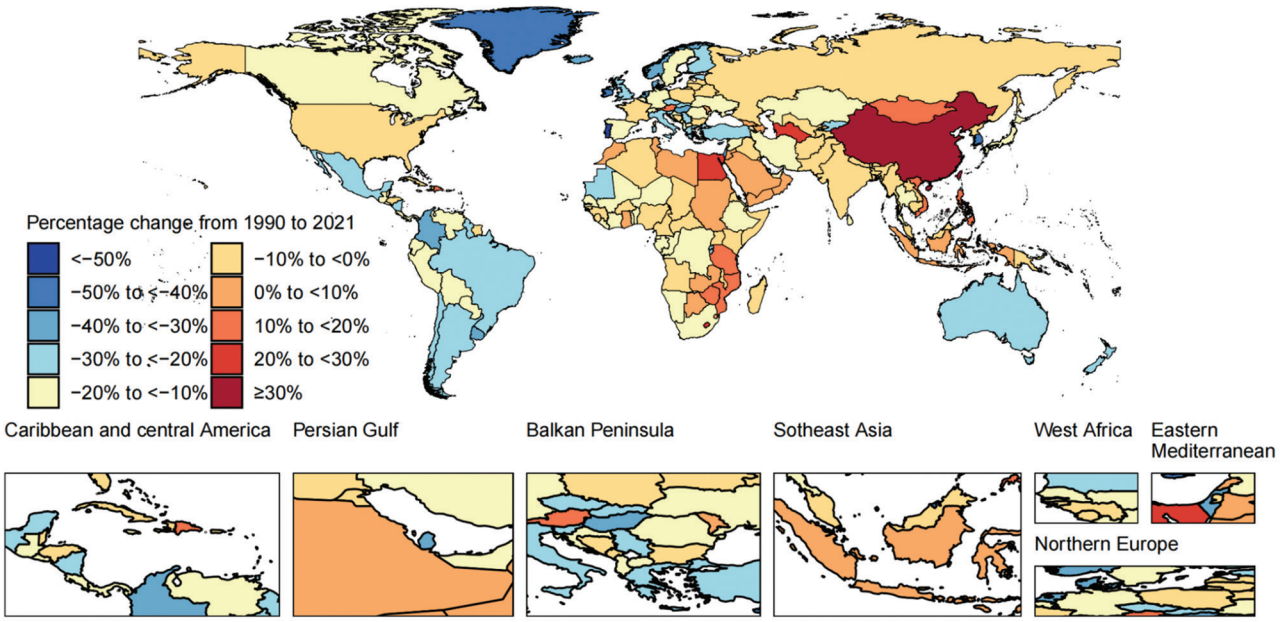

Figure 3. Percentage change of age-standardized point prevalence rate of ischemic stroke per 100,000 population from 1990 to 2021, by country and territory

−49.4%), and Republic of Korea (−49.6%; 95% UI: −51.4% to −47.7%) had the most significant decreases of ASR prevalence rates (Table S1 and Figure 3). The national ASR point incidence of ischemic stroke in 2021 ranged from 38.9 to 214.4 cases per 100,000. The countries with the highest ASR incidence rates were North Macedonia (214.4; 95% UI: 190.5 to 239.9), Bulgaria (168.9; 95% UI: 149.2 to 188.3), and Botswana (163.1; 95% UI: 140.4 to 187.1). Conversely, the lowest incidence estimates were observed in Malta (38.9; 95% UI: 33.9 to 44.5), Puerto Rico (39.2; 95% UI: 33.6 to 45.5), and Ireland (39.6; 95% UI: 34.4 to 45.7) (Table S2 and Figure S7). In 2021, the national ASR DALY rates of ischemic stroke ranged from 180.9 to 3,037.4 per 100,000. The highest rates were in North Macedonia (3,037.4; 95% UI: 2,559.0 to 3,507.5), Egypt (2,462.6; 95% UI: 1,969.1 to 3,002.4), and Bulgaria (2,383.6;

95% UI: 2,105.1 to 2,689.8), while the lowest rates were in Puerto Rico (180.9; 95% UI: 154.4 to 208.2), Switzerland (202.3; 95% UI: 174.2 to 225.8), and Singapore (205.8; 95% UI: 174.5 to 237.2) (Table S3 and Figure S8). In addition, Figures S9 and S10 show the percentage changes of age-standardized incidence and DALY rates from 1990 to 2021.

3.4. Age and sex patterns

In 2021, the global prevalence of ischemic stroke was higher in males, with 35.2 million cases among men (95% UI: 32.6 to 37.8) and an ASR of 881.9 per 100,000, which represents a decrease of 2.6% since 1990. Women reported a total of 34.7 million cases (95% UI: 32.1 to 37.3) with an ASR of 769.4 per 100,000, showing a decrease of 5.3%. The incidence rates decreased by 12.2% in men and 19.5% in women. DALYs decreased by 29.5% in men and 40.0% in women.

Age profiles showed that ischemic stroke prevalence increased across age ranges, reaching a maximum at 70–74 years before declining in older groups (Figure S11). The number of incident cases peaked in the 70–74 age group for both males and females, followed by a decline in older age groups (Figure 4). In 2021, the DALY rate was higher in males and increased with age. DALY counts increased with age, peaking at 70–74 years in males and 80–84 years in females, then decreasing beyond those ages (Figure S12).

3.5. Association with the SDI

Overall, the age-standardized DALY rate from ischemic stroke exhibited a trend where it initially increased with the SDI up to a certain point, and then declined at both the global level and across GBD regions (Figure 5). Regionally, health loss exceeded SDI-predicted levels in Eastern Europe, Central Europe, and Central Asia. In contrast, regions like high-income Asia Pacific, Southern Sub-Saharan Africa, and South Asia had lower-than-expected burdens. At the national level in 2021, the age-standardized DALY rate for ischemic stroke showed an approximate positive correlation with SDI, with the burden increasing alongside socioeconomic development up to an SDI of about 0.8. Countries such as Bulgaria, North Macedonia, and Georgia exhibited higher-than-expected burdens, while countries like Japan, Singapore, and Australia had significantly lower-than-expected burdens (Figures S13 and S14).

3.6. Attributable risk factors

In 2021, high systolic blood pressure accounted for the largest share of ASR ischemic stroke DALYs (58.38%), followed by high LDL cholesterol (29.82%) and high fasting plasma glucose (17.58%) (Figure 6). The percentage contributions of high systolic blood pressure and high body mass index were higher in females than in males, whereas the contributions of smoking, ambient particulate matter pollution, and a diet high in sodium were higher in

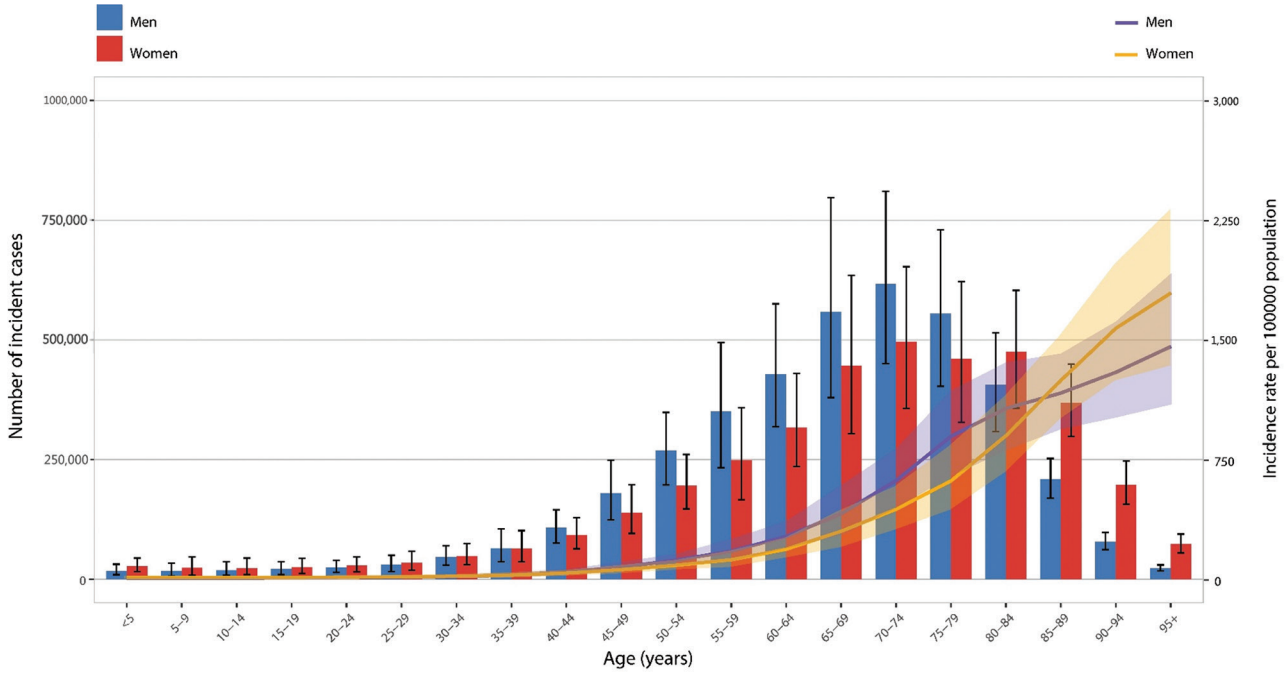

Figure 4. Global number and age-standardized rates of incidence of ischemic stroke per 100,000 population by age and sex (2021)

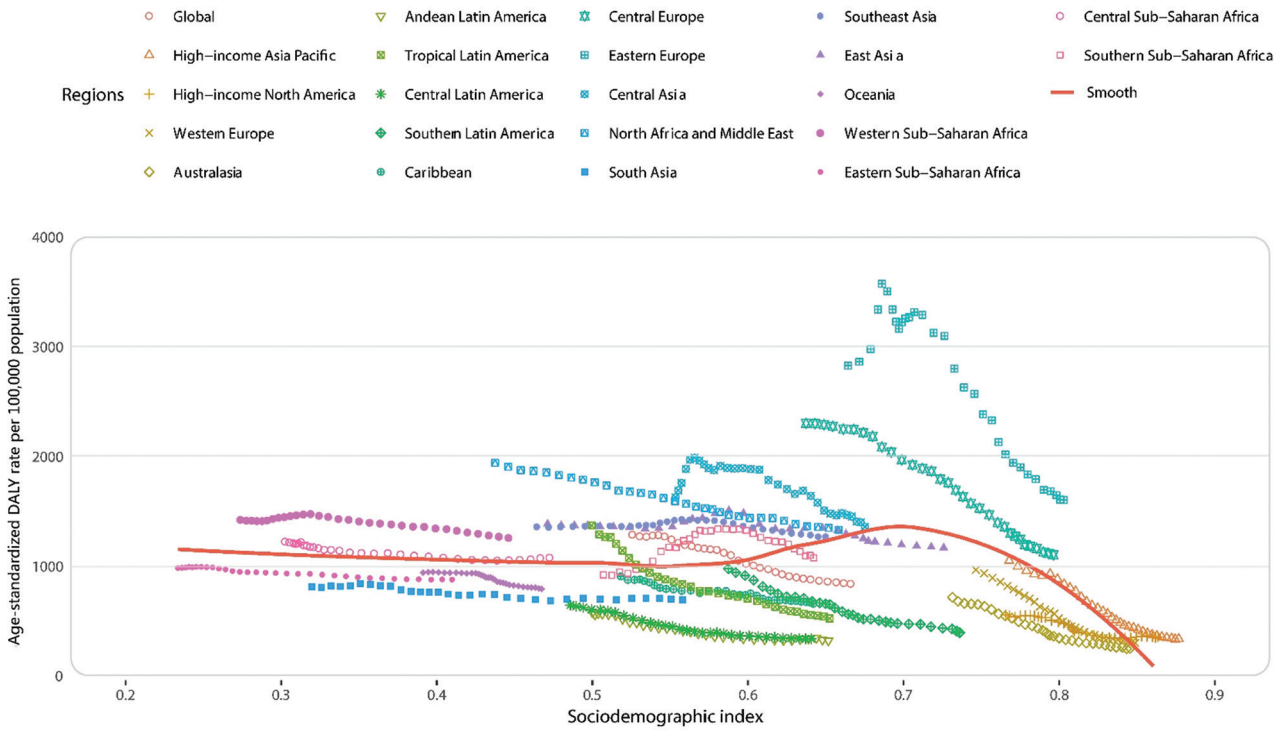

Figure 5. Age-standardized disability-adjusted life year (DALY) rates for ischemic stroke for the Global Disease Burden regions by sociodemographic index (1990–2021)

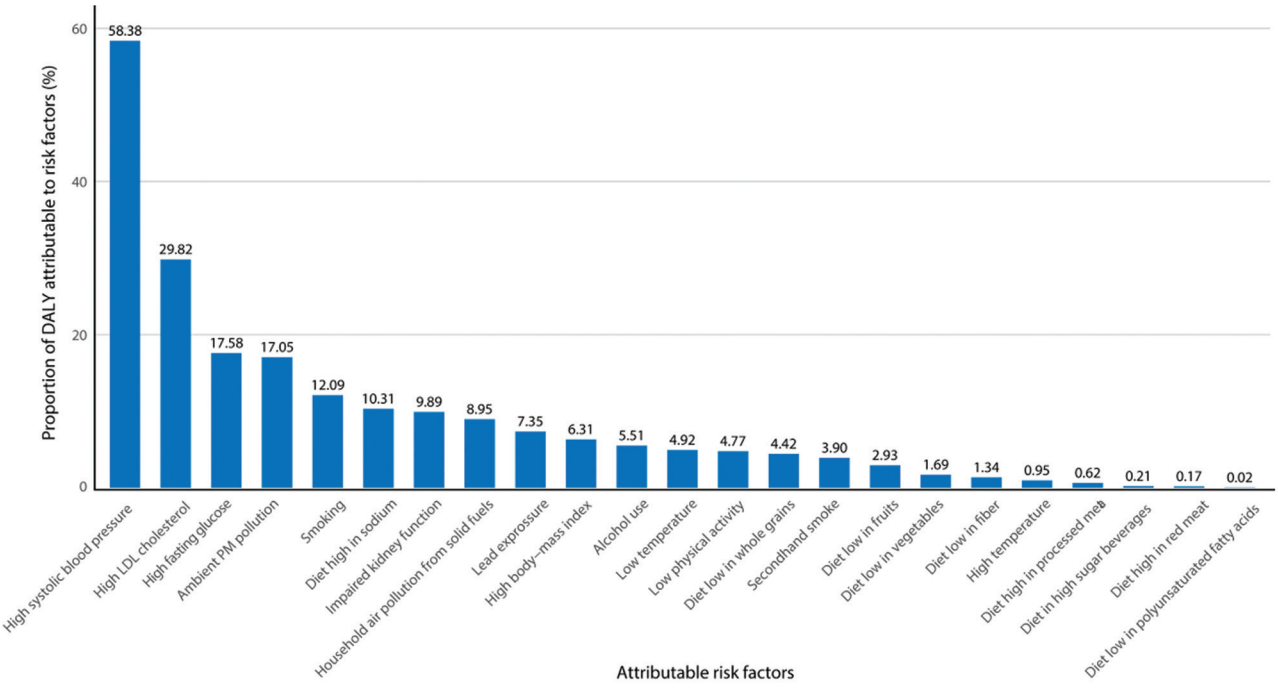

Figure 6. Proportion of ischemic stroke disability-adjusted life years (DALY) attributable to 23 risk factors globally
Abbreviation: LDL: Low-density lipoprotein.

males (Figure S15). The impact of attributable risk factors varied across different SDI levels. In high-SDI regions, high systolic blood pressure and high LDL cholesterol were the top contributors, while in low-SDI regions and

low–middle SDI regions, high systolic blood pressure, lead exposure, and household air pollution from solid fuels were predominant factors (Figure S16). Age-specific heterogeneity was evident in the DALY fractions attributed to each risk factor. The DALY fraction linked to elevated systolic blood pressure increased across age ranges, peaked at 60–64, then decreased. High fasting plasma glucose showed a monotonic rise with age. Smoking displayed an inverse age gradient, highest at 50–54 (22.1%) and reduced thereafter. The contributions of a diet high in sodium and high body mass index also varied by age, generally peaking in middle age and then decreasing. Conversely, DALYs attributable to high LDL cholesterol decreased with age. Diet low in whole grains, second-hand smoke, diet low in fruits, diet low in vegetables, and diet low in fiber showed higher attributable shares in younger age groups (Figure S17).

4. Discussion

Using estimates from the GBD 2021 data, this study provides a comprehensive global, regional, and national description of ischemic stroke burden and its associated risk factors between 1990 and 2021. The global burden of ischemic stroke shows significant trends: although the ASRs of prevalence, incidence, and DALY rate have generally shown a decline over this period, the absolute numbers of prevalent cases, incident cases, and DALYs have increased. This increase is likely attributable to population growth and aging, as well as advancements in healthcare and improved screening capabilities, leading to the wider recognition of ischemic stroke cases. These factors underscore the growing impact of ischemic stroke on global health.[9]

Ischemic stroke was once considered a disease of wealthy countries, but it has now become a major cause of death and disability in low- and middle-income countries. In 1990, the prevalence and incidence of ischemic stroke were highest in high-SDI regions. By 2021, regions with middle-SDI levels exhibited the highest ASR prevalence, incidence, and DALY rates of ischemic stroke, while high-SDI regions had the lowest ASR incidence and DALY rates per 100,000 individuals. These regional disparities can be attributed to several factors, including differences in healthcare infrastructure, access to medical services, and socioeconomic conditions.[10] From 1990 to 2021, high-SDI regions experienced the largest declines in age-standardized incidence and DALY rates of ischemic stroke, whereas age-standardized prevalence showed a slight increase, likely reflecting improved post-stroke survival and population aging. In high-SDI regions, significant improvements in stroke prevention, early detection, and acute management have contributed to the observed reductions in ASRs.[11] Conversely, in low- and middle-SDI regions, rapid population growth, urbanization, and lifestyle changes, such as increased prevalence of hypertension, diabetes, and unhealthy diets, have likely contributed to the rising absolute numbers.[2,12,13] In addition, varying levels of investment in healthcare and public health initiatives across regions play an important role in these disparities.[14]

We found that the global incidence of ischemic stroke exhibited notable differences between males and females. The number of incident cases increased with age for both sexes, peaking in the 70–74-year age group. Men showed higher numbers of incident cases compared to women across most age groups. However, after the age of 80, the incidence rates in women surpassed those in men. These sex differences may be attributed to several factors. Men generally have higher exposure to stroke risk factors such as smoking, high cholesterol, and hypertension, which contribute to the higher incidence of ischemic stroke in younger age groups. For women, the higher incidence rates after age 80 could be linked to the loss of protective effects from estrogen after menopause and a higher prevalence of age-related comorbidities, particularly the occurrence of atrial fibrillation.[15-17] This aligns with the higher incidence of atrial fibrillation in women over 80 compared to men, and the generally higher life expectancy of women, indicating the need for increased attention to thromboembolic stroke risk in elderly women with atrial fibrillation.[18,19]

In our study, we found that the leading risk factors for ASR DALYs due to ischemic stroke in 2021 were high systolic blood pressure, high LDL cholesterol, and high fasting plasma glucose. These findings underscore the critical role of modifiable risk factors in the burden of ischemic stroke.[20] Addressing these factors is important for effective stroke prevention and management.[21] In addition, the impact of these risk factors varies by sex and age. For example, the percentage contributions of high systolic blood pressure and high body mass index were higher in females than in males, whereas the contributions of smoking, alcohol use, ambient particulate matter pollution, and diet high in sodium were higher in males. These sex differences may be related to societal and cultural roles.[19] For women, especially those post-menopause, managing blood pressure and body weight could be crucial in reducing stroke risk. For men, improving lifestyle factors such as reducing smoking rates and alcohol use are key targets.[22]

Age-specific trends in attributable risk factors reveal that the proportion of DALYs due to high systolic blood pressure increases with age, peaking in the 60–64-year age group before decreasing. This pattern suggests that interventions aimed at controlling blood pressure in

middle-aged and older adults could substantially reduce the burden of ischemic stroke.[23] Similarly, the burden attributable to high fasting plasma glucose increases with age. However, studies have shown that intensive glucose-lowering treatment does not reduce the risk of stroke compared to standard glycemic control.[24] Therefore, greater emphasis should be placed on improving dietary habits and engaging in regular exercise to manage body mass index.[25] Conversely, smoking, high LDL cholesterol, high body mass index, and poor dietary habits have a greater impact on younger individuals, indicating that younger adults should pay more attention to developing healthy lifestyle habits.[26,27]

The variation in risk factor contributions across different SDI levels also underscores the need for region-specific strategies. In high-SDI regions, high systolic blood pressure and high LDL cholesterol are predominant risk factors, suggesting that lifestyle modifications and medication adherence are critical areas of focus. In contrast, in low- and middle-SDI regions, factors such as lead exposure and household air pollution from solid fuels are more significant. Increasing evidence indicates that air pollution is an emerging risk factor for stroke.[28] Over the past few decades, rapid urbanization and industrialization have led to rising levels of air pollution, which has become increasingly important in the occurrence of diseases, particularly in low- and middle-SDI regions. Studies have shown that exposure to particulate matter 2.5 can lead to elevated markers of plaque vulnerability, such as matrix metalloproteinases, and increase systemic inflammation and thrombogenicity.[29,30]

5. Limitations

This study provides a comprehensive description of global, regional, and national temporal patterns of ischemic stroke and its associated risk factors using data from the GBD 2021 study; however, several limitations should be acknowledged. First, all analyses were based on the GBD 2021 data, whereas more recent GBD updates now provide later estimates for stroke burden. Our findings should therefore be interpreted as a snapshot of patterns within the 1990–2021 GBD 2021 cycle rather than as the definitive current state of global ischemic stroke burden. Second, our work relies on secondary estimates generated by the GBD collaboration using proprietary and complex modeling procedures that we could not independently reproduce. Although our own data extraction, aggregation, and regression analyses are fully transparent and replicable, their validity depends on the accuracy of the underlying GBD models and input data. Third, there is inherent statistical uncertainty in these estimates, particularly in countries and regions with sparse or low-quality primary data, so national-level estimates should be interpreted with caution. Heterogeneity in case definitions, data collection systems, and coding practices, as well as differences in the completeness and quality of data sources, may further affect comparability across settings. Finally, despite advances in diagnostic tools, ischemic stroke remains underdiagnosed or misdiagnosed in many parts of the world, which may lead to underestimation of its true prevalence and associated burden.

6. Conclusion

Our study provides a comprehensive evaluation of the global, regional, and national burden of ischemic stroke from 1990 to 2021. The findings highlight a significant shift in the incidence of ischemic stroke from high-SDI regions to middle and low-SDI regions. Despite a decline in ASRs of prevalence, incidence, and DALYs, the absolute numbers have increased due to population growth, aging, and advancements in healthcare, leading to improved screening capabilities. High systolic blood pressure, high LDL cholesterol, and high fasting plasma glucose were identified as major risk factors, with notable variations across different SDI levels and between sexes. These findings underscore the necessity for targeted public health interventions and effective management strategies that address regional and demographic differences, aiming to mitigate the growing impact of ischemic stroke globally.

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Conflict of interest

Yan Yao is one of the Editors-in-Chief of this journal but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Other authors declare that they have no competing interests.

Author contributions

Conceptualization: Lihui Zheng, Yan Yao
Formal analysis: Likun Zhou, Shengsong Zhu, Zhuxin Zhang, Jing Luo
Investigation: Xi Peng, Le Li
Methodology: Sheng Su, Zhenhao Zhang, Yulong Xiong
Writing–original draft: Xi Peng, Le Li
Writing–review & editing: Lihui Zheng, Yan Yao

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data are publicly available from the Global Health Data Exchange query tool (http://ghdx.healthdata.org/gbd-results-tool).

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Brain & Heart

MEETING REPORT

The clinical practice messages from the "Heart Brain and Vessels" meeting in June 2024 held in Aosta (Italy)

Feola Mauro[1]*, and Scacciatella Paolo[2]*

[1]Division of Cardiology, Regina Montis Regalis Hospital, Azienda Sanitaria Locale CN1, Mondovi, Italy

[2]Division of Cardiology, Parini Regional Hospital, Aosta, Italy

(This article belongs to the *Special Issue: Correlation Between Ischemic Heart Disease and Cerebrovascular Disease: The Clinical Practice Messages from the Aosta Meeting in June 2024*).

Abstract

Ischemic heart disease (IHD) and cerebrovascular disease (CVD) are two of the leading causes of morbidity and mortality worldwide. Both conditions are closely related, as they share common risk factors and pathophysiological mechanisms. The clinical overlap between IHD and CVD has been elucidated in the "Heart Brains and Vessels" Meeting held in June 2024 in Aosta (Italy). In this document, the authors underline the risk of cardioembolic stroke in heart disease, the updated therapy for treating strokes, and the prevention of embolization. Finally, the authors emphasize the importance of establishing Heart and Brain Teams utilizing multidisciplinary approach to treating these diseases, at least in the medical hub centers.

Keywords: Cardioembolic stroke; Patency of foramen ovale; Endovascular thrombectomy

***Corresponding authors:**
Feola Mauro
(mauro.feola@aslcn1.it)
Scacciatella Paolo
(pscacciatella@ausl.vda.it)

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Ischemic heart disease (IHD) and cerebrovascular disease (CVD) are two of the leading causes of morbidity and mortality worldwide. Both conditions are closely related, as they share common risk factors and pathophysiological mechanisms. The clinical overlap between IHD and CVD can be attributed to several factors:

1. *Shared risk factors.* Both diseases are influenced by similar risk factors, including hypertension, hyperlipidemia, diabetes mellitus, smoking, and sedentary lifestyle. Individuals with IHD often exhibit these risk factors, which increase their likelihood of developing CVD.
2. *Atherosclerosis.* The underlying process of atherosclerosis contributes to both conditions. The build-up of plaque in the arteries can lead to ischemia in both the heart and the brain. If the plaque break, it can cause thrombosis, which may lead to myocardial infarction in the heart or ischemic stroke in the brain.
3. *Inflammation and endothelial dysfunction.* Chronic inflammation and endothelial dysfunction play significant roles in the development of both IHD and CVD. Inflammatory markers are often elevated in patients with either condition, indicating the presence of a systemic response that can affect vascular health throughout the body.
4. *Outcomes and prognosis.* Patients with a history of IHD are at a higher risk of experiencing cerebrovascular events. The presence of one disease often predicts the

development of the other, resulting in worse outcomes and increased mortality rates. The considerations exploring the clinical correlation between IHD and CVD highlights the importance of examining updated treatments for atherosclerosis, as well as reperfusion therapy and the best preventive strategies for the prevention of IHD and CVD.

In this meeting, Amisano *et al.* overviewed the new horizons in the stroke revascularization treatment, considering the thrombolytic therapy and the endovascular thrombectomy. Separately, Marchisio *et al.* presented a case report of percutaneous occlusion of patent foramen ovale and offered a discussion on clinical decision-making and imaging approach to invasive procedure. The procedure of atrial fibrillation ablation combined with left atrial appendage closure was revisited in the meeting, with a presentation by Battaglia *et al.* On the other hand, Delnevo *et al.* presented a summary dedicated to the pharmacological innovation in the treatment of hypercholesterolemia in cardioneurovascular syndromes. Besides, Giannino *et al.* overviewed the four-pillar treatment for chronic heart failure with reduced left ventricular function, without disregarding the role of emerging treatment that might be therapeutically effective. The plenary session of this meeting ended with Pristipino *et al.*'s review of classical indications, recent updates, and new consensus perspectives for the closure of patent foramen ovale.

In conclusion, through this special issue featuring papers stemming from the "Heart Brain and Vessels" meeting held in Aosta, we would like to emphasize the need to consider predisposing conditions to cardioembolic stroke, alongside atrial fibrillation, patency of foramen ovale and heart failure, that are preventable and treatable. We would also like to highlight the exigency of establishing Heart and Brain Teams utilizing multidisciplinary approach to treating these diseases and condition, at least in medical hub centers.

Conflict of interest

Both Feola Mauro and Scacciatella Paolo are the Guest Editors of this special issue, and Feola Mauro serves as the Editorial Board Member for this journal, but none of them were, in any way, involved in the editorial and peer-review process conducted for this paper, directly or indirectly. The authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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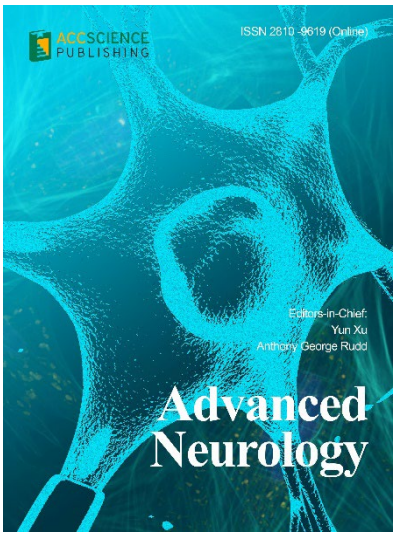

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