Safety Platform for Emergency vACcines

AESI Case Definition Companion Guide

Thrombosis and Thromboembolism

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Authors: Barbara Law, Marta Rojo Villaescusa

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TABLE OF CONTENTS

DOCUMENT INFORMATION....2

DOCUMENT HISTORY....3

DEFINITIONS & ACRONYMS....4

1. Background....7
2. OBJECTIVES OF THIS DELIVERABLE....7
3. Methods....7
4. Results....8
5. Recommendations & discussion....9
6. References....9

APPENDIXES

APPENDIX 1 Thrombosis and Thromboembolism Diagnostic Codes: ICD-9/10-CM and MedDRA....20
APPENDIX 2. Thrombosis and Thromboembolism Background Rates....35
APPENDIX 3 Thrombosis and Thromboembolism Risk Factors....73
APPENDIX 4. Thrombosis and Thromboembolism Case Definition Key Caveats for Diagnosis, Data Analysis and Presentation....83
APPENDIX 5.Thrombosis and Thromboembolism Data Abstraction and Interpretation Forms WITH ALGORITHMS FOR ASSESSING LEVEL OF CERTAINTY....87
APPENDIX 6. Methodology: Brief Summary....96

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DOCUMENT INFORMATION

Main Author(s)	Barbara Law Marta Rojo Villaescusa (sub-contracted)	E-mail: Barbara.law@cepi.net martusred@gmail.com
WP Leader	Barbara Law	E-mail: barbara.law@cepi.net

SPEAC Project Lead	Robert Chen	E-mail: robert.chen@cepi.net
Scientific Coordinator	Miriam Sturkenboom	E-mail: miriam.sturkenboom@cepi.net

Description of the deliverable	This deliverable collates into a single document the SPEAC Thrombosis and Thromboembolism resources (Risk factors, background rates, ICD9/10-CM & MedDRA codes), tools (data abstraction & interpretation form, tabular summary of key case definition criteria and algorithm for level of certainty determination, pictorial level of certainty algorithm) and guidance (real time investigation, data collection, analysis and presentation This guide can be used by stakeholders to assess the occurrence of Thrombosis and Thromboembolism in several settings including as an adverse event following immunization. Note: this guide accompanies the Thrombosis and Thromboembolism case definition specifically. A separate guide will be prepared for Thrombocytopenia Thrombosis Syndrome.
Key words	Thrombosis and Thromboembolism , Brighton case definition, risk factors, background rates, ICD-9-CM, ICD-10-CM, MedDRA, case definition level of certainty.

DOCUMENT HISTORY

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DEFINITIONS & ACRONYMS

AEFI	Adverse Event Following Immunization
AESI	Adverse Events of Special Interest
AFib	Atrial Fibrillation
AIS	Acute ischemic stroke
ANCA	Anti-Neutrophil Cytoplasmic Antibody
BC	Brighton Collaboration
CAD	Coronary Artery Disease
CD	Case Definition
CDCP	Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness and Innovation
CI	Confidence Interval
CMV	Cytomegalovirus
CPRD	Clinical Practice Research Datalink (UK)
CRP	C Reactive Protein
CSS	Churg Strauss Syndrome
CT	Computed Tomography
CUI	Concept Unique Identifier
CVA	Cerebrovascular accident
CVT	Cerebral Vein Thrombosis
CVST	Cerebral Venous Sinus Thrombosis
CXR	Chest X-Ray
DTaP-IPV	Diphtheria Tetanus acellular pertussis with inactivated polio combo vaccine
DVT	Deep vein thrombosis
EBV	Epstein Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ER	Emergency Room
GCA	Giant Cell Arteritis (type of large vessel vasculitis)
GPA	Granulomatosis with polyangiitis (type of small vessel vasculitis)
GP	General Practice (as an outpatient setting for population studies)
GPRD	General Practice Research Database (UK medical database 1994-2012)
HBV	Hepatitis B Virus
HF	Heart Failure
HHV	Human Herpes Virus
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSV	Herpes Simplex Virus
HZ	Herpes Zoster
IBD	Inflammatory Bowel Disease (includes Crohn's disease & Ulcerative Colitis)
IC	Information Component (Bayesian measure of disproportionality)
ICAM-1	Intercellular adhesion molecule 1
ICD-9-CM	International Classification of Diseases-9th Revision-Clinical Modification
ICD-10-CM	International Classification of Diseases-10th Revision-Clinical Modification
ICI	Immune Checkpoint Inhibitor

ICPC-2	International Classification for Primary Care Version 2
ICU	Intensive Care Unit
IOM	Institute of Medicine (now the National Academy of Medicine)
IPV	Inactivated Polio Vaccine
IRR	Incidence Rate Ratio
IVIG	Intravenous Immune Globulin
lang	Language (relevant to literature search instructions)
LMIC	Lower or Middle Income Country
LOC	Level of Certainty
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings (used for indexing articles for PubMed)
MI	Myocardial Infarction
MMR	Measles Mumps Rubella vaccine
MPA	Microscopic polyangiitis (type of small vessel vasculitis)
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
N	No
noexp	Literature search term to turn off automatic explosion of MeSH headings
NOS	Not otherwise stated
OC	Oral contraceptive
OPV	Oral Polio Vaccine
PAC	Premature Atrial Contraction
PAI-1	Plasminogen activator inhibitor-1
PAN	Polyarteritis nodosa
PAP	Plasmin-antiplasmin
PCR	Polymerase Chain Reaction
PE	Pulmonary embolus
PNH	Paroxysmal Nocturnal Hemoglobinuria
PCV	Polycythema vera
PVT	Portal vein thrombosis
Read-CTv3	READ Clinical Terminology version 3
ROR	Reporting Odds Ratio
RSV	Respiratory Syncytial Virus
SARS	Severe Acute Respiratory Syndrome (caused by coronavirus)
SD	Standard Deviation
SNOMEDCT	SNOMED Clinical Terminology
SPEAC	Safety Platform for Emergency Vaccines
TAK	Takayasu's Arteritis (type of large vessel vasculitis)
TB	Tuberculosis
Tdap	Tetanus diphtheria acellular pertussis vaccine (formulated for ≥7 year olds)
T-Echo	Transthoracic echocardiogram
TF	Tissue factor
ti	Title (used for literature search)
tiab	Title & abstract (used for literature search)
U	Unknown
UC	Ulcerative colitis
UMLS	Unified Medical Language System

VAERS	Vaccine Adverse Event Reporting System
V/Q	Ventilation/Perfusion – type of scan used to detect pulmonary embolus
VTE	Venous thromboembolism
VZV	Varicella Zoster Virus
Y	Yes

INTRODUCTION

1. Background

CEPI has contracted with the Brighton Collaboration (BC), through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.

A key aspect of this harmonization has been creation of lists of priority potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI target diseases.

SPEAC Work Package 2 is creating resources and tools for the AESI including:

1. Tabular summaries of risk factors and background rates for each AESI.
2. Guidance on AESI real time investigation, data collection, analysis and presentation.
3. Spreadsheet summaries of ICD9/10 and MedDRA codes for each AESI.
4. Tools to facilitate capturing the specific clinical data needed to meet AESI case definitions across a variety of settings applicable to clinical trials, epidemiologic studies and individual case causality assessment. These include:
    a. Data abstraction and interpretation forms to facilitate capturing data from medical charts and applying it to determine a given AESI case definition level of certainty.
    b. Tabular checklists that are a stand-alone tool useful for summarizing key clinical data needed to determine the level of diagnostic certainty for a given case definition.
    c. Tabular logic and pictorial decision tree algorithms, also stand-alone tools, to facilitate correct application of key clinical data to determine the level of diagnostic certainty for each AESI.
    d. Glossary of terms relevant to anaphylaxis and the neurologic AESI.

All tools and resources noted above are compiled together into a companion guide for each Brighton AESI case definition. That is the purpose of this deliverable, which focuses on Thrombosis and Thromboembolism. This guide does not address Thrombocytopenia Thrombosis Syndrome (TTS) as that will be the subject of a separate case definition and companion guide.

2. Objective of this deliverable

To collate SPEAC & BC tools and resources that have been developed for Thrombosis & Thromboembolism.

3. Methods

The methods for developing each of the tools included in this guide were detailed in previously completed SPEAC deliverables as follows:

- Thrombosis and Thromboembolism Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM, MedDRA and SNOMEDCT-US Codes
- Thrombosis and Thromboembolism background rates and risk factors: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- Thrombosis and Thromboembolism Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers

- Thrombosis and Thromboembolism Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation

The methods are briefly described in Appendix 6 of this Guide along with links to source documents which have more detailed methodology. A systematic search was conducted for risk factors and background rates. The methods section in Appendix 6 has been amended to include the approach and specific search strategy used.

4. Results

4.1 Systematic Search for Background incidence and Risk Factors

A total of 2949 articles were retrieved of which 2747 were screened out for the following reason: 376 duplicates, 1 commentary, 790 focused on treatment, diagnosis or prevention and 1580 non-contributory to risk factors or general population background incidence.
Of 202 articles screened in for full text review there were 68 with potential to provide data on background incidence of thrombosis and thromboembolism including pulmonary embolism and ischemic stroke. Only 8 articles provided original source data.[24, 36, 37, 41-44] . Links to original source data in the remaining publications identified 101 with original source data that are included in the Appendix 2 tables for background incidence of: deep vein thrombosis (Table 1), Pulmonary embolism (Table 2), venous thromboembolism (Table 3), cerebral venous thrombosis (Table 4), cerebral venous sinus thrombosis (Table 5), ischemic stroke (Table 6), all cause stroke, not broken down by type (Table 7), cerebral infarction (Table 8), abdominal thrombosis (Table 9), venous thromboembolism in pregnancy (Tables 10A and 10B) and ischemic stroke in pregnancy (Tables 11A and 11B). The European ACCESS study[40] was published after the searches were done, and data were added to the tables for venous thromboembolism, cerebral venous thrombosis and ischemic stroke.

All 202 screened in articles were also reviewed regarding risk factors for thrombosis and thromboembolism, 37 were excluded because they were related to bleeding as opposed to a clotting disorder (14 idiopathic thrombocytopenia, 6 hemorrhagic stroke, 4 Henoch Schönlein Purpura, 4 Thrombotic Thrombocytopenic Purpura, 4 non-specified bleeding issues, 2 sepsis, 1 Disseminated Intravascular Coagulation, 1 Heparin-induced thrombocytopenia, 1 vasculitis). Among the remaining 165 articles, 46 contributed to an understanding of risk factors and are included in the guide: 34 on venous thrombosis and thromboembolism in general[117-9, 121-145, 148-151, 153, 154], 12 with a specific focus: 5 ischemic stroke[120, 147, 152, 161, 162], 3 cerebral venous thrombosis/sinus thrombosis[158,159,165], 2 pulmonary embolus[156,164] and 1 each for DVT[146] and MI[163]. 2 additional references were identified in the included article citations [155, 160] and one recent publication from an e-mail alert[157]. Two articles could not be retrieved for review and the remaining 117 were considered non-contributory to the understanding of risk factors, including 18 which had already been included as contributing to background incidence.

All outputs are provided in separate appendices as shown below:

1. Thrombosis and Thromboembolism diagnostic Codes: ICD-9-CM, ICD-10-CM, MedDRA and SNOMEDCT-US
2. Thrombosis and Thromboembolism background rates
3. Thrombosis and Thromboembolism risk Factors
4. Thrombosis and Thromboembolism case definition key caveats for diagnosis, data analysis and presentation plus recommendations for real time investigation.
5. Thrombosis and Thromboembolism data abstraction and interpretation forms with algorithms for assessing level of certainty.
6. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

5. Recommendations & discussion

This guide brings together many resources and tools related to the AESI of Thrombosis and Thromboembolism including: ICD-9/10-CM and MedDRA codes for data entry or database searching; background rates; risk factors; guidance for real time investigation; and tools for collecting and interpreting clinical data to apply the Brighton Thrombosis and Thromboembolism case definition and determine the level of diagnostic certainty.

The choice of tabular or pictorial algorithm is up to the user in terms of what is best suited to the situation and the assessor. SPEAC recommends that the tools be used in order to assign levels of certainty for all identified AEFI with features of Thrombosis and Thromboembolism. This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

6. References

1. Gollamudi J, Sartain SE, Navaei AH et al. Thrombosis and Thromboembolism: Brighton Collaboration case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Submitted to Vaccine Aug 10, 2022.
2. Becker BFH, Avillach P, Romio S, van Mulligen EM, Weibel D, Sturkenboom MCJM, Kors J. CodeMapper: Semi-automatic coding of case definitions. A contribution from the ADVANCE project. Pharmacoepidemiology and Drug Safety, 2017 (8) 26: 998-1005. Doi:10.1002/pds.4245
3. McCray AT, Burgun A, Bodenreider O. Aggregating UMLS semantic typesfor reducing conceptual complexity. Studies H ealth Technology Information, 2001 84(Pt 1): 216-20. PMID: 11604736; PMCID: PMC4300099.
4. Rogers F. Medical subject headings. Bull Med Libr Assoc, 1963. 51(1): 114-6. PMID: 13982385; PMCID: PMC197951.
5. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Safety, 1999. 0(2):109-17. Doi: 10.2165/00002018-199920020-00002.
6. Schuemie MJ, Jelier R, Kors JA. Peregrine: Lightweight gene name normalization by dictionary lookup. In: Proc of the Second Biocreative Challenge Evaluation Workshop., 2007. 131–133.
7. Stein PD, Kayali F, Olson RE. Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey. J Pediatr (2004) 145(4):563–5. doi:10.1016/j.jpeds.2004.06.0216
8. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med 2004;117:19–25.
9. Stein PD, Kayali F, Olson RE, Milford CE. Pulmonary thromboembolism in Asians/ Pacific Islanders in the United States: analysis of data from the National Hospital Discharge Survey and the United States Bureau of the Census. Am J Med 2004; 116:435–42
10. Kniffen WD, Baron JA, Barrett J et al. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. Arch Int Med 1994; 154: 861±866.
11. Silverstein MD, Heit JA, Mohr DN et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism. A 25- year population-based study. Arch Int Med 1998; 158: 585±593.
12. Anderson FA, Brownell Wheeler H et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Int Med 1991; 151: 933±938.

13. White RH, Zhou H, Romano PS. Incidence of idiopathic deep venous thrombosis and secondary thromboembolism among ethnic groups in California. Annals Int Med 1998; 128: 737±740.
14. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. Am J Med 2013;126:832.e13–21.
15. Andrew M, David M, Adams M, Ali K, Anderson R, Barnard D, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood (1994) 83(5):1251–7.
16. Vazquez FJ, Posadas-Martinez ML, Vicens J, Gonzalez Bernaldo de Quiros F, Giunta DH. Incidence rate of symptomatic venous thromboembolic disease in patients from a medical care program in Buenos Aires, Argentina: a prospective cohort. Thromb J 2013;11:16.
17. Jang MJ, Bang SM, Oh D. Incidence of venous thromboembolism in Korea: from the Health Insurance Review and Assessment Service database. J Thromb Haemost 2011;9:85–91
18. Cheuk BL, Cheung GC, Cheng SW. Epidemiology of venous thromboembolism in a Chinese population. Br J Surg 2004;91:424–8.
19. Ho WK, Hankey GJ, Eikelboom JW. The incidence of venous thromboembolism: a prospective, community-based study in Perth, Western Australia. Med J Aust 2008;189:144–7.
20. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC,Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007; 5: 692–9.
21. Severinsen MT, Johnsen SP, Tjonneland A, Overvad K, Dethlefsen C, Kristensen SR. Body height and sex-related differences in incidence of venous thromboembolism: a Danish follow-up study. Eur J Intern Med 2010;21:268–72
22. Nordström M, Lindblad B, Bergqvist D, Kjellström T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med. 1992 Aug;232(2):155-60. doi: 10.1111/j.1365-2796.1992.tb00565.x. PMID: 1506812.
23. Huerta C, Johansson S, Wallander MA, Garcia Rodriguez LA. Risk factors and shortterm mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch Intern Med 2007;167:935–43
24. Apenteng PN, Hobbs FR, Roalfe A, Muhammad U, Heneghan C, Fitzmaurice D. Incidence of venous thromboembolism in care homes: a prospective cohort study
25. Oger E for the EPI-GETBO Study Group. Incidence of venous thromboembolism: A community-based study in Western France. Thromb and Haemost 2000; 83: 657±660.
26. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med 2011;171:831–7.
27. DeMonaco NA, Dang Q, Kapoor WN, Ragni MV. Pulmonary embolism incidence is increasing with use of spiral computed tomography. Am J Med 2008; 121: 611–7. https://doi.org/10.1016/j.amjmed.2008.02.035
28. Molina JA, Jiang ZG, Heng BH, Ong BK. Venous thromboembolism at the National Healthcare Group, Singapore. Ann Acad Med Singapore 2009; 38: 470–8. https://pubmed.ncbi.nlm.nih.gov/19565096/

29. Kroger K, Moerchel C, Moysidis T, Santosa F. Incidence rate of pulmonary embolism in Germany: data fromthe federal statistical office. J Thromb Thrombolysis 2010;29: 349–53.
30. White RH, Zhou H, Murin S,HarveyD. Effect of ethnicity and gender on the incidence of venous thromboembolism in a diverse population in California in 1996. Thromb Haemost 2005; 93: 298–305.
31. Gomes JP, Shaheen WH, Truong SV, Brown EF, Beasley BW, Gajewski BJ. Incidence of venous thromboembolic events among nursing home residents. J Gen Intern Med 2003; 18: 934–6.
32. Sabapathy CA, Djouonang TN, Kahn SR, Platt RW, Tagalakis V. Incidence trends and mortality from childhood venous thromboembolism: a population-based cohort study. J Pediatr (2016) 172:175–80.e171. doi:10.1016/j.jpeds.2016.02.017
33. Lee CH, Lin LJ, Cheng DL, Kao Yang YH, Chen JY, Tsai LM. Incidence and cumulative recurrence rates of venous thromboembolism in the Taiwanese population. J Thromb Haemost 2010;8:1515–23.
34. Liu HS, Kho BC, Chan JC, Cheung FM, Lau KY, Choi FP, et al. Venous thromboembolism in the Chinese population experience in a regional hospital in Hong Kong. Hong Kong Med J 2002 Dec;8(6):400 5.
35. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation 2010;121:1896–903.
36. Kevane B, Day M, Bannon N, Lawler L, Breslin T, Andrews C, Johnson H, Fitzpatrick M, Murphy K, Mason O, O'Neill A, Donohue F, Ní Áinle F. Venous thromboembolism incidence in the Ireland east hospital group: a retrospective 22-month observational study. BMJ Open. 2019 Jun 21;9(6):e030059. doi: 10.1136/bmjopen-2019-030059. PMID: 31230035; PMCID: PMC6596982.
37. Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. Thromb Haemost. 2014 Aug;112(2):255-63. doi: 10.1160/TH13-09-0793. Epub 2014 Apr 3. PMID: 24695909.
38. Guijarro R, San Roman CM, Perello JI, Nuno E, Efficiency Group of the Internal Medicine Services of Andalusia, Strategic Plan of SADEMI (Andalusia Society of Internal Medicine). A study of hospital discharges for venous thromboembolism in the south of Spain. An analysis of 19,170 cases from a regional database from 1998 to 2001. Eur J Intern Med 2005;16:279–86.
39. Pulanić D, Gverić-Krečak V, Nemet-Lojan Z, Holik H, Coha B, Babok-Flegarić R, Komljenović M, Knežević D, Petrovečki M, Zupančić Šalek S, Labar B, Nemet D. Venous thromboembolism in Croatia - Croatian Cooperative Group for Hematologic Diseases (CROHEM) study. Croat Med J. 2015 Dec;56(6):550-7. doi: 10.3325/cmj.2015.56.550. PMID: 26718761; PMCID: PMC4707926.
40. Willame C, Dodd C, Gini R et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines. 2021. https://zenodo.org/record/5255870#.Yh521hPMJ70 (accessed Mar 1, 2022)
41. Coutinho JM, Zuurbier SM, Aramideh M, Stam J. The incidence of cerebral venous thrombosis: a cross-sectional study. Stroke 2012; 43: 3375–7. https://doi.org/10.1161/strokeaha.112.671453
42. Heller C, Heinecke A, Junker R, Kn€ofler R, Kosch A, Kurnik K, Schobess R, Von Eckardstein A, Str€ater R, Zieger B, Nowak-G€ottl U. Cerebral venous thrombosis in children: a multifactorial origin. Circulation 2003; 108: 1362–7. https://doi.org/10.1161/01.cir.0000087598.05977.45
43. deVeber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley DJ, Camfield CS, David M, Humphreys P, Langevin P, MacDonald EA, Gillett J, Meaney B, Shevell M, Sinclair DB, Yager J; Canadian Pediatric Ischemic Stroke Study Group. Cerebral sinovenous thrombosis in children. N Engl J Med. 2001 Aug 9;345(6):417-23. doi: 10.1056/NEJM200108093450604. PMID: 11496852. https://doi.org/10.1056/nejm2001080934506043

44. Devasagayam S, Wyatt B, Leyden J, Kleinig T. Cerebral venous sinus thrombosis incidence is higher than previously thought: a retrospective population-based study. Stroke 2016; 47: 2180–2. https://doi.org/10.1161/strokeaha.116.0136174
45. Berfelo F J, Kersbergen KJ, van Ommen CH, et al. Neonatal cerebral sinovenous thrombosis from symptom to outcome. Stroke 2010 ; 41 : 1382 – 8. https://doi.org/10.1161/strokeaha.110.5835425
46. Ghiasian M, Mansour M, Mazaheri S, Pirdehghan A. Thrombosis of the cerebral veins and sinuses in Hamadan, West of Iran. J Stroke Cerebrovasc Dis 2016;25:1313-9 10.1016/j.jstrokecerebrovasdis.2016.02.022
47. Kleindorfer D, Broderick J, Khoury J, et al. The unchanging incidence and case-fatality of stroke in the 1990s: a population-based study. Stroke 2006; 37: 2473–78.
48. Corbin DOC, Poddar V, Hennis A, et al. Incidence and case fatality rates of first-ever stroke in a black Caribbean population: the Barbados register of strokes. Stroke 2004; 35: 1254–58. https://doi.org/10.1161/01.str.0000127371.24658.df
49. Jamrozik K, Broadhurst RJ, Lai N, Hankey GJ, Burvill PW, Anderson CS. Trends in the incidence, severity, and short-term outcome of stroke in Perth, Western Australia. Stroke 1999; 30: 2105–11.
50. Islam MS, Anderson CS, Hankey GJ, et al. Trends in incidence and outcome of stroke in Perth, Western Australia during 1989 to 2001: the Perth community stroke study. Stroke 2008; 39: 776–82.
51. Feigin V, Carter K, Hackett M, et al. Ethnic disparities in incidence of stroke subtypes: Auckland Regional Community Stroke Study, 2002–2003. Lancet Neurol 2006; 5: 130–39.
52. Vangen-Lonne AM, Wilsgaard T, Johnsen SH, et al. Time trends in incidence and case fatality of ischemic stroke: the tromso study 1977–2010. Stroke 2015; 46: 1173–1179.
53. Rosengren A, Giang KW, Lappas G, et al. Twenty-fouryear trends in the incidence of ischemic stroke in Sweden from 1987 to 2010. Stroke 2013; 44: 2388–2393. https://doi.org/10.1161/strokeaha.113.001170
54. Kristensen B, Malm J, Carlberg B, et al. Epidemiology and etiology of ischemic stroke in young adults aged 18 to 44 years in northern Sweden. Stroke 1997; 28: 1702–1709. https://doi.org/10.1161/01.str.28.9.1702
55. Bejot Y, Daubail B, Jacquin A, et al. Trends in the incidence of ischaemic stroke in young adults between 1985 and 2011: the Dijon Stroke Registry. J Neurol Neurosurg Psychiatry 2014; 85: 509–513.
56. Rasura M, Spalloni A, Ferrari M, et al. A case series of young stroke in Rome. Eur J Neurol 2006; 13: 146–152.
57. Alzamora MT, Sorribes M, Heras A, et al. Ischemic stroke incidence in Santa Coloma de Gramenet (ISISCOG), Spain. A community-based study. BMC Neurology. 2008; 8:5. [PubMed: 18371212]
58. Vaartjes I, O'Flaherty M, Capewell S, Kappelle J, Bots M. Remarkable decline in ischemic stroke mortality is not matched by changes in incidence. Stroke. 2013; 44:591–597. [PubMed: 23212165]
59. Tsiskaridze A, Djibuti M, van MG, et al. Stroke incidence and 30-day case-fatality in a suburb of Tbilisi: results of the fi rst prospective population-based study in Georgia. Stroke 2004; 35: 2523–28. https://doi.org/10.1161/01.str.0000144683.96048.98
60. Jacobs BS, Boden-Albala B, Lin IF, et al. Stroke in the young in the northern Manhattan stroke study. Stroke 2002; 33: 2789–2793. https://doi.org/10.1161/01.str.0000038988.64376.3a
61. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. Neurology 2012; 79: 1781–1787. https://doi.org/10.1212/wnl.0b013e318270401d
62. N. L. Cabral, A. R. R. Gonc¸alves, A. L. Longo et al., "Trends in stroke incidence, mortality and case fatality rates in Joinville, Brazil: 1995–2006," Journal of Neurology, Neurosurgery and Psychiatry, vol. 80, no. 7, pp. 749–754, 2009. https://doi.org/10.1136/jnnp.2008.16447563
63. Thrift AG, Dewey HM, Macdonell RAL, McNeil JJ, Donnan GA. Incidence of the Major Stroke Subtypes: Initial Findings From the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke 2001; 32: 1732–38.

64. J. A. Stewart, R. Dundas, R. S. Howard, A. G. Rudd, and C. D. A. Wolfe. Ethnic differences in incidence of stroke: prospective study with stroke register. British Medical Journal 1999; 318(7189): 967–971.
65. Syme PD, Byrne AW, Chen R, Devenny R, Forbes JF. Community based stroke incidence in a Scottish population: the Scottish Borders Stroke Study. Stroke 2005; 36: 1837–43.
66. Marini C, Totaro R, De Santis F, et al. Stroke in young adults in the community-based L'Aquila registry: incidence and prognosis. Stroke 2001; 32: 52–56.
67. Corso GBE, Giardini G. Community-base study of stroke incidence in the Aosta Valley, Italy. CARe-Cerebrovascular Aosta Registry: years 2004–2005. Neuroepidemiology 2009; 32: 186–95.
68. R. D. Brown, J. P. Whisnant, J. D. Sicks, W. M. O'Fallon, and D. O. Wiebers, "Stroke incidence, prevalence, and survival: secular trends in Rochester,Minnesota, through 1989," Stroke, vol. 27, no. 3, pp. 373–380, 1996.
69. Lavados PM, Sacks C, Prina L, et al. Incidence, 30-day case-fatality rate, and prognosis of stroke in Iquique, Chile: a 2-year community-based prospective study (PISCIS project). Lancet 2005; 365: 2206–15. https://doi.org/10.1016/s0140-6736(05)66779-7
70. Tanaka H, Ueda Y, Date C, et al. Incidence of stroke in Shibata, Japan: 1976–1978. Stroke 1981; 12: 460–66.
71. Anderson CS, Jamrozik KD, Burvill PW, Chakera TM, Johnson GA, Stewart-Wynne EG. Determining the incidence of diff erent subtypes of stroke: results from the Perth Community Stroke Study, 1989–1990. Med J Aus 1993; 158: 85–89.
72. H. Ellekjær, J. Holmen, B. Indredavik, and A. Terent, "Epidemiology of stroke in Innherred, Norway, 1994 to 1996: incidence and 30-day case-fatality rate," Stroke, vol. 28, no. 11, pp. 2180–2184, 1997. https://doi.org/10.1161/01.str.28.11.2180
73. K. L. Mettinger, C. E. Soderstrom, and E. Allander, "Epidemiology of acute cerebrovascular disease before the age of 55 in the Stockholm County 1973–77: I. Incidence and mortality rates," Stroke, vol. 15, no. 5, pp. 795–800, 1984.
74. J. Bamford, P. Sandercock, M. Dennis, J. Burn, and C.Warlow, "A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project—1981–86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage," Journal of Neurology Neurosurgery and Psychiatry, vol. 53, no. 1, pp. 16–22, 1990.
75. Wolfe CD, Giroud M, Kolominsky-Rabas P, et al. Variations in stroke incidence and survival in 3 areas of Europe. European Registries of Stroke (EROS) Collaboration. Stroke 2000; 31: 2074–79.
76. P. Nencini, D. Inzitari,M. C. Baruffiet al., "Incidence of stroke in young adults in Florence, Italy," Stroke, vol. 19, no. 8, pp.977–981, 1988.
77. G. D'Alessandro, M. Di Giovanni, L. Roveyaz et al. Incidence and prognosis of stroke in the Valle d'Aosta, Italy: first-year results of a community-based study. Stroke 1992; 23(12): 1712–1715.
78. G. D'Alessandro, E. Bottacchi, M. Di Giovanni et al. Temporal trends of stroke in Valle d'Aosta, Italy. Incidence and 30-day fatality rates. Neurological Sciences 2000; 21(1): 13–18.
79. Lauria G, Gentile M, Fassetta G, et al. Incidence and prognosis of stroke in the Belluno Province, Italy: first-year results of a community-based study. Stroke 1995; 26: 1787–93.
80. Di Carlo A, Inzitari D, Galati F, et al. A prospective communitybased study of stroke in southern Italy: the Vibo Valentia incidence of stroke study (VISS). Methodology, incidence and case fatality at 28 days, 3 and 12 months. Cerebrovasc Dis 2003; 16: 410–17.
81. P. L. Kolominsky-Rabas, C. Sarti, P. U. Heuschmann et al. A prospective community-based study of stroke in Germany—the Erlangen Stroke Project (ESPro): incidence and case fatality at 1, 3, and 12 months. Stroke 1998; 29(12): 2501–2506.
82. Vemmos KN, Bots ML, Tsibouris PK, et al. Stroke incidence and case fatality in southern Greece: the Arcadia stroke registry. Stroke 1999; 30: 363–70.

83. Moran K, Choi HY, Kim KA et al. Incidence, prevalence and complications of Budd–Chiari syndrome in South Korea: a nationwide, population-based study. Liver Int 2016; 36(7):1067-73. Doi:10.1111/liv.13008
84. Rajani R, Björnsson E, Bergquist A, et al. The epidemiology and clinical features of portal vein thrombosis: a multicentre study. Aliment Pharmacol Ther. 2010;32(9):1154-62. doi: 10.1111/j.1365-2036.2010.04454.x.
85. Rajani R, Melin T, Björnsson E et al. BuddChiari syndrome in Sweden: epidemiology, clinical characteristics and survival – an 18-year experience. Liver Int 2009; 29:253–9.
86. Acosta S, Alhadad A, Svensson P, Ekberg O. Epidemiology, risk and prognostic factors in mesenteric venous thrombosis. Br J Surg. 2008; 95(10):1245–1251. doi:10.1002/bjs.6319
87. Almdal TP, Sørensen TI. Incidence of parenchymal liver diseases in Denmark, 1981 to 1985: analysis of hospitalization registry data. The Danish Association for the Study of the Liver. Hepatology 1991; 13:650–5.
88. Søgaard KK, Darvalics B, Horváth-Puhó E, Sørensen HT. Survival after splanchnic vein thrombosis: a 20-year nationwide cohort study. Thromb Res. 2016; 141:1–7. doi:10.1016/j.thromres.2016.02.024
89. Ollivier-Hourmand I, Allaire M, Goutte N et al. French Network for Vascular Disorders of the Liver. The epidemiology of Budd-Chiari syndrome in France. Dig Liver Dis. 2018; 50(9):931-937. doi: 10.1016/j.dld.2018.04.004.
90. Ageno W, Dentali F, Pomero F et al. Incidence rate and case fatality rates of portal vein thrombosis and Budd-Chiari Syndrome. Thromb Haemost 2017; 117:1–7.
91. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol. 2006; 194(5):1311-1315. doi:10.1016/j.ajog.2005.11.008
92. Liu S, Rouleau J, Joseph KS, et al. Epidemiology of pregnancy-associated venous thromboembolism: a population-based study in Canada. J Obstet Gynaecol Can2009; 31(7):611-620. doi:10.1016/S1701-2163(16)34240-2
93. Chan LY, Tam WH, Lau TK. Venous thromboembolism in pregnant Chinese women. Obstet Gynecol. 2001;98(3):471-475. doi:10.1016/s0029-7844(01)01476-4 2005;143(10):697-706. doi:10.7326/0003-4819-143-10-200511150-00006
94. Jang MJ, Bang SM, Oh D. Incidence of pregnancy-associated venous thromboembolism in Korea: from the Health Insurance Review and Assessment Service database. J Thromb Haemost 2011; 9(12):2519-2521. doi:10.1111/j.1538-7836.2011.04518.x
95. Sharma S, Monga D. Venous thromboembolism during pregnancy and the post-partum period: incidence and risk factors in a large Victorian health service. Aust N Z J Obstet Gynaecol. 2008; 48(1):44-49. doi:10.1111/j.1479-828X.2007.00799.x
96. Morris JM, Algert CS, Roberts CL. Incidence and risk factors for pulmonary embolism in the postpartum period. J Thromb Haemost 2010; 8(5):998-1003. doi:10.1111/j.1538-7836.2010.03794.x
97. Simpson EL, Lawrenson RA, Nightingale AL, Farmer RD. Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database. BJOG Int J Obstet Gynaecol 2001; 108(1):56-60. doi:10.1111/j.1471-0528.2001.00004.x
98. Macklon NS, Greer IA. Venous thromboembolic disease in obstetrics and gynaecology: the Scottish experience. Scott Med J. 1996; 41(3):83-86. doi:10.1177/003693309604100305
99. Andersen BS, Steffensen FH, Sørensen HT, et al. The cumulative incidence of venous thromboembolism during pregnancy and puerperium--an 11 year Danish population-based study of 63,300 pregnancies. Acta Obstet Gynecol Scand. 1998; 77(2):170-173.
100. Galambosi PJ, Gissler M, Kaaja RJ, Ulander VM. Incidence and risk factors of venous thromboembolism during postpartum period: a population-based cohort-study. Acta Obstet Gynecol Scand 2017; 96(7):852-861. doi:10.1111/aogs.13137
101. Jacobsen AF, Skjeldestad FE, Sandset PM. Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium--a register-based case-control study. Am J Obstet Gynecol. 2008; 198(2):233.e1-7. doi:10.1016/j.ajog.2007.08.041

102. Lindqvist P, Dahlbäck B, Marŝál K. Thrombotic risk during pregnancy: a population study. Obstet Gynecol 1999; 94(4):595-599. doi:10.1016/s0029-7844(99)00308-7
103. Lindqvist PG, Torsson J, Almqvist A, Björgell O. Postpartum thromboembolism: severe events might be preventable using a new risk score model. Vasc Health Risk Manag 2008; 4(5):1081-1087. doi:10.2147/vhrm.s2831
104. Soomro RM, Bucur IJ, Noorani S. Cumulative incidence of venous thromboembolism during pregnancy and puerperium: a hospital-based study. Angiology. 2002; 53(4):429-434. doi:10.1177/000331970205300409
105. Heit JA, Kobbervig CE, et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005; 143(10):697-706. doi:10.7326/0003-4819-143-10-200511150-00006
106. Sultan AA, West J, Tata LJ, et al. Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study. Br J Haematol 2012; 156(3):366-373. doi:10.1111/j.1365-2141.2011.08956.x
107. Virkus RA, Løkkegaard ECL, Bergholt T, et al. Venous thromboembolism in pregnant and puerperal women in Denmark 1995-2005. A national cohort study. Thromb Haemost 2011; 106(2):304-309. doi:10.1160/TH10-12-0823
108. Salonen Ros H, Lichtenstein P, Bellocco R, et al. Increased risks of circulatory diseases in late pregnancy and puerperium. Epidemiol Camb Mass 2001; 12(4):456-460. doi:10.1097/00001648-200107000-00016
109. James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. Obstet Gynecol 2005; 106(3):509-516. doi:10.1097/01.AOG.0000172428.78411.b0
110. Liu S, Chan WS, Ray JG, et al. Stroke and Cerebrovascular Disease in Pregnancy. Stroke 2019; 50(1):13-20. doi:10.1161/STROKEAHA.118.023118
111. Jeng JS, Tang SC, Yip PK. Incidence and etiologies of stroke during pregnancy and puerperium as evidenced in Taiwanese women. Cerebrovasc Dis Basel Switz 2004; 18(4):290-295. doi:10.1159/000080354
112. Liang CC, Chang SD, Lai SL, et al. Stroke complicating pregnancy and the puerperium. Eur J Neurol 2006; 13(11):1256-1260. doi:10.1111/j.1468-1331.2006.01490.x
113. Wiebers DO, Whisnant JP. The incidence of stroke among pregnant women in Rochester, Minn, 1955 through 1979. JAMA 1985; 254(21):3055-3057.
114. Salonen Ros H, Lichtenstein P, Bellocco R, et al. Increased risks of circulatory diseases in late pregnancy and puerperium. Epidemiol Camb Mass 2001; 12(4):456-460. doi:10.1097/00001648-200107000-00016
115. Ban L, Sprigg N, Abdul Sultan A, et al. Incidence of First Stroke in Pregnant and Nonpregnant Women of Childbearing Age: A Population-Based Cohort Study From England. J Am Heart Assoc 2017; 6(4):e004601. doi:10.1161/JAHA.116.004601
116. Ban L, Abdul Sultan A, Stephansson O, et al. The incidence of first stroke in and around pregnancy: A population-based cohort study from Sweden. Eur Stroke J 2017; 2(3):250-256. doi:10.1177/2396987317706600.
117. Stein PD, Matta F. Epidemiology and incidence: the scope of the problem and risk factors for development of venous thromboembolism. Crit Care Clin 2011; 27:907-32. Doi:10.1016/j.ccc.2011.09.006
118. Wendelboe AM, Raskob CE. Global burden of thrombosis: Epidemiologic aspects. Circulation Research 2016; 118: 1340-7. DOI: 10.1161/CIRCRESAHA.115.306841
119. Cushman M. Epidemiology and risk vactors for venous thrombosis. Semin Hematol 2007; 44(2): 62-69.
120. Putaala J. Ischemic stroke in young adults. Continuum 2020; 26(2): 386-414.
121. Valeriani E, Riva N, Di Nisio, Ageno W. Splanchnic Vein Thrombosis: Current Perspectives. Vascular Health and Risk Management 2019: 15:449-61
122. Shatzel JJ, O'Donnell M, Olson SR et al. Venous thrombosis in unusual sites: a practical review for the hematologist. EurJHaematology 2019; 102:53-62. Doi:10.1111/ejh.13177
123. Ruppert A, Lees M, Steinle T. Clinical burden of venous thromboembolism. 2010; 26(10):2465-2473.
124. Engbers MJ, Van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. J Thrombosis and Haemostasis; 8:2105-2112. DOI:10.1111/j.1538-7836.2010.03986.x

125. Reitsma PH, Versteeg HH, Middeldorp S. Mechanistic view of risk factors for venous thromboembolism. Arterioscler thromb Vasc Biol 2012; 32:563-568. DOI:10.1161/ATVBAHA.111.242818
126. Kourlaba G, Relakis J, Kontodimas S et al. A systematic review and meta-analysis of the epidemiology and burden of venous thromboembolism among pregnant women. Int J Gyn&Obst 2016; 132:4-10. http://dx.doi.org/10.1016/j.jigo.2015.06.054
127. Parunov LA, Soshitova NP, Ovanesov MV et al. Review Epidemiology of venous thromboembolism (VTE) associated with pregnancy. Birth Defects Research (Part C) 2015; 105:167-184. Doi:10.1002/bdrc.21105
128. Zakai NA, Mcclure LA. Racial differences in venous thromboembolism. J Thrombosis and Haemostasis 2011; 9:1877-82. DOI: 10.1111/j.138-7836.2011.04443.x
129. Tang L, Hu Y. Ethnic diversity in the genetics of venous thromboembolism. Thrombosis and Haemostasis 2015; 114:901-9. http://dx.doi.org/10.1160/TH15-04-0330
130. Reitsma PH. Genetics in thrombophilia. Haemostaseologie 2015; 35:47-51. http://dx.doi.org/10.482/HMO-14-11-0062
131. Clark P, Wu O. ABO blood groups and thrombosis: a causal association, but is there value in screening? Future Cardiol 2011; 7(2): 191-201.
132. Little I, Vinogradova Y, Orton E et al. Venous thromboembolism in adults screened for sickle cell trait: a population-based cohort study with nested case-control analysis. BMJ Open 2017; 7:e012665. Doi:10.1136/bmjopen-2016-012665.
133. Dentali F, Ageno W, Rancan E et al. Seasonal and monthly variability in the incidence of venous thromboembolism. Thrombosis Haemostasis 2011; 106:439-447. Doi:10.1160/TH11-02-0116
134. Cheng YJ, Liu ZH, Yao FJ et al. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. PLoS Med 2013, 10(9): e1001515. Doi:10.1371/journal.pmed.1001515.
135. Sevestre MA, Soudet S. Epidemiology and risk factors for cancer-associated thrombosis. Journal de Medecine Vasculaire 2020; 45:653-7. RF
136. Prandoni P, Piccioli A. Thrombosis as a harbinger of cancer. Curr Opin Hematol 2006; 13:362-365.
137. Ungprasert P, Wijampreecha K, Tanratana P et al. Risk of venous thromboembolism in patients tih celiac disease: a systematic review and meta-analysis. J Gastroenterology and Hepatology 2016; 31:1240-1245.doi:10.1111/jgh.13282
138. Magro F, Soares JB, Fernandes D. Venous thrombosis and prothrombotic factors in inflammatory bowel disease. World J Gaastroenterol 2014; 20(17):4857-72. Doi:10.3748/wjg.v20.i17.4857.
139. Peng KP, Chen YT, Fuh JL et al. Association between migraine and risk of venous thromboembolism: a nationwide cohort study. Headache 2016; 56:1290-9.
140. Darvall KAL, Sam RC, Silverman SH et al. Obesity and thrombosis. Eur J Vasc Endovasc Surg 2007; 33:223-233. Doi:10.1016/j.ejvs.2006.10.006
141. Rahmani J, Roudsari AH, Bawadi H et al. Relationship between body mass index, risk of venous thromboembolism and pulmonary embolism: a systematic review and dose-response metanalysis of cohort studies among four million participants. Thrombosis Research 2020; 192:64-72. https://doi.org/10.1016/j.thromres.2020.05.014
142. Alonso-Fernandez A, Toledo-Pons N, Garcia-Rio F. Obstructive sleep apnea and venous thromboembolism: Overview of an emerging relationship. Sleep Medicine Reviews 2020; 50 published online Nov14, 2019. https://doi.org/10.1016/j.smrv.2019.101233
143. Springer J, Villa-Forte A. Thrombosis in vasculitis. Curr Opin Rheumatol 2013; 25:19-25. Doi:10.197/BOR.0b013e32835ad3ca
144. Ungprasert P, Koster MJ, Thongprayoon C, Warrington KJ. Risk of venous thromboembolism among patients with vasculitis: a systematic review and meta-analysis. Clin Rheumatol 2016; 35:2741-7. Doi 10.1007/s10067-016-3394-7
145. Goeijenbier M, van Wissen M, van de Weg C et al. Review: viral infections and mechanisms of thrombosis and bleeding. J Med Virology 2012; 84:1680-1696.
146. Wang CC, Chang CT, Liu CL et al. Hepatitis C virus infection associated with an increased risk of deep vein thrombosis. Medicine 2015; 94(38); doi: 10.1097/MD.0000000000001585

147. Wang ZW, Li Y, Huang LY et al. Helicobacter pylori infection contributes to high risk of ischemic stroke: evidence from a meta-analysis. J Neurol 2012; 259: 2527-2537. DOI: 10.1007/s00415-012-6558-7.
148. Lidegaard O, Milsom I, Geirsson RT, Skjeldestad FE. Hormonal contraception and venous thromboembolism. Acta Obstet Gynecol Scand 2012; 91:769-778. DOI: 10.1111/j.1600-0412.2012.01444.x
149. Paran D, Herishanu Y, Elkayam O et al. Venous and arterial thrombosis following administration of intravenous immunoglobulins. Blood Coagulation and Fibrinolysis 2005; 16:313-8.
150. Kunutsor SK, Seidu S, Khunti K. Depression, antidepressant use, and risk of venous thromboembolism: systematic review and meta-analysis of published observational evidence. AnnMed 2018; 50(6):529-537. https://doi.org/10.1080/07853890.2018.1500703
151. Jonsson AK, Spigset O, Hagg S. Venous thromboembolism in recipients of antipsychotics: Incidence, mechanisms and management. CNS Drugs 2012; 26(8): 649-662.
152. Institute of Medicine, in Adverse effects of vaccines: Evidence and Causality. Stratton K et al., Editors. 2012, National Academies Press (US): Washington (DC).
153. Donahue JG, Kieke BA, Yih WK et al. Varicella vaccination and ischemic sstroke in children: is there an association? Pediatrics 2009; 123(2): 33228-234.
154. Smeeth L, Thomas AJ, Hall R et al. Risk of myocardial infarction and stroke after acute infection or vaccination. NEJM 2004; 351(25): 2611-18.
155. Dudley MZ, Halsey NA, Omer SB et al. The state of vaccine safety science: systematic reviews of the evidence. Lancet ID 2020; published online April 9. https://doi.org/10.1016/S1473-3099(20)30130-4.
156. Dudley MZ, Salmon DA, Halsey NA et al. The Clinician's Vaccine Safety REsource Guide: Optimizing prevention of vaccine-preventable diseases across the lifespan. Springer International PUblishing AG, part of Springer Nature 2018. Chapter 44. Do vaccines cause myocardial infarction or stroke? pp 297-303.
157. Maglione MA, Das GC, Raaen L et al. Safety of vaccines used for routine imunization in the United States. Evidence Report/Technology Assessment No 215, 2014. Agency for Healthcare Research and Quality: Rockville MD
158. Siriwardena AN, Gwini SM, Coupland CA. Influenza vaccination, pneumococcal vaccination and risk of acute myocardial infarction: matched case-control study.
159. Gwini, S.M., C.A. Coupland, and A.N. Siriwardena, The effect of influenza vaccination on risk of acute myocardial infarction: self- controlled case-series study. Vaccine, 2011. 29(6): p. 1145–9.
160. Macintyre, C.R., et al., Ischaemic heart disease, influenza and influenza vaccination: a prospective case control study. Heart, 2013. 99(24): p. 1843–8.
161. Chiang, M.H., et al., Association between influenza vaccination and reduced risks of major adverse cardiovascular events in elderly patients. Am Heart J, 2017. 193: p. 1–7.
162. Hsu, S.Y., et al., A Matched Influenza Vaccine Strain Was Effective in Reducing the Risk of Acute Myocardial Infarction in Elderly Persons: A Population-Based Study. Medicine (Baltimore), 2016. 95(10): p. e2869.
163. Lavallee, P.C., et al., Influenza vaccination and cardiovascular risk in patients with recent TIA and stroke. Neurology, 2014. 82(21): p. 1905–13.
164. Siriwardena, A.N., Z. Asghar, and C.C. Coupland, Influenza and pneumococcal vaccination and risk of stroke or transient ischaemic attack-matched case control study. Vaccine, 2014. 32(12): p. 1354–61.
165. Asghar, Z., C. Coupland, and N. Siriwardena, Influenza vaccination and risk of stroke: Self-controlled case-series study. Vaccine, 2015. 33(41): p. 5458–63.
166. Lee, K.R., et al., Effect of Influenza Vaccination on Risk of Stroke: A Systematic Review and Meta-Analysis. Neuroepidemiology, 2017. 48(3–4): p. 103–10.
167. Lin HC et al. Association of influenza vaccination and reduced risk of stroke hospitalization among the elderly: a population-based case-control study. Int J Environ Res Public Health 2014; 11(4): 3639-49.
168. Vila-Corcoles, A., et al., Evaluating clinical effectiveness of pneumococcal vaccination in preventing stroke: the CAPAMIS Study, 3-year follow-up. J Stroke Cerebrovasc Dis, 2014. 23(6): p. 1577–84.

169. Gee, J., et al., Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine, 2011. 29(46): p. 8279–84.
170. Vichnin, M., et al., An Overview of Quadrivalent Human Papillomavirus Vaccine Safety: 2006 to 2015. Pediatr Infect Dis J, 2015. 34(9): p. 983–91.
171. Tseng, H.F., et al., Pneumococcal vaccination and risk of acute myocardial infarction and stroke in men. JAMA, 2010. 303(17): p. 1699–706.
172. Ochoa-Gondar, O., et al., Evaluating the clinical effectiveness of pneumococcal vaccination in preventing myocardial infarction: The CAPAMIS study, three-year follow-up. Vaccine, 2014. 32(2): p. 252–7.
173. Eurich, D.T., et al., Pneumococcal vaccination and risk of acute coronary syndromes in patients with pneumonia: population- based cohort study. Heart, 2012. 98(14): p. 1072–7.
174. Vlachopoulos, C.V., et al., Association between pneumococcal vaccination and cardiovascular outcomes: a systematic review and meta-analysis of cohort studies. Eur J Prev Cardiol, 2015. 22(9): p. 1185–99.
175. Hedlund, J., et al., Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in elderly people: a 1-year follow-up. Vaccine, 2003. 21(25–26): p. 3906–11.
176. Tseng, H.F., et al., Safety of zoster vaccine in adults from a large managed-care cohort: a Vaccine Safety Datalink study. J Intern Med, 2012. 271(5): p. 510–20.
177. Keating, G.M., Shingles (herpes zoster) vaccine (zostavax((R))): a review of its use in the prevention of herpes zoster and postherpetic neuralgia in adults aged >/=50 years. Drugs, 2013. 73(11): p. 1227–44.
178. Daley, M.F., et al., Safety of diphtheria, tetanus, acellular pertussis and inactivated poliovirus (DTaP-IPV) vaccine. Vaccine, 2014. 32(25): p. 3019–24.
179. Fullerton, H.J., et al., Infection, vaccination, and childhood arterial ischemic stroke: Results of the VIPS study. Neurology, 2015. 85(17): p. 1459–66.
180. MacDonald SE, Dover DC, Hill MD et al. Is varicella vaccination associated with pediatri arterial ischemic stroke? A population-based cohort study. Vaccine 2018; 36:2764-7. DOI 10.1016/j.vaccine.2018.04.012
181. Yang Q, Chang A, Tong X, Merritt MA. Herpes Zoster vaccine live and risk of stroke among Medicare beneficiaries: A population-based cohort study. Stroke 2021; 52:1712-21. DOI: 10.1161/STROKEAHA.120.032788
182. Varbo A, Nordestgaard BG. Remnant cholesterol and risk of ischemic stroke in 112,512 individuals from the general population. Ann Neurol 2019; 85:550-9. Doi: 10.1002/ana.254
183. Warny M, Helby J, Birgens HS et al. Arterial and venous thrombosis by high platelet count and high hematocrit: 108521 individuals from the Copenhagen General Population Study. J Thromb Haemost 2019; 17:1898-1911.
184. Awotoye J, Fashanu OE, Lutsey PL et al. Resting heart rate and incident venous thromboembolism: the multi-ethnic study of atherosclerosis. Open Heart 2020; 7:ee001080. Doi:10.1136/openhrt-2019-001080.
185. Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. Arch Intern Med 2000; 160: 769-774.
186. Putaala J. Ischemic stroke in the young: Current perspectives on incidence, risk factors, and cardiovascular prognosis. European Stroke Journal 2016; 1:28-40. Doi: 10.1177/2396987316629860
187. Koptya I, Sarecka-Hujar B, Sordyl J, Sordyl lR. The role of genetic risk factors in arterial ischemic stroke in pediatric and adult patients. A critical review. MolBiolRep 2014; 41:4241-51. DOI: 10.1007/s11033-014-3295-2.
188. O'Donnell MJ, Chin SL, Rangarajan S et al. Global and regionl effets of potentially modifiable risk factors associated with acute stroke in 32 countreis (INTERSTROKE): a case control study. Lancet 2016; 388:761-5. http://dx.doi.org/10.1016/S0140-6736(16)30506-2
189. Cengel A, Tanindi A. Myocardial infarction in the young. J Postgrad Med 2009; 55:305-13.
190. ESHRE Capri Workshop Group. Venous thromboembolism in women: a specific reproductive heatlh risk. Human Reproduction Update 2013; 19(5): 471-482. doi: 10.1093/humupd/dmt028
191. Wong P, Baglin T. Epidemiology, risk factors and sequelae of venous thromboembolism. Phlebology 2012; 27(Suppl 2):2-11. DOI: 10.1258/phleb.2012.012S31.

192. Stein PD, Matta F.Acute pulmonary embolism Curr Probl Cardiol. 2010 Jul;35(7):314-76. doi: 10.1016/j.cpcardiol.2010.03.002. 3-23-2021 https://pubmed.ncbi.nlm.nih.gov/20682170 https://doi.org/10.1016/j.cpcardiol.2010.03.002
193. Ropper AH, Klein JP. Cerebral Venous Thrombosis. NEJM 2021; 385:59-64. DOI: 1.1056/NEJMra2106545
194. Duman T, Uluduz D, Midi I et al. A multicenter study of 1144 patients with cerebral venous thrombosis: the VENOST study. J Stroke and Cerebrovascular Diseases 2017; 26(8): 1848-1857. http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.04.020
195. Al-Sulaimon A. Clinical aspects, diagnosis and management of cerebral vein and dural sinus thrombosis: A literature review. Saudi J Medicine & Medical Sciences 2019; 7:137-145
196. Kalita J, Chandra S, Kumar B, DVST form a tertiary care teaching hospital in India. Neurologist 2016; 21:35-8.
197. Stam J. Cerebral venous and sinus thrombosis: Incidence and cases. Advances in Neurology 2003; 92:225-32.
198. Capecchi M, Abbattista M, Martinelli I. Cerebral venous sinus thrombosis. J Thrombosis and Haemostasis 2018; 16:1918-31. doi: 10.1111/jth.14210.
199. Zaidi AU, Hutchins KK, Rajpurkar M. Pulmonary embolism in children. Front Pediatr. 2017 Aug 10;5:170. doi: 10.3389/fped.2017.00170. eCollection 2017. 3-23-2021 https://doi.org/10.3389/fped.2017.00170
200. Ichord R. Front Pediatr. 2017 Jul 27;5:163. doi: 10.3389/fped.2017.00163. eCollection 2017. 3-23-2021 https://doi.org/10.3389/fped.2017.00163
201. deVeber G, Andrew M. Cerebral sinovenous thrombosis in children. NEJM 201; 345:417-423

APPENDIX 1

Thrombosis and Thromboembolism Diagnostic Codes: ICD-9/10-CM and MedDRA

4.1 Thrombosis and Thromboembolism Diagnostic Codes: ICD-9/10-CM and MedDRA

TABLE 1. NARROW TERMS FOR THROMBOSIS AND THROMBOEMBOLISM

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA v24.1	ICD9CM	ICD10CM	SNOMEDCT_US 2022_03
C0085307	Embolism and thrombosis	Embolism and thrombosis Embolism and thrombosis NOS Embolus/thrombosis NOS	10014523			195440001 195440003
C0155774	Other venous embolism and thrombosis	Other venous embolism and thrombosis Other venous embolism & thrombosis Venous embolism and thrombosis, other	10033036 10033035 10047225	453	I82	195435006
C0155775, C0265049, C0265050	Embolism and thrombosis of the vena cava	Embolism and thrombosis of vena cava Vena cava thrombosis and embolism	10014512 10047196 10047193 10047195		I82.2	195437003 50817002 83938003
C2883080	Embolism and thrombosis of vena cava and other thoracic veins	Embolism and thrombosis of vena cava and other thoracic veins Vena cava embolism Vena cava thrombosis	10047193 10047195		I82.2	
C2883081	Embolism and thrombosis of superior vena cava	Embolism and thrombosis of superior vena cava Embolism and thrombosis of superior vena cava NOS			I82.21 I82.210	
C2883082	Acute embolism and thrombosis of superior vena cava				I82.210	
C2883084	Acute embolism and thrombosis of inferior vena cava				I82.220	
C2883086	Embolism and thrombosis of brachiocephalic (innominate) vein				I82.29	
C2883087	Embolism and thrombosis of other thoracic veins				I82.29	
C2883088	Acute embolism and thrombosis of other thoracic veins				I82.290	
C0155773	Portal Vein Thrombosis	Portal vein thrombosis Pyelethrombosis	10036206 10037611 10043633	452	I81	17920008 155455003

		Thrombosis portal vein				
C0856761	Budd-Chiari Syndrome	Budd-Chiari syndrome Budd Chiari syndrome Syndrome Budd-Chiari Hepatic venous outflow obstruction Hepatic vein obstruction	10006537 10006536 10042793 10019714 10051567	453.0	I82.0	195436007 82385007
C0155776, C0268793, C0238457	Embolism and thrombosis of the renal vein	Embolism and thrombosis of renal vein Other venous embolism and thrombosis of renal vein Renal vein embolism Renal vein thrombosis	10014508 10038547 10038548 10056966	453.3	I82.3	195438008 39291006 123268008 15842009
C2883090, C0149871	Acute embolism and thrombosis of deep veins of lower extremity	Deep vein thrombosis Acute embolism & thrombosis of deep veins of lower extremity	10051055 10012107 10013877 10043642	453.40	I82.4	128053003 128057002 155454004 195403006 266328001
C2883091	Acute embolism and thrombosis of unspecified deep veins of lower extremity				I82.40	
C2883092	Acute embolism and thrombosis of femoral vein				I82.41	
C2883093	Acute embolism and thrombosis of right femoral vein				I82.411	
C2883094	Acute embolism and thrombosis of left femoral vein				I82.412	
C2883095	Acute embolism and thrombosis of femoral vein, bilateral				I82.413	
C2883096	Acute embolism and thrombosis of unspecified femoral vein				I82.419	
C2883097	Acute embolism and thrombosis of iliac vein				I82.42	
C2883098	Acute embolism and thrombosis of right iliac vein				I82.421	
C0155777	Embolism and thrombosis of other specified veins	Embolism and thrombosis of other specified veins Embolism and thrombosis of other specified veins [X]Embolism and thrombosis of other specified veins	10014507		I82.8 I82.89	 195629001
C0494623	Embolism and thrombosis of unspecified vein				I82.9	
C0155749	Arterial embolus and thrombosis	Arterial embolism and thrombosis Arterial embolus and thrombosis Arterial embolus and thrombosis Arterial embolism and thrombosis NOS	10003156	444	I74	 155434000 155438002 195315009

		Arterial embolism and thrombosis NOS Arterial embolic and thrombotic occlusion				195345007 266262004
C0040038	Thromboembolism	Thromboembolism Thromboembolism NOS Embolism and thrombosis of unspecified site Other venous embolism and thrombosis of unspecified site Thromboembolus Thromboembolic disorder Thromboembolism - lesion	 10014511 10043565 10043566 10043567	 453.9		13713005 371039008 134356002
C03040726	Venous embolism	Venous embolism Venous embolism NOS Embolism venous Embolism of vein NOS Embolus of vein NOS	10074664 10047226 10014522		 I82.90	234049002 195441004 155457006
C1861172	Venous thromboembolism		10066899			
C0019154	Hepatic Vein Thrombosis		10019713	453.0	I82.0	195436007 38739001

TABLE 2. NARROW TERMS FOR PULMONARY THROMBOSIS, THROMBOEMBOLISM

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT_US
C0034065	Pulmonary embolism	Pulmonary embolism Pulmonary embolism Pulmonary embolism NOS Pulmonary artery embolism Embolus pulmonary Embolus pulmonary	 10014521 10014537 10034191 10037377 10037380 10050071 10082134	 415.1 	I26 I26.99 	59282003 194882001 155326007 266292008
C0151946	Pulmonary thrombosis	Pulmonary thrombosis Pulmonary thrombosis NOS Thrombosis pulmonary Pulmonary venous thrombosis	10037437 10037438 10043635 10037459			69357003
C0340535	Acute massive pulmonary embolism	Acute massive pulmonary embolism	10000853			233936003
C0375267	Other pulmonary embolism and infarction		10032438	415.19		
C0494583	Pulmonary embolism with mention of acute cor pulmonale				I26.0	
C0494584	Pulmonary embolism without mention of acute cor pulmonale				I26.9	
C4290143	Pulmonary (acute)(artery)(vein) thromboembolism				I26	
C0524702	Pulmonary thromboembolism		10037436			233935004
C0034066	Pulmonary embolism with pulmonary infarction		10037378	415.1		1001000119102
C0034074	Pulmonary Infarction		10021760 10037409 10037410			64662007
C0392108	Pulmonary venous thrombosis		10037459			77892009

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TABLE 3. NARROW TERMS FOR CEREBRAL THROMBOSIS AND CEREBRAL VENOUS SINUS THROMBOSIS

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT_US
C0079102	Cerebral thrombosis	Cerebral thrombosis Cerebral thrombosis (vessel unspecified) Cerebral thrombosis NOS Thrombosis cerebral	10008132 10008133 10050549 10043619	434.0		155401002
C0151945	Thrombosis of cerebral veins	Cerebral venous thrombosis Thrombosis of cerebral veins	1000813810043621			95455008
C2882442	Cerebral vein thrombosis, nonpyogenic	Nonpyogenic thrombosis of cerebral vein	10029661 10057725 10029661 10057725		I67.6	123269000 42970005 123269000 42970005
C0338580	Cerebral venous thrombosis of cortical vein					230722002
C0155731	Nonpyogenic thrombosis of intracranial venous sinus	Nonpyogenic thrombosis of intracranial venous sinus Nonpyogenic thrombosis of intracranial venous sinus		437.6	I67.6	42970005 123269000
						14246007
C0340731	Embolism of intracranial venous sinus	Embolism of intracranial venous sinus Embolism central nervous system venous sinus NOS				14246007 192758000
C0037198	Sinus Thrombosis, intracranial	Cerebral venous sinus thrombosis Superior sagittal sinus thrombosis Transverse sinus thrombosis	10083037 10042567 10044457 10008209 10022776 10061251			192759008 72094000

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C0238454	Cavernous sinus thrombosis	Cavernous sinus thrombosis Aseptic cavernous sinus thrombosis Thrombosis of cavernous venous sinus	10007830 10084527			89980009
C0270644	Embolism of cavernous venous sinus					23819000
	Embolism cavernous sinus					192754003
C0270639	Lateral sinus thrombosis	Thrombosis of lateral venous sinus Thrombosis transverse sinus	10044457			21258007 192761004
C0270645	Embolism of lateral venous sinus	Embolism of lateral venous sinus Embolism transverse sinus				80758005 192757005
C0235502	Thrombophlebitis of cerebral vein		10043574			95461006
C0154662	Phlebitis and thrombophlebitis of intracranial venous sinuses		10034887	325		
C0751827	Thrombophlebitis of lateral venous sinus Thrombophlebitis lateral venous sinus					78682001 192772009
C0494450	Intracranial and intraspinal phlebitis and thrombophlebitis				G08	

TABLE 4.NARROW TERMS FOR STROKE IN GENERAL AND FOR ISCHEMIC STROKE

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT_US
C0007785	Cerebral infarction	Cerebral infarction Cerebral infarction Cerebral infarction, unspecified Cerebral infarct Cerebral infarct Cerebral infarct Cerebral infarction NOS Cerebral infarction nos	10008117 10008118 10021755		I63*	 20059004 155405006 195188006 195191006 266256009 266315008 432504007
C0348635	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries [X]Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries			I63.5	 195247002 195599001
C0348636	Other cerebral infarction	Other cerebral infarction Other cerebral infarction [X]Other cerebral infarction			I63.8 I63.89	 195600003
C0917798	Cerebral Ischemia	Cerebral ischemia Cerebral ischaemia, NOS Cerebral ischaemia Ischemia cerebral Ischemia cerebrovascular Ischaemia cerebral	10008121 10008120 10023029 10023030 10055749 10055750	437.1	I67.82	287731003 38609002

		Ischaemia cerebrovascular				
C0038454	Cerebrovascular accident	Stroke NOS Stroke, not specified as haemorrhage or infarction Accident cerebrovascular Accident cerebrovascular Cerebrovascular accident Cerebrovascular accident Cerebrovascular accident Cerebrovascular accident NOS CVA CVA – Cerebrovascular accident unspecified Stroke Apoplexy Stroke and cerebrovascular accident unspecified	10000374 10008190 10008191 10011693 10042244 10003004		I63.9 I64	313267000 155405006 266315008 155388006 230690007 266312006 195208004 195208004 82797006 270883006
C0751956	Acute cerebrovascular accidents					457551000124104
C0393952	Infarction – precerebral					
C0236073	Cerebellar infarction	Cerebellar infarction	10008034			95460007

C1446220	Infarction of basal ganglia	Basal ganglia infarction Infarction of basasl ganglia	10069020			 413102000
C0521542	Brain stem infarction	Brain stem infarction	10006147			95457000
C0348647	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries [X]Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries			I63.2 I63.29	 195246006 195612004
C0028790	Cerebral artery occlusion	Occlusion of cerebral arteries Cerebral arterial occlusion Cerebral arterial occlusion Cerebral arterial occlusion Cerebral artery occlusion Cerebral artery occlusion NOS Cerebral artery occlusion NOS Cerebral artery occlusion, unspecified Cerebral artery thrombosis	10030006 10008089 10008091 10008092	434 434.9		 20059004 155405006 195188006 195191006 266256009 266315008 432504007 7
C0007274 C0028790 C0521542 C1262152		Carotid artery thrombosis Cerebellar artery thrombosis Brain stem thrombosis Basilar artery thrombosis Precerebral artery thrombosis	10007688 10008023 10062573 10063093 10074717			
C0948008	Ischemic stroke	Ischaemic stroke	10061256			422504002
C3648410	Ischemic stroke without residual deficits					725132001
C1298680 C0242129	Thrombotic stroke		10043647			373606000 371040005

C0262469	Embolic stroke	Embolic stroke	10014498			371041009
C3178801	Stroke, Lacunar					230698000
C0521542	Brain Stem Infarctions	Brain stem stroke Basal ganglia stroke	10068644 10071043			95457000 195192004 230697005
C0007780	Cerebellar embolism Thrombosis of precerebral artery Embolism of precerebral artery	Carotid arterial embolus Cerebral artery embolism Brain stem embolism	10008088 10008108 10008109 10014515 10014530 10074717 10085250	434.1	I65	75543006 155402009 48601002 40276003

TABLE 5. NARROW TERMS FOR MYOCARDIAL INFARCTION

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT_US
C1510446	Acute ischemic heart disease	Acute ischaemic heart disease unspecified Acute ischaemic heart disease Acute ischemic heart disease			I24.9	 32598000 413439005
C0155626	Acute myocardial infarction	Acute myocardial infarction, unspecified Acute myocardial infarction Acute myocardial infarction Acute myocardial infarction Acute myocardial infarction Acute myocardial infarction, unspecified site Acute myocardial infarction of unspecified site, episode of care unspecified	 10000891 10000928 10000929	 410 410.9 410.90	I21.9 I21	 155304006 194796000 266288001 57054005

		Myocardial infarction acute Acute myocardial infarction NOS	10028597			194811003
C0010072	Coronary thrombosis	Coronary (artery) thrombosis Coronary (artery) thrombosis Coronary artery thrombosis Coronary artery thrombosis Coronary thrombosis Coronary thrombosis Thrombosis coronary	 10011091 10011108 10043622		I21 I22 	 66514008 155304006 194796000 266288001 398274000
C0264686	Coronary artery embolism		10011084			
C0027051	Myocardial infarction	Cardiac infarction Cardiac infarction Myocardial infarction Myocardial infarction Attack – heart Attack – heart Attack – heart Attack heart (NOS) Attack coronary Heart attack Infarct myocardial Myocardial infarct MI	 10028596 10003724 10003723 10019250 10021758 10028595 10027524		I21 I22 	 233824008 22298006 155304006 194796000 266288001 66514008
C0155627	Acute myocardial infarction of anterolateral wall		10000892	410.0		70211005
C0494580	Acute subendocardial myocardial infarction	Acute subendocardial myocardial infarction Subendocardial infarction, episode of care unspecified Acute myocardial infarction, subendocardial infarction, episode of care unspecified	 10000921	 410.70	I21.4	
C0155652	True posterior wall infarction, episode of care unspecified	True posterior wall infarction, episode of care unspecified Acute myocardial infarction, true posterior wall infarction, episode of care unspecified	 10000925	410.60		

C0264696	Microinfarct of heart	Microinfarct of heart Microinfarction of heart				42531007 194824003
C0264706	True posterior myocardial infarction	True posterior myocardial infarction True posterior wall infarction Acute myocardial infarction, true posterior wall infarction	 10000924	 410.6		194802003 34644005

TABLE 6. NARROW TERMS FOR MICROANGIOPATHY

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10 CM	SNOMEDCT_US
C2717961	Thrombotic Microangiopathies	Thrombotic microangiopathy Thrombotic microangiopathy Thrombotic microangiopathy NOS	10043645 10043646	446.6	M31.1	126729006 78129009 195360005
C0265026	Capillary thrombosis	Capillary thrombosis Capillary thrombosis				195388004 17810004
C0155765	Disease of capillaries	Microangiopathy Microangiopathy NOS Disease of capillaries Diseases of capillaries Disease of capillaries, unspecified Disease of capillaries NOS Diseases of capillaries NOS Diseases of capillaries NOS Disorder of capillaries Capillary disease Capillary disease Capillary disorder Capillary disorder NOS	10062198 10050444 10013109 10007189 10007190	 448 	 I78 I78.9 	57223003 155446001 195390003 155449008 266324004 58729003 195250004 195380006

TABLE 7. NARROW TERMS FOR PREGNANCY AND POST-PARTUM THROMBOSIS AND THROMBOEMBOLISM

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10 CM	SNOMEDCT_US
C0342044	Antepartum deep vein thrombosis	Deep phlebothrombosis in pregnancy Deep phlebothrombosis, antepartum Deep phlebothrombosis, antepartum, unspecified as to episode of care or not applicable Deep phlebothrombosis, antepartum, antepartum condition or complication Antepartum deep vein thrombosis Antenatal deep vein thrombosis Antenatal deep vein thrombosis unspecified Antenatal deep vein thrombosis NOS		 671.3 671.30 671.33	O22.3	 49956009 156268003 200231004 200234007
C0342039	Postpartum deep phlebothrombosis	Deep Phlebothrombosis in the puerperium Deep phlebothrombosis, postpartum Deep phlebothrombosis, postpartum, postpartum condition or complication Postpartum deep phlebothrombosis Postnatal deep vein thrombosis DVT– deep venous thrombosis unspecified Postnatal deep vein thrombosis unspecified Postnatal deep vein thrombosis NOS		 671.4 671.44	O87.1	 56272000 156269006 200235008 200236009 200239002
C1868778 C1263829		Venous thrombosis in pregnancy Postpartum venous thrombosis	10067030 10036300			
C0157552	Obstetrical blood clot embolism	Obstetrical blood-clot embolism Obstetrical blood-clot embolism, unspecified as to episode of care or not applicable		673.2 673.20		60601008
C1279439	Obstetric blood-clot pulmonary embolism	Obstetrical pulmonary embolism Obstetric blood-clot pulmonary embolism Obstetric blood-clot pulmonary embolism unspecified Obstetric blood-clot pulmonary embolism NOS	10029925			 200299000 200300008 200305003

C0495169	Embolism following abortion and ectopic and molar pregnancy	Embolism following ectopic and molar pregnancy Embolism following abortion or ectopic and molar pregnancies		639.6	O08.2	
10043586		Thrombophlebitis neonatal	10043586			
C0549457		Cerebral infarction foetal	10008119			

TABLE 8. BROAD SEARCH TERMS FOR THROMBOSIS AND THROMBOEMBOLISM

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10 CM	SNOMEDCT_US
C1367972	Phlebitis and thrombophlebitis	Thrombophlebitis Phlebitis and thrombophlebitis Phlebitis and thrombophlebitis of unspecified site Phlebitis and thrombophlebitis NOS Phlebitis and thrombophlebitis NOS	10043570	 451 451.9	 I80 I80.9	 195394007 195431002 195434005
C0265060	Phlebitis of deep veins of lower extremity					25114006
C0155770	Phlebitis and thrombophlebitis of other deep vessels of lower extremities	Phlebitis and thrombophlebitis of other deep vessels of lower extremities [X]Phlebitis and thrombophlebitis of other deep vessels of lower extremities Phlebitis and thrombophlebitis of deep veins of lower extremities,,other	10034890	 451.19	I80.29	 195627004
C0340712	Phlebitis and thrombophlebitis of lower extremities, unspecified	Phlebitis and thrombophlebitis of lower extremities unspecified Phlebitis and thrombophlebitis of lower extremities, unspecified Phlebitis and thrombophlebitis of the leg NOS	10034888 10034889	 451.2		 195418007

C0340692	Phlebitis and thrombophlebitis of other sites	Phlebitis and thrombophlebitis of other site Phlebitis and thrombophlebitis of other sites Phlebitis and thrombophlebitis of other sites	10034891 10034892	 451.8 451.89	I80.8	
C0265066	Thrombophlebitis of the femoral vein	Phlebitis and thrombophlebitis of deep femoral vein Phlebitis and thrombophlebitis of femoral vein (deep)(superficial) Thrombophlebitis of the femoral vein		 451.11	I80.1	1748006 195410000
C0265053	Thrombophlebitis of lower extremities					46253008
C0152250	Thrombophlebitis migrans			453.1	I82.1	
C1704436	Peripheral Arterial Diseases	Peripheral arterial disease Peripheral arterial disease	10067825			399957001 91523003
C2945695	Limb ischemia	Limb ischemia				21631000119105

APPENDIX 2.
Thrombosis and Thromboembolism Background Rates

2.1 Thrombosis and Thromboembolism Background Rates

TABLE 1. Deep Venous Thrombosis (Alone)

Country [reference]	Study years	Population (Age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
GLOBAL, AFRICA, MIDDLE EAST: NONE FOUND					
AMERICAs					
Stein[7] USA National data	1979-2001	0-1 2-14 15-17 Total	8.7 2.1 9.9 4.2		
Cushman[8] USA National	1987-1997	≥45	117		
Stein[9] USA National	1990-1999	All ages White	104 (2,128,000)		
		All ages African American	107(344,000)		
		All ages Asian/ Pacific Islander	22(18,000)		
Kniffen[10] USA National	1986-1989	70-79 ≥80	246 299	244 273	248 311
Silverstein[11] USA Minnesota	1966-1990	0-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 ≥85 Total	 48[42938-52] (938)	0.6 5 13 18 20 30 35 37 70 59 128 130 213 229 320 161 47[42-52] (377)	0.3 18 41 51 46 35 47 51 49 63 100 95 148 176 206 275 50 [46-54] (561)

	1986-1990	0-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 ≥85 Total	 49[43-56] (230)	0 6 0 13 36 34 48 49 25 69 113 163 282 307 328 120 51[40-61] (99)	0 11 30 31 34 19 34 41 25 91 79 136 168 193 303 396 48[40-57] (131)
Anderson[15] USA Massachusetts	1985-1986	0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 ≥80 Overall	0 3 14 25 17 43 119 232 291 48[43-54]	0 7 16 37 24 43 144 265 263 48[40-57]	0 0 11 14 10 42 99 211 303 48[41-57]
White[13] USA California	1991-1994	>18 White	23.0		
		>18 African American	29.3		
		>18 Hispanic	13.9		
		>18 Asian or Pacific Islander	6.0		
Tagalakis[14] Canada	2000-2009	0-19 20-29 30-39 40-49 50-59 60-69 70-79 ≥80 Total	5[5-6] (937) 24[23-25] (2207) 37[36-38] (3859) 55[54-57] (6861) 93[91-95] (9862) 165[162-168] (11,590) 271[266-276] (12,733) 410[402-418] (10,265) 78[78-79] (58,314)		
Andrew[15] Canada Hospital admissions	1990-1992	0.1-18	53 (137)		

Vazquez[16] Argentina	2006-2012	> 17	48[44-51] (896)		
ASIA					
Jang[17] Korea	2004	0–9		0.10	0.00
		10–19		0.23	0.26
		20–29		1.71	1.21
		30–39		2.71	1.69
		40–49		4.20	3.43
		50–59		6.09	5.28
		60–69		11.00	12.37
		70–79		15.25	20.07
		≥ 80		26.26	16.81
		Total	3.91	3.72	4.09
	2005	0–9		0.00	0.00
		10–19		0.31	0.25
		20–29		1.33	1.47
		30–39		2.93	2.18
		40–49		3.92	3.34
		50–59		6.23	5.28
		60–69		9.83	13.38
		70–79		14.93	21.50
		≥ 80		23.51	20.24
		Total	3.99	3.55	4.43
	2006	0–9		0.07	0.00
		10–19		0.56	0.13
		20–29		2.11	1.28
		30–39		3.20	1.36
		40–49		4.76	3.30
		50–59		7.03	5.89
		60–69		14.02	11.09
		70–79		26.66	22.86
		≥ 80		29.95	25.75
		Total	4.52	4.73	4.30
	2007	0–9		0.00	0.00
		10–19		0.28	0.19
		20–29		1.97	1.11
		30–39		4.11	1.91
		40–49		5.36	3.70
		50–59		7.82	5.52
		60–69		16.62	14.35
		70–79		25.47	21.93
		≥ 80		24.53	22.64
		Total	4.84	5.12	4.55
	2008	0–9		0.23	0.04
		10–19		0.36	0.56
		20–29		1.86	1.43

		30–39 40–49 50–59 60–69 70–79 ≥ 80 Total	 5.31	3.40 4.91 8.09 14.87 24.34 35.69 4.90	2.65 4.77 5.77 14.78 31.84 31.39 5.73
Cheuk[18] China	2000-2001	0-4 5-14 15-44 45-64 ≥65 All ages	0.5 0.8 7.2 9.6 81.1 17.1 (2304)	1.0 0.7 9.9 10.6 65.3 16.9	0.0 0.9 4.5 8.6 97.0 17.3
AUSTRALIA/OCEANIA					
Ho[19] Australia	2003–2004	All ages		58 [41–75] (47)	47 [32–62] (39)
EUROPE					
Naess[20] Norway	1995–2001	20–24 25–29 30–34 35–39 40–44 45–49 50–54 55–59 60–64 65–69 70–74 75–79 80–84 ≥85 Total	 93[85–102]	0 (0) 4[1–25] (1) 15[6–41] (4) 16[6–43] (4) 20[8–47] (5) 50[29–86] (13) 72[45–111] (18) 89[55–142] (17) 114[71–184] (17) 162[108–244] (23) 185[126–272] (26) 353[260–479] (41) 373[256–544] (27) 405[259–636] (19) 84[73–96] (215)	21[7–66] (3) 8[2–32] (2) 25[11–56] (6) 39[20–74] (9) 17[6–44] (4) 82[53–127] (20) 72[44–115] (17) 91[56–146] (17) 93[55–157] (14) 113[70–182] (17) 145[96–218] (23) 294[219–395] (44) 384[287–514] (45) 473[354–631] (46) 103[91–116] (267)
Severinsen[21] Denmark	1993-1997	50-64	65[58–72] (358)	87[76–99]	44[37–53]
Nordstrom[22] Sweden	1987	< 20 20-29 30-39 40-49 50-59 60-69 70-79 > 80 Total	 	0(0) 6(1) 25(4) 69(10) 285(36) 327(43) 564(52) 765(24) 155(170)	5(1) 11(2) 26(4) 97(14) 103(14) 217(35) 429(61) 822(65) 162(196)
Huerta[23] UK	1994-2000	20-79	40.3		
Apenteng[24] UK	2013-2014	All ages mean 85.1	590[190 -1380] (5)		
Oger[25] France	1998-1999	0-19 20-39	124[112 -136] (407)	2 (1) 33 (18)	2 (1) 42 (22)

		40-59 60-74 ≥75 Total		3 (39) 388 (70) 660 (47) 105[90-122] (175)	76 (29) 319 (76) 703 (104) 132[116-150] (232)

TABLE 2. Pulmonary Embolism: *with DVT; ** without DVT; ***With or without DVT

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
GLOBAL - NONE					
AFRICA - NONE					
AMERICAs					
Stein[7] USA National data***	1979-2001	0-1 2-14 15-17 All	2.2 0.4 2.0 0.9		
Cushman[8] USA National***	1987-1997	≥45	45		
Stein[9] USA National**	1990-1999	All ages - White	36		
		All ages African American	40		
		All ages – Asian & Pacific Islander	7		
Kniffen[10] USA National**	1986-1989	65-74 70-79 ≥65 ≥80	148 196 190 267	165 216 200 283	136 182 184 260
Wiener[26] USA National**	1993-1998	≥18	58.8 to 62.3		
	1998-2006	≥18	62.3 to 112.3		
Silverstein[11] USA Minnesota***	1966-1990	0-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 ≥85		0.3 (1) 4 (4) 16 (12) 7 (7) 18 (17) 16 (12) 44 (29) 51 (29) 66 (32) 99 (42) 171 (59) 254 (70) 489 (101) 404 (60) 826 (75) 758 (47)	0 (0) 8 (8) 10 (11) 21 (23) 29 (28) 40 (31) 37 (25) 45 (26) 73 (37) 59 (27) 107 (43) 154 (55) 202 (64) 337 (88) 497 (94) 690 (123)

		Total	69[65-73] (1280)	82[76-89] (597)	60[55-64] (683)
	1986-1990	0-14		0 (0)	0 (0)
		15-19		6 (1)	0 (0)
		20-24		12 (2)	5 (1)
		25-29		4 (1)	19 (5)
		30-34		16 (4)	0 (0)
		35-39		10 (2)	5 (1)
		40-44		42 (7)	11 (2)
		45-49		35 (5)	20 (3)
		50-54		51 (6)	58 (7)
		55-59		79 (8)	41 (4)
		60-64		50 (4)	90 (8)
		65-69		177 (12)	86 (7)
		70-74		363 (18)	154 (11)
		75-79		139 (5)	241 (15)
		80-84		656 (14)	546 (27)
		≥85		663 (11)	433 (23)
		Total	47[40-53] (214)	56[45-67] (100)	40[32-48] (114)
Anderson[12] Massachusetts**	1985-1986	0-9	0	0	0
		10-19	2	2	2
		20-29	6	4	8
		30-39	7	7	7
		40-49	12	24	0
		50-59	19	27	11
		60-69	73	86	62
		70-79	84	108	69
		≥80	159	206	140
		Overall	23[19-27] (131)	25[19-31]	21[17-27]
DeMonaco[27] USA Pennsylvania**	1997	all ages	47 (5775)	42 (2447)	53 (3328)
	1998	all ages	508 (6143)	46 (2639)	56 (3504)
	1999	all ages	52 (6415)	47 (2687)	60 (3728)
	2000	all ages	57 (6987)	49 (2938)	64 (4049)
	2001	all ages	63 (7699)	53 (3153)	71 (4546)
Tagalakis[14] Canada**	2000-2009	0-19	2[1-2] (264)		
		20-29	13[12-14] (1233)		
		30-39	19[18-20] (1969)		
		40-49	27[27-28] (3413)		
		50-59	49[48-50] (5185)		
		60-69	93[90-95] (6520)		
		70-79	170[166-174] (7981)		
		≥80	275[269-282] (6882)		
		Total	45[45-46] (33,447)		
Vazquez[16] Argentina **	2006-2012	≥17	22[20 –25] (440)		

ASIA					
Jang[17] Korea **	2004	0–9		0.00	0.00
		10–19		0.23	0.06
		20–29		1.24	0.89
		30–39		2.02	0.82
		40–49		2.06	1.84
		50–59		2.86	4.10
		60–69		10.36	15.07
		70–79		21.64	30.15
		≥ 80		35.72	29.68
		Total	3.74	3.01	4.47
	2005	0–9		0.00	0.00
		10–19		0.17	0.13
		20–29		1.03	0.64
		30–39		2.01	0.99
		40–49		2.50	1.53
		50–59		3.60	4.79
		60–69		10.76	16.79
		70–79		22.27	36.38
		≥ 80		39.52	33.04
		Total	4.11	3.21	5.03
	2006	0–9		0.00	0.00
		10–19		0.28	0.19
		20–29		1.50	0.87
		30–39		2.12	1.64
		40–49		3.06	2.48
		50–59		3.76	3.59
		60–69		11.95	15.90
		70–79		28.04	41.10
		≥ 80		49.76	45.91
		Total	4.71	3.79	5.65
	2007	0–9		0.07	0.00
		10–19		0.33	0.12
		20–29		1.24	0.89
		30–39		2.36	1.63
		40–49		3.01	2.61
		50–59		5.24	4.74
		60–69		15.74	18.78
		70–79		35.89	53.16
		≥ 80		67.24	56.43
		Total	5.73	4.63	6.87
	2008	0–9		0.00	0.00
		10–19		0.22	0.22
		20–29		2.54	1.01
		30–39		3.26	1.50
		40–49		3.32	3.40

		50–59 60–69 70–79 ≥ 80 Total	 7.01	7.10 17.41 47.50 64.58 5.71	5.58 22.20 65.37 71.92 8.34
Molina[28] Singapore	2006	0-14 15-24 25-34 35-44 45-54 55-64 65-74 75-84 85+ All Ages	0 (0) 3 (5) 8 (18) 10 (26) 11 (27) 30 (42) 57 (46) 124 (47) 125 (13)	 15 (108)	 15 (116)
Cheuk[18] China**	2000-2001	0-4 5-14 15-44 45-64 ≥65 Total	0.0 0.1 1.4 2.5 18.6 3.9	0.0 0.1 1.6 2.4 14.5 3.4	0.0 0.0 1.3 2·7 22·6 4.3
AUSTRALIA/OCEANIA					
Ho[19] Australia***	2003-2004	Total		31[19–43] (25)	31[19–43] (26)
EUROPE					
Naess[20] Norway**	1995-2001	20–24 25–29 30–34 35–39 40–44 45–49 50–54 55–59 60–64 65–69 70–74 75–79 80–84 ≥85 Total	 50[44–56]	13[3–53] (2) 0 (0) 4[1–27] (1) 12[4–37] (3) 24[11–52] (6) 15[6–41] (4) 16[6–42] (4) 36[17–76] (7) 74[41–133] (11) 85[48–149] (12) 157[103–238] (22) 146[91–235] (17) 249[157–394] (18) 149[71–313] (7) 44[37–53] (114)	14[4–57] (2) 16[6–43] (4) 21[9–50] (5) 13[4–40] (3) 21[9–50] (5) 0 (0) 46[26–84] (11) 37[18–78] (7) 40[18–89] (6) 100[60–166] (15) 69[38–125] (11) 167[113–247] (25) 205[137–305] (24) 267[182–393] (26) 55[0.47–0.65] (144)
Severinsen[21] Denmark***	1993-1997	50-64	51[45–57] (283)	54[45–64]	48[41–57]
Huerta[23] UK ***	1994-2000	20-79	34.2		
Aperteng[24] UK**	2013-2014	all ages (mean age 85.1)	120[3-660] (1)		

Oger[25] France**	1998-1999	0-19 20-39 40-59 60-74 ≥75 Total	60[52 -69]	. (0) 7(4) 48(18) 144(26) 421(30) 47[37-59] (78)	. (0) 15 (8) 29 (11) 134 (32) 500 (74) 71[59-85] (125)
Kroger[29] Germany**	2005	<10 10–29 30–49 50–69 70–90 >90		0 5 28 119 342 369	0 11 26 96 363 419
	2006	<10 10–29 30–49 50–69 70–90 >90		0 6 29 124 347 303	0 11 27 96 361 402
	2007	<10 10–29 30–49 50–69 70–90 >90		1 6 30 124 345 356	1 11 28 94 372 408
MIDDLE EAST-NONE					

TABLE 3. Venous Thromboembolism (not broken down by DVT/PE or other. Only put in this table studies that reported just on VTE without DVT or PE)

Country [citation]	Study years	Population (Age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA - NONE					
AMERICAs					
White[30] USA California	1996	≥ 18	90[88.8-91.2]	85[84-87]	93[92-95]
Gomes[31] USA Kansas	1997-1998	median age, 85 years	1300[1100 -1510] (155)		
Sabapathy[32] Canada	1994-2004	1-5 6-10 11-14 15-17 1- 17	0.4[0.3-0.5] (69) 0.3[0.2-0.4] (50) 0.6[0.5-0.7] (96) 1.6[1.4-1.8] (272) 2.9[2.6-3.1] (487)	2.1[1.8-2.4] (182)	3.7[3.3-4.1] (305)
ASIA					
Lee[33] Taiwan	2001-2002	> 18	15.9 (5347)	14.4 (2463)	17.4 (2884)
Molina[28] Singapore	2006	0-14 15-24 25-34 35-44 45-54 55-64 65-74 75-84 85+ Total	1 (3) 7 (13) 27 (62) 32 (86) 47 (118) 86 (124) 226 (184) 475 (181) 842 (88)	51 (387)	62 (473)
Liu[34] China-Hong Kong	1997-2000	21-100	16.6 (376)		
AUSTRALIA/OCEANIA NONE					
EUROPE					
Holst[35] Denmark	1976-2007	≥20	269[252-286] (969)		
Kevane[36] Ireland	2016-2017	<18 18–25 26–45 46–65 66–85 >85	[0-1] (4) 74[51-96] (76) 187[167-208] (599) 421[383-459] (853) 1050[964-1137] (1026) 1603[1281-1926] (171)		

Martinez[37] UK Black font indicates rates for first VTE episode Red font are rates in incidence/100 person years for recurrent VTE episode among those with a first VTE episode. **rates for ethnic sugroups age-standardized	2001-2011	<18 18-29 30-39 40-49 50-59 60-69 70-79 80-89 ≥90 All ages Recurrent VTE (M&F) <18 18-29 30-39 40-49 50-59 60-69 70-79 80-89 ≥90 All age White Black Asian	1.7[1.4-2.1](90) 32.6[30.8-34.4](1266) 53.8[51.5-56.1](2064) 62.1[59.7-64.6](2543) 99.6[96.3-102.9](3569) 176.9[172-181.8](5084) 327.7[319.8-335.7](6606) 543.3[529.5-557.1](5980) 714.2[679.4-750.3](1579) 107[105.8–108.2](28781) Recurrent VTE (M&F) 5.2[3.0-8.4](16) 6.7[5.9-7.6](250) 5.6[5-6.2](361) 4.8[4.4-5.3](393) 4.3[4-4.7](525) 4.6[4.3-4.9](729) 4.5[4.2-4.9](783) 5.2[4.7-5.6](530) 6.2[5-7.7](84) 4.9[4.7-5](3671) 190.8** 203.0** 121.7**	1.4[1.0-1.9](37) 22.3[20.2-24.5](438) 45.6[42.7-48.7](887) 65.6[62.1-69.1](1365) 112[107.2-117](2026) 192.2[185-199.5](2734) 322.1[310.6-333.9](2964) 483.4[462.4-505.2](1989) 581.2[520.2-647.4](330) 95.9[94.3–97.6](12770) Recurrent DVT (M&F) 3.2[1.5-5.9](10) 4.8[4.1-5.6](180) 4.1[3.6-4.6](268) 3.1[2.8-3.6](256) 2.5[2.3-2.8](306) 2.5[2.3-2.7](396) 2.4[2.2-2.6](414) 2.5[2.2-2.8](252) 3.0[2.2-4.1](41) 2.8[2.7-2.9](2123)	2.1[1.5-2.7](53) 43.2[40.2-46.2](828) 62.1[58.6-65.8](1177) 58.6[55.3-62](1178) 86.9[82.6-91.3](1543) 161.9[155.4-168.6](2350) 332.4[321.7-343.4](3642) 578.8[561-597](3991) 760.2[718.6-1197](1249) 117.9[116–119.7](16011) Recurrent PE (M&F) 1.9[0.7-4.2](6) 1.9[1.5-2.4](70) 1.4[1.2-1.8](93) 1.7[1.4-2.0](137) 1.8[1.6-2.1](219) 2.1[1.9-2.3](333) 2.1[1.9-2.4](369) 2.7[2.4-3.0](278) 3.2[2.3-4.3](43) 2.0[1.9-2.2](1548)
Guijarro[38] Spain	2001	All	30.6		
Pulanic[39] Croatia	2011	13-97	118.5 (663)		
Netherlands[40] PHARMO Database Network	2017	All	Inpatient: 46.83 [45.45-48.27] GP and inpatient: 237.93 [223.93-252.59]		
Denmark[40] Danish Registries (DCE-AU) in and outpatient	2010	All	181.90 [178.40-185.47]		
Spain[40] BIFAP	2017	All	GP based: 216.28 [213.32-219.27] GP and inpatient: 267.34 [262.43-272.32]		
Spain[40] SIDIAP	2017	All	GP based: 216.28 [213.3-219.27] GP and inpatient: 267.34 [262.43-272.32]		
Spain[40] FISABIO	2017	All	201.01[197.22-204.87]		

in and outpatient					
Italy[40] ARS database Inpatient only and Emergency room	2017	All	226.66[220.16-233.30]		
United Kingdom[40] CPRD & HES	2017	All	174.70 [170.42-179.06]		
MIDDLE EAST-NONE					

TABLE 4. Cerebral Venous Thrombosis

Country [reference]	Study years	Population (Age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA	NONE				
AMERICAs	NONE				
ASIA	NONE				
AUSTRALIA/OCEANIA	NONE				
EUROPE					
Coutinho[41] Netherlands	2008-2010	18–30 31–50 ≥51 Overall	1.64[1.05–2.44] 1.71[1.26–2.27] 0.77[0.48–1.16] 1.32[1.06–1.61] (94)	0.75[0.49–1.09]	1.86[1.44–2.36]
Heller[42] Germany	1995-2002	Neonates (< 28days) From 28 days to 18 years	2.6 (40) 0.35 (109)		
Netherlands[40] PHARMO Database Network	2017	All ages	Inpatient: 0.79 [0.62-1.00] GP and inpatient: 0.88 [0.24-2.26]		
Denmark[40] Danish Registries (DCE-AU) in and outpatient	2010	All ages	0.97 [0.74-1.27]		
Spain[40] BIFAP	2017	All ages	GP based: 0.32 [0.21- 0.45] GP and inpatient: 0.47 [0.29-0.73]		
Spain[40] SIDIAP	2017	All ages	GP based: 0.14 [0.06- 0.28] GP and inpatient: 0.59 [0.27-1.13]		
Spain[40] FISABIO in and outpatient	2017	All ages	1.15 [0.88-1.47]		
Italy[40] ARS database Inpatient only and Emergency room	2017	All ages	1.33 [0.87-1.93]		
Italy[40] PEDIANET database GP based	2018	0-14	1.26[0.03-7.0]		
United Kingdom[40] CPRD & HES	2017	All ages	0.14[0.04-0.32]		
MIDDLE EAST	NONE				

TABLE 5. Cerebral Venous Sinus Thrombosis

Country [reference]	Study years	Population (Age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA	NONE				
AMERICAs					
Humphreys[43] Canada	1992-1997	0-18	0.67[0.55-0.76] (160)		
ASIA	NONE				
AUSTRALIA/OCEANIA					
Devasagayam[44] Australia	2005-2011	19–84	1.57[1.29–1.90] (105)		
EUROPE					
Berfelo[45] Netherlands	2000 2001 2002 2003 2004 2005 2006 2007	Neonates	1.4[0.04–8.01] (1) 5.8[1.58–14.86] (4) 2.9[0.35–10.51] (2) 5.6[1.54–14.43] (4) 1.5[0.04–8.15] (1) 5.9[1.62–15.25] (4) 2.9[0.36–10.80] (2) 12[5.20–23.73] (8)		
Netherlands[40] PHARMO Database Network	2017	All ages	Inpatient: 0.79 [0.62-1.00] GP and inpatient: 0.88 [0.24-2.26]		
MIDDLE EAST					
Ghiasian[46] Iran	2009-2015	15-66	1.349 (151)		

TABLE 6. Stroke: Ischemic or Occlusive

Country reference	Study years	Population (Age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA	NONE				
AMERICAs					
Kleindorfer[47] USA Ohio/Kentucky	1993–1994	All ages	163[155–171]		
	1999	All ages	186[177–194]		
Corbin[48] Barbados	2001	<15 15–24 25–34 35–44 45–54 55–64 65–74 75–84 >85 Total	0 (0) 0[0–8] (1) 5[0–13] (2) 25[1–41] (10) 73[42–105] (21) 190[125–255] (33) 518[403–633] (78) 888[698–1078] (83) 1767[1324–2210] (60) 120[107–134] (288)		
ASIA	NONE				
AUSTRALIA/ OCEANIA					
Jamrozik[49] Australia	1989-1990	All ages	72	97	51
	1995-1996	All ages	58	77	41
Islam[50] Australia	1989-1990	All ages	86[74–100]	118[96–144]	62[49–79]
	1995-1996	All ages	71[61–83]	93[75–115]	52[41–66]
	2000-2001	All ages	54[46–65]	63[50–80]	48[38–62]
Feigin[51] New Zealand	2002-2003	15–64 65–74 75–84 ≥ 85 Total Standardized	34[30–38] (268) 444[394-501] (264) 904[814–1006] (342) 1263[1081–1477] (158) 102[96–108] (1032)	40[34–47] (152) 568[486–663] (160) 1013[865-1186] (154) 1156[854-1564] (42) 118[109–129] (508)	28[24–34] (116) 333[274–403] (104) 832[721–959] (188) 1307[1090-1568] (116) 87[80–95] (524)

EUROPE					
Vangen-Lonne[52] Norway	1977–1980	30–49		11[3–44] (2)	0
	1981–1985	30–49		36[19–67] (10)	0
	1986–1990	30–49 50–64		16[6–37] (5) 55[18–171] (3)	9[3–29] (3)
	1991–1995	30–49 50–64 65–74 75–84 ≥ 85		22[10–46] (7) 204[143–290] (31) 1479[932–2347] (18) 1460[656–3249] (6) 3595[899–14373] (2)	18[8–40] (6) 196[111–345] (12) 381[158–915] (5) 1305[679–2508] (9) 1939[485–7753] (2)
	1996–2000	30–49 50–64 65–74 75–84 ≥ 85		43[26–71] (15) 234[175–314] (45) 919[714–1184] (60) 1539[1149–2061] (45) 2765[1570–4869] (12)	16[7–36] (6) 112[73–172] (21) 491[356–678] (37) 1236[955–1598](58) 1355[802–2287](14)
	2001–2005	30–49 50–64 65–74 75–84 ≥ 85		35[18–66] (9) 331[263–415] (74) 867[670–1122] (58) 2036[1613–2569] (71) 3605[2374–5475] (22)	24[11–51] (7) 96[62–147] (21) 449[319–632] (33) 1350[1070-1699](73) 2599[1941-3482](45)
	2006–2010	30–49 50–64 65–74 75–84 ≥ 85		67[38–118] (12) 222[169–290] (53) 657[503–858] (54) 1754[1380–2228] (67) 2555[1682–3881] (22)	19[7–52] (4) 93[62–139] (23) 309[212–450] (27) 1074[834–1384](60) 2119[1582–2838] (45)
Rosengren[53] Sweden	1987–1992	18–44 45–54 55–64 65–74 75–84	7.17 (1402) 51.3 (3182) 188 (9620) 606 (30414) 1568 (50063)		
	1993–1998	18–44 45–54 55–64 65–74 75–84	8.13 (1565) 64.1 (4774) 221 (11511) 689 (32979) 1705 (57516)		
	1999–2004	18–44 45–54 55–64 65–74 75–84	8.26 (1565) 63.7 (4629) 208 (13353) 614 (27459) 1523 (53312)		
	2005–2010	18–44 45–54 55–64 65–74	9.55 (1864) 61.4 (4350) 189 (13696) 503 (24867)		

		75–84	1278 (42960)		
Kristensen[54] Sweden	1991-1994	18-24 25-34 35-44 18-44	2.5[0-6.9] 5.6[0.2-11.0] 22.9[12.0-33.8] 11.3[6.7-16.1]	2.9[0-9.4] (3) 6.0[0-13.8] (9) 28.2[16.2-40.4] (4) 13.6[6.4-20.8] (5)	2.1[0-8.8] (2) 5.2[0-13.4] (7) 17.0[3.5-30.5] (24) 8.9[2.8-15.0] (33)
Bejot[55] France	1985–1993	<55	8.1[6.5-10.1] (82)		
	1994–2002	<55	10.7[8.8 -12.8] (110)		
	2003–2011	<55	18.1[15.6-20.9] (183)		
Rasura[56] Italy	1992-2001	14–24 25–47 Total	2.0[1.6–2.5] (38) 14.0[11.6–16.4] (356) 8.8[7.7–9.9] (394)	1.9[1–2.7] (19) 13.4[11–15.9] (169)	2.2[1.2–3.2] (19) 14.6[12.1–17] (187)
Alzamora[57] Spain	2003	< 45 45–49 50–54 55–59 60–64 65–69 70–74 75–79 80–84 ≥ 85 Total crude Total Standardized (Europe)	4[0–9] (3) 59[1–116] (4) 135[55–215] (11) 105[37–174] (9) 271[146–396] (18) 276[145–407] (17) 788[532–1040] (36) 1110[787–1520] (38) 1340[897–1910] (29) 1610[1090-2280] (31) 169[145–192] (196) 172[148–196]	8[0–18] (3) 60[6–214] (2) 210[92–409] (8) 191[59–323] (8) 406[226–677] (14) 293[128–555] (9) 1080[690–1620] (23) 1300[775–2060] (18) 1550[800–2690] (12) 1840[885–3360] (10) 184[149–219] (107) 219[176–261]	(0) 57[6–201] (2) 69[0–147] (3) 23[0–68] (1) 125[31–323] (4) 260[116–507] (8) 533[287–909] (13) 982[604–1510] (20) 1220[714–1950](17) 1520[946–2310](21) 153[121–185] (89) 133[105–160]
Vaartjes[58] Netherlands	1997	35–64 65–74 75–84 85–94		65 410 917 1659	39.9 277 757 1743
	1998	35–64 65–74 75–84 85–94		67 425 958 1788	40.1 277 785 1736
	1999	35–64 65–74 75–84 85–94		67 416 920 1764	42.7 271 788 1708
	2000	35–64 65–74 75–84 85–94		64 395 898 1637	41.2 267 764 1747
	2001	35–64		65	41.7

		65–74 75–84 85–94		409 910 1763	259 805 1897
	2002	35–64 65–74 75–84 85–94		70 428 941 1785	49.4 263 833 1961
	2003	35–64 65–74 75–84 85–94		73 416 940 1845	48.0 273 819 1948
	2004	35–64 65–74 75–84 85–94		74 429 956 1797	48.4 265 815 1902
	2005	35–64 65–74 75–84 85–94		78 401 936 1831	53.2 257 774 1834
Tsiskaridze[65] Georgia	2000 – 2003	0–44 45–54 55–64 65–74 75–84 ≥85 All ages	3[0.7–10] (3) 21[4–62] (3) 218[154–301] (37) 387[288–509] (51) 627[417–905] (28) 343[71–999] (3) 89[74–106] (125)	5[0.5–16] (2) 32[4–115] (2) 164[85–286] (12) 340[208–525] (20) 568[245–1116] (8) 373[9–2061] (1) 69[50–92] (45)	2[0.05–11] (1) 13[0.3–71] (1) 260[168–383] (25) 424[288–601] (31) 654[400–1008] (20) 339[41–1215] (2) 106[84–132] (80)
Netherlands[40] PHARMO Database Network	2017	All ages	Inpatient: 76.74 [74.94-78.58] GP and inpatient: 269.56 [254.64- 285.12]		
Denmark[40] Danish Registries (DCE-AU) in and outpatient	2010	All ages	168.39 [165.02-171.83]		
Spain[40] BIFAP	2017	All ages	GP based: 123.09 [120.86- 125.35] GP and inpatient: 195.30 [191.11- 199.56]		
Spain[40] SIDIAP	2017	All ages	GP based: 161.09 [157.80- 164.43] GP and inpatient: 201.30 [194.22- 208.58]		
Spain[40] FISABIO in and outpatient	2017	All ages	308.15 [303.43- 312.93]		
Italy[40]	2017	All ages			

ARS database Inpatient only and Emergency room			263.60 [256.59- 270.76]		
United Kingdom[40] CPRD & HES	2017	All ages	132.19 [128.47- 135.98]		
MIDDLE EAST	NONE				

TABLE 7. All stroke

Country reference	Study years	Population (Age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA	NONE				
AMERICAs					
Jacobs[60] USA NewYork	1993-1997	20-44		25	21
Kleindorfer[47] USA Ohio/ Kentucky	1993–1994	all	182[174–190]		
	1999	all	206[198–216]		
Kissela[61] USA Ohio	1993-1994 Black	20–44 45–54 20–54 55–64 65–74 75–84 85+	46[31–62] 236[165–308] 83[64–101] 414[307–521] 961[778–1145] 1344[1042–1645] 1910[1276–2543]		
	1993-1994 white	20–44 45–54 20–54 55–64 65–74 75–84 85+	12[9–15] 76[61–91] 26[22–31] 237[206–269] 536[485–587] 1063[971–1156] 1685[1485–1885]		
	1999 Black	20–44 45–54 20–54 55–64 65–74 75–84 85+	48[33–64] 293[223–362] 105[85–125] 483[369–598] 777[609–945] 920[678–1162] 1831[1262–2400]		
	1999 white	20–44 45–54 20–54 55–64 65–74	18[14–22] 82[68–97] 35[[30–40] 217[188–247] 541[489–594]		

		75–84 85+	1071[981–1161] 1763[1569–1957]		
	2005 Black	20–44 45–54 20–54 55–64 65–74 75–84 85+	58[40–75] 305[242–369] 128[106–149] 524[414–635] 837[660–1014] 959[725–1193] 1029[641–1417]		
	2005 white	20–44 45–54 20–54 55–64 65–74 75–84 85+	26[20–31] 96[81–111] 48[42–53] 209[183–235] 463[412–513] 780[706–855] 1297[1142–1452]		
Cabrai[62] Brazil	2005–2006	<75 ≥75 All Adjusted to Brazilian population All Adjusted to world Segi's population.	50.3[46.0–54.9] 36.4[32.1–41.2] 86.6[80.5–93.0] 105.4[98.0–113.2]		
ASIA	NONE				
AUSTRALIA/ OCEANIA					
Jamrozik[49] Australia	1989-1990	All ages	104	137	78
	1995-1996	All ages	76	96	59
Islam[50] Australia	1989-1990	All ages	126[111–143]	165[140–196]	96[79–116]
	1995-1996	All ages	92 [80–106]	116[96–141]	74
	2000-2001	All ages	74[63–86]	85[69–105]	65[52–81]
Thrift[63] Australia	1996–1997	0–14 15–24 25–34 35–44 45–54 55–64 65–74 75–84 ≥85 Total	0(0) 5[0–16] (1) 30[8–52] (7) 44[15–73] (9) 105[54–156] (16) 213[133–293] (27) 535[403–666] (63) 1290[1027–1554] (91) 2900[2189–3611] (62) 206[182–231] (276)		

		Total Standardized rate	100[80–119]		
EUROPE					
Stewart[64] UK	1995-1996	<15 15-24 25-34 35-44 45-54 55-64 65-74 75-84 >84 total/crude standardized to word standardized to European	1[0-6] (1) 4[1-13] (3) 13[8-22] (15) 28[16-46] (16) 87[61-121] (36) 221[178-272] (91) 516[443-598] (177) 891[764-1032] (177) 1892[1533-2311] (96) 131[120-141] (612) 82[75-89] 125[115-135]	2[0-12] (1) 3[0-17] (1) 19[9-34] (10) 32[15-60] (9) 98[60-152] (20) 308[237-394] (63) 599[485-732] (95) 879[683-1115] (68) 1913[1199-2896](22) 128[114-144] (289) 96[84-107] 143[126-160]	0[0-13] (0) 5[0-19] (2) 9[3-20] (5) 34[10-51] (7) 78[43-123] (16) 136[90-196] (28) 445[354-552] (82) 898[737-1083] (109) 1887[14822369](74) 133[118-148] (323) 70[61-78] 108[96-120]
Syme[65] Scotland	1998–2000	0–14 15–24 25–34 35–44 45–54 55–64 65–74 75–84 ≥85 Total Total Standardized rates	0[0–10] (0) 0[0–17] (0) 18[6–43] (5) 31[15–58] (10) 131[94–179] (40) 255[196–326] (64) 659[554–777] (140) 1587[1385–1812](220) 2400[1985–2878](117) 280[258–304] (596) 110[90–133]		
Bejot[55] France	1985–1993	<55 55–64 65–74 75–84 85+ Total	11.6[9.6 -13.9] (117) 115[97 -137] (135) 299[265-335] (288) 711[651-776] (508) 1025[903-1159] (254) 76.6[72.1-81.0]		
	1994–2002	<55 55–64 65–74 75–84 85+ Total	12.7[10.6 -15.1] (131) 147[125 -172] (159) 328[293 -366] (322) 674[616 -735] (496) 1059[951-1175] (354) 80.7[76.2 - 85.2]		
	2003–2011	<55 55–64 65–74 75–84 85+	20.2[17.6 -23.2] (205) 130[112 -150] (179) 341[304 -381] (308) 745[687 – 806] (622) 1130[1026 -1242](428)		

		Total	88.5[83.9 - 93.1]		
Marini[66] Italy	1994-1998	0–14 15–24 25–34 35–44 Total	1.24[0.26–3.62] (3) 2.87[1.05–6.25] (6) 8.21[4.87–12.97] (18) 30.40[22.27-38.85](62) 10.18[8.14–12.57] (89)	2.42[0.50–7.08] (3) 3.78[1.03–9.68] (4) 9.09[4.36–16.72] (10) 36.59[25.75-50.48] (38)	. 1.94[0.23–6.99] (2) 7.32[3.15–14.41] (8) 23.98[14.82–36.71] (24)
Corso[67] Italy	2004–2005	0–14 15–24 25–34 35–44 45–54 55–64 65–74 75–84 >85 All ages	3[0–11] (1) 14[0–36] (3) 14[0–31] (5) 40[13–66] (17) 58[22–95] (20) 166[102–230] (52) 462[346–577] (122) 1112[896–1328] (201) 2420[1843–2997](132) 223[197–249] (553)	6[0–23] (1) 9[0–34] (1) 11[0–32] (2) 55[11–98] (12) 74[17–132] (13) 239[131–346] (38) 632[433–831] (77) 1326[941–1712] (90) 2611[1452–3770(38) 224[186–261] (272)	(0) 19[0–57] (2) 17[0–44] (3) 24[0–54] (5) 42[0–85] (7) 91[23–158] (14) 316[185–446] (45) 983[726–1240](111) 2350[1686-3013] (94) 223[186–260](281)
MIDDLE EAST	NONE				

TABLE 8. Cerebral infarction

Country reference	Study years		Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA	NONE				
AMERICAs					
Brown[68] USA Minnesota	1950-1959	all ages	181 (511)		
	1960-1969	all ages	130 (513)		
	1970-1979	all ages	105 (553)		
	1980-1989	all ages	120 (821)		
Lavados[69] Chile	2000	0–24 25–34 35–44 45–54 55–64 65–74 75–84 ≥85 Total* Total**	1.7[0.3–4.9] (3) 3.0[0.4–10.9] (2) 11.2[4.5–23.1] (7) 46.3[28.3–71.5] (20) 198.5[145.8–263.9] (47) 361.3[268.2–476.4](50) 659.7[475.5–879.8] (42) 762.5[416.9-1279.4](14) 46.6[39.8–53.3] (185) 59.6[51.0–68.2]	2.2[0.2–7.8] (2) 2.9[0.07–16.3] (1) 12.7[3.5–33] (4) 54.1[28–94.5] (12) 271[185–382] (32) 418[273–612] (26) 861.4[533–1317](21) 1000[324–2334] (5) 51.4[46.3–56.5](103) 63.0[50.8–75.1	1.2[0.03–6.4] (1) 3.1[0.08–17.8] (1) 9.7[2–28.4] (3) 38.1[14.4–75.1] (8) 126.5[70.7–208.6](15) 315.0[201.8-468.7](24) 534.6[330.9-817.2](21) 792.3[362.3–503.9](9) 41.8[33.3–51.9] (82) 52.0[40.7–63.2]
ASIA					
Tanaka[70] Japan	1976-1978	20-29 30-39 40-49 50-59 60-69 70-70 ≥ 80 Total	0 (0) 0 (0) 0.11 (4) 0.73 (19) 3.80 (74) 7.58 (83) 18.59 (60) 1.51 (240)	0 (0) 0 (0) 0.24 (4) 1.35 (16) 6.25 (54) 11.57 (53) 22.28 (25) 2.02 (152)	0 (0) 0 (0) 0 (0) 0.21 (3) 1.84 (20) 4.71 (30) 16.62 (35) 1.05 (88)
AUSTRALIA/OCEANIA					
Anderson[71] Australia	1989-1990	0-54 55-64 65-74 75-84 85+ Total* Total**	12[5-19] (19) 171[103-239] (36) 494[353-635] (71) 1043[787-1299] (96) 1499[908-2090] (37) 124[105-143] (259) 72[55-89]		
Thrift[63] Australia	1996-1997	0–14 15–24 25–34 35–44	0 (0) 0 (0) 13[0–27] (3) 25[3–46] (5)		

		45–54 55–64 65–74 75–84 ≥85 Total* Total**	79[34–123] (12) 165[95–236] (21) 390[278–503] (46) 992[761–1224] (70) 2011[1416–2606] (43) 149[129–170] (200) 71[55–88]		
EUROPE					
Ellekjaer[72] Norway	1994-1996	15-44 45-54 55-64 65-74 75-84 ≥85 Total	7[2-16] (5) 22[6-56] (5) 175[113-259] (25) 579[463-718] (86) 1399[1183-1654] (143) 1937[1470-2499] (58) 232[207-260] (322)		
Mettinger[73] Sweden Stockholm	1973-1977	<25 25-34 35-44 45-54 <55	1 (25) 3 (38) 10 (91) 37 (332) 9 (486)		
Bamford[74] UK	1981-1986	<45 45-54 55-65 65-74 75-84 85+ Total	10 (18) 40 (17) 230 (87) 590 (167) 1190 (189) 1500 (67) 130 (545)		
Stewart[64] UK	1995-1996	All	87[76 -96] (423)		
Wolfe[75] UK London	1995-1997	All European-standardized	86.0[79.1–92.9]		
Syme[65] Scotland	1998-2000	0–14 15–24 25–34 35–44 45–54 55–64 65–74 75–84 ≥85 Total Total*	0[0–10] (0) 0[0–17] (0) 11[2–32] (3) 25[11–49] (8) 102[69–144] (31) 147[104–203] (37) 503[413–609] (107) 1198[1022–1394] (166) 1375[1065–1746] (67) 197[179–217] (419) 71[55–90]		
Wolfe[75] France Dijon	1995-1997	All** to Europe	87.3[79.1–92.9]		

Marini[66] Italy	1994-1998	0–14 15–24 25–34 35–44 Total	0.83[0.10–2.98] (2) 0.96[0.12–3.45] (2) 3.65[1.57–7.19] (8) 19.12[13.39–26.49] (39) 5.83[4.38–7.60] (51)		
Nencini[76] Italy	1983-1985	15-34 35-44 Total	0.9[0.2-2.5] 8.2[4.6-13.6] 3.4[2.0-5.4] (18)		
D'Alessandro[77] Italy	1989	0		141 (80) 170	155 (90) 126
D'Alessandro[78] Italy	1997	All ages	238[210-266] (282)	223[185-261] (133)	252[212-292] (151)
Corso[55] Italy	2004–2005	0–14 15–24 25–34 35–44 45–54 55–64 65–74 75–84 >85 Total	3[0–11] (1) 14[0–36] (3) 14[0–31] (5) 40[13–66] (17) 58[22–95] (20) 166[102–230] (52) 462[346–577] (122) 1112[896–1328] (201) 2420[1843–2997](132) 223[197–249] (553)	6[0–23] (1) 9[0–34] (1) 11[0–32] (2) 55[11–98] (12) 74[17–132] (13) 239[131–346] (38) 632[433–831] (77) 1326[941–1712] (90) 2611[1452–3770](38) 224[186–261] (272)	. (0) 19[0–57] (2) 17[0–44] (3) 24[0–54] (5) 42[0–85] (7) 91[23–158] (14) 316[185–446] (45) 983[726–1240](111) 2350[16863013](94) 223[186–260](281)
Lauria[79] Italy	1992-1993	0-34 35-44 45-54 55-64 65-74 75-84 ≥85 Total	0 (0) 14[3-35] (4) 38[18-69] (10) 131[89-184] (32) 462[375-563] (99) 1044[862-1262] (111) 2757[2117-3528] (63) 150[133-168] (319)	0 (0) 20[4-58] (3) 54[21-111] (7) 200[125-302] (22) 631[473-820] (54) 1261[909-1702] (42) 2083[1039-3728](11) 137[115-162] (139)	0 (0) 7[0.1-38] (1) 22[2-79] (3) 74[35-136] (10) 350[255-469] (45) 951[739-1207] (69) 2885[2155-3779] (52) 162[139-187] (180)
DiCarlo[80] Italy	1996	0-44 45–54 55–64 65–74 75–84 ≥85 Total	5[1–9] (6) 48 [17–79] (9) 106[60–153] (20) 437[334–540] (69) 1073[851–1294] (90) 1432[988–1875] (40) 131[114–147] (234)	3[1–8] (2) 51[6–97] (5) 120[49–191] (11) 603[423–783] (43) 1435[1029–1841](48) 1622[801–2442] (15) 140[115–164] (124)	7[1–14] (4) 44[1–87] (4) 93[32–154] (9) 300[185–415] (26) 833[581–1084] (42) 1338[813–1862] (25) 122[99–144] (110)
Kolominsky-Rabas[81] Germany	1994-1996	0–24 25–34 35–44 45–54 55–64 65–74 75–84 ≥ 85 Total	0 (0) 0.03[0.01–0.08] (3) 0.14[0.05–0.32] (4) 0.64[0.40–0.98] (16) 1.47[1.08–1.97] (33) 4.26[3.50–5.14] (78) 9.76[8.14–11.62] (90) 16.81[13.26–21.04](54) 1.37[1.24–1.51] (278)	0 (0) 4[1–13] (2) 7[0–32] (1) 96[56–156] (12) 160[102–240] (17) 531[401–690] (40) 1017[733–1377] (30) 1932[1216–2920](16) 119[102–139] (118)	0 (0) 2[0-10] (1) 22[6-56] (3) 32[11-74] (4) 136[85-206] (16) 353[265–463] (38) 957[764–1185] (60) 1594[1196–2084] (38) 154[134–175] (160)

Wolfe[75] Germany Erlangen	1995-1997	All ** (to Europe)	105.7[95.6–115.9]		
Vemmos[82] Greece	1993-1995	18–34 35–44 45–54 55–64 65–74 75–84 ≥85 Total* Total**	2.4[Not calculated(NC)] (1) 16.6[NC] (2) 58.9[27–91] (13) 157.8[113–203] (47) 423.3[340–508] (97) 1065.1[910–1220](179) 2203.7[1789-2619] (106) 276.7[251–302] (447) 249.2[217–281]	0 (0) 23.1[NC] (3) 95.4[39–152] (11) 186.9[118–256] (28) 501.3[370–632] (56) 1070.7[849–1292](89) 2703.9[2045-3362](63) 298.6[262–336] (250) 288.9[240–338]	5.3[NC] (1) 9.1[NC] (1) 19.0[NC] (2) 128.3[71–186] (19) 349.9[243–457] (41) 1059.6[842–1277] (90) 1733.9[1220–2248] (43) 253.1[218–288] (197) 208.7[167–251]
MIDDLE EAST					

*=crude rates; **=standardized rates

TABLE 9. Other Thrombosis (Abdominal)

Country [reference]	Study years	Thrombosis Site	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
				All	Males	Females
AFRICA -	NONE					
AMERICAs	NONE					
ASIA						
Moran[83] S Korea	2009-2013	Budd-Chiari Syndrome	0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 ≥80 All Ages	0.014 0.021 0.035 0.066 0.076 0.174 0.226 0.160 0.155 0.087	0.084	0.091
AUSTRALIA/OCEANIA - NONE						
EUROPE						
Rajani[84] Sweden	1995-2004	Portal Vein	All ages	0.7 [0.3-1.2]		
Rajani[85] Sweden	1986-2003	Budd-Chiari Syndrome	All ages	0.08 (12)		
Acosta[86] Sweden	2000-2006	Mesenteric Vein	0-49 50-59 60-69 70-79 ≥80 All ages	1.1 [0.6-1.8] (13) 4.5 [2.1-8.2] (10) 4.8 [2.1-9.5] (8) 11.3 [5.8-16.8] (16) 3.7 [1.0-9.4] (4) 2.7 [3.5] (51)	1.4 [0.7-2.7] (9) 6.3 [2.5-13.0] (7) 3.8 [0.8-11.1] (3) 12.0 [4.8-24.6] (7) 2.8 [0.1-15.8] (1) 3.0 [1.9-4.1] (27)	0.7 [0.2-1.7] (4) 2.7 [0.5-7.8] (3) 10.8 [4.9-20.5] (5) 4.0 [0.8-11.8] (9) 4.0 [0.8-11.8] (3) 2.5 [1.4-3.5] (24)
Almdal[87] Denmark	1981-1985	Portal Vein	0-89	0.27 [0.2-0.4] (69)	0.32 [0.2-0.4] (39)	023 [-.2-0.4] (30)
		Budd-Chiari Syndrome		0.05 [0-0.1] (13)	0.07 [0-0.1] (9)	0.03 [0-0.1] (4)
Sogaard[88] Denmark	1994-2013	Portal Vein	1994-2013	21 (1500)		
		Hepatic Vein		3 (204)		
		Mesenteric Vein		3 (211)		
Olivier-Hourmand[89] France	2010	Budd-Chiari Syndrome	≥18	0.068 (178)		
Ageno[90] Italy	2002-2012	Portal Vein Thrombosis	52-73		3.80	1.75
		Budd-Chiari Syndrome	36-68		0.20	0.22
MIDEAST	NONE					

TABLE 10A. Venous Thromboembolism in Pregnancy and Postpartum period. Incidence denominator expressed in deliveries or pregnancies. Case ascertainment method indicated after Country: * indicates diagnostic codes only; ** indicates diagnosis based on appropriate imaging study or confirmed physician diagnosis with appropriate signs and symptoms plus anticoagulation therapy; *** coded diagnosis supplemented by evidence of anticoagulation therapy. The duration of the puerperium is indicated in brackets in the Pregnancy Period column.

Country reference	Study years	Event	Pregnancy Period	Population (age in years)	Incidence rate per 1000 Deliveries [95% confidence interval] (total cases)
AFRICA	NONE				
AMERICAs					
James[91] USA *	2000-2001	VTE	Whole pregnancy and puerperium[a]	<20 20-24 25-29 30-34 35-39 40+ All ages	1.47 [1.33-1.61] (1399) 1.58 [1.50-1.66] (3201) 1.67 [1.59-1.75] (3667) 1.73 [1.63-1.83] (3424) 2.13 [1.97-2.29] (2067) 2.75 [2.36-3.14] (577) 1.72 (14,355)
Liu[92] Canada *	1991-2005	DVT	Antepartum [b]	All Ages	0.39 (1493)
			Peripartum [b]		0.54 (2089)
			Postpartum [b]		0.28 (1095)
			Total		1.21 (4677)
		PE	Antepartum [b]		0.17 (667)
			Peripartum [b]		0.20 (768)
			Postpartum [b]		0.18 (679)
			total		0.54 (2114)
ASIA					
Chan[93] HongKong **	1998-2000	VTE	Whole pregnancy and puerperium (≤42 days after delivery)	34.6 ± 4.4	1.88 [1.18-2.58] (32)
Jang[94] Korea *	2006-2010	VTE	Whole pregnancy and postpartum (Not defined)	15-24 25-29 30-34 35-40 >40 All ages	0.047 [0.17–1.03] 0.071 [0.052–0.094] 0.076 [0.057–0.098] 0.147[0.099–0.210] 0.233[0.076–0.543] 0.082 [0.069–0.096]
AUSTRALIA/OCEANA					
Sharma[95] Australia **	1999-2006	VTE	Whole pregnancy and postpartum (6 weeks after miscarriage, stillbirth or liveborn delivery)	>30	1.14 (8)
Morris[96] Australia *	2001-2006	PE	Postpartum (<7 weeks after delivery)	All ages	0.45 (230)

EUROPE					
Simpson[97] UK *	1988	VTE	Pregnancy and puerperium (Not defined)	All ages	0.73[0.45-1.00] (27)
	1989				1.01 [0.70-1.32](40)
	1990				1.04[0.73-1.35] (43)
	1991				0.89[0.60-1.18] (37)
Note: counted all liveborn infants and stillborns if occurred at or after 24 completed weeks of gestation	1992				0.82[0.54-1.09] (34)
	1993				0.71[0.45-0.96](29)
	1994				0.70[0.44-0.95](29)
	1995				0.60[0.35-0.85] (22)
	1996				0.86[0.56-1.15] (32)
	1997				1.17[0.82-1.52] (43)
	1988-1997				0.85[0.76-0.94] (336)
	1988-1997			<25	0.76[0.58-0.93] (72)
				25-34	0.83[0.71-0.94] (207)
				>35	1.15[0.85-1.45] (57)
	1988-1997		Antenatal	All ages	0.28 (109)
			Postnatal (Not defined)	All ages	0.65 (256)
Macklon[98] Scotland *	1981-1992	DVT	Antenatal	<35	0.615
				≥35	1.216
			Postnatal (Not defined)	<35	0.304
				≥35	0.72
Andersen[99] Denmark	1984-1989	VTE	Pregnancy	≤49	0.31[0.15–0.80]
			puerperium (≤ 2 months after delivery)		0.75[0.47–1.12]
			Pregnancy & Puerperium		0.52[0.36–0.73]
	1990-1994		Pregnancy		0.18[0.07–0.40]
			Puerperium		0.49[0.27–0.80]
			Pregnancy & Puerperium		0.33[0.21–0.51]
	1984-1994		Pregnancy		0.49[0.14–0.79]
			Puerperium		1.23[0.87–1.70]
			Pregnancy & Puerperium		0.85[0.64–1.11]

Galambosi[100]				0-6		0.670 (425)
Finland * Note: The Medical Birth Register contains information on all live births and stillbirths with gestational age of ≥22 weeks or with a birthweight of ≥500 g from all delivery units in Finland	2001-2011	VTE	Days postpartum	7-13	15-49	0.046 (29)
				14-20		0.069 (44)
				21-27		0.058 (37)
				28-34		0.058 (33)
				35-41		0.052 (36)
				42-48		0.057 (20)
				49-55		0.032 (36)
				56-62		0.057 (35)
				63-69		0.055 (32)
				70-76		0.054 (26)
				77-83		0.050 (32)
				84-90		0.041 (26)
				91-97		0.039 (25)
				98-104		0.049 (31)
				105-111		0.046 (29)
				112-118		0.054 (34)
				119—125		0.038 (24)
				126-132		0.036 (23)
				133-139		0.028 (18)
				140-146		0.049 (31)
				147-153		0.047 (30)
				154-160		0.043 (27)
				161-167		0.046 (29)
				168-174		0.047 (30)
				175-180		0.022 (14)
				0-180		1.84 (1169)

				13-24	0.45[0.43-0.49]
			Antenatal	25-29	0.45[0.42-0.48]
				30-34	0.49[0.45-0.51]
				35-54	0.66[0.63-0.69]
				All ages	0.49[0.46-0.52]
			Postnatal (Not defined)	13-24	0.56[0.53-0.59]
				25-29	0.48[0.45-0.51]
		VTE		30-34	0.45[0.41-0.47]
				35-54	0.66[0.63-0.69]
				All ages	0.51[0.48-0.54]
Jacobsen[101] Norway **	1990-2003		Antenatal & Postnatal	13-24	1.01[1.004-1.016]
				25-29	0.93[0.91-0.94]
				30-34	0.94[0.93-0.95]
				35-54	1.31[1.28-1.36]
				All ages	1.003[1.000-1.006]
		PE	Antenatal	All ages	0.06[0.045-0.075]
			Postnatal	All ages	0.22[0.19-0.25]
			Antenatal & Postnatal	All ages	0.27[0.24-0.30]
		DVT	Antenatal	All ages	0.43[0.40-0.46]
			Postnatal	All ages	0.30[0.27-0.33]
			Antenatal & Postnatal	All ages	0.73[0.70-0.77]
Lindqvist[102] Sweden *	1990-1993	DVT or PE	Pregnancy (from 240 days before delivery through 6 weeks postpartum)	All ages	1.3
Lindqvist[103] Sweden **	1990-2005	DVT or PE	Postpartum only (defined as first 6 weeks post-delivery)	All ages	0.71
MIDEAST					
Soomro[104] Saudi Arabia **	1986-1998	DVT	Pregnancy and puerperium (not defined)	22-48	0.88[0.57-1.29] (35)
		PE			0.67[0.41-0.93] (27)

[a] Pregnancy admission defined as any discharge record with a pregnancy-related diagnosis (ICD-9 codes 630-648) or a delivery code (ICD-9 codes 74 for cesarean delivery and 72, 73, 75, v27,or 650-659 for vaginal delivery). Postpartum admission: any discharge record that included a postpartum diagnosis (ICD-9 codes 660-677) and did not include a delivery code.

[b] Antepartum hospitalizations included records with a pregnancy-related ICD code, with a fifth digit indicating an antepartum condition. Peripartum hospitalizations were identified by well-defined ICD codes indicative of childbirth. Postpartum hospitalizations included records with a pregnancy-related ICD code indicating a
postpartum condition

TABLE 10B. Venous Thromboembolism in Pregnancy and Postpartum period. Incidence denominator expressed in person years. Case ascertainment method indicated after Country: * indicates diagnostic codes only; ** indicates diagnosis based on appropriate imaging study or confirmed physician diagnosis with appropriate signs and symptoms plus anticoagulation therapy. The duration of the puerperium is indicated in brackets in the Pregnancy Period column.

Country reference	Study years	Event	Pregnancy Period	Population (age in years)	Incidence rate per 100,000 woman years [95% confidence interval] (total cases)
AFRICA	NONE				
AMERICAs					
Heit[105] USA-MN **	1966-1995	DVT	Whole pregnancy	15-19	200.6 (15)
				20-24	71.5 (7)
				25-29	56.2 (8)
				30-34	95.5 (8)
				≥35	149.8 (4)
				All ages	85.2 [58.3-120.3] (32)
			Postpartum (defined as delivery of a newborn no more than 3 months before event date, including delivery of a stillborn infant after the first trimester)	15-19	240.7 (2)
				20-24	337.0 (11)
				25-29	400.6 (19)
				30-34	358.2 (10)
				≥35	224.7 (2)
				All ages	351.4 [255.4–471.8] (44)
			Pregnancy and Postpartum	15-19	210.6 (7)
				20-24	137.8 (18)
				25-29	142.3 (27)
				30-34	161.2 (18)
				≥35	168.5 (6)
				All ages	151.8[119.6–190.0] (76)
		PE	Whole pregnancy	15-19	40.1 (1)
				20-24	0.0 (0)
				25-29	0.0 (0)
				30-34	35.8 (3)
				≥35	0.0 (0)
				All ages	10.6 [2.9–27.3] (4)
			Postpartum	15-19	0.0 (0)
				20-24	153.2 (5)
				25-29	147.6 (7)
				30-34	71.6 (2)
				≥35	674.2 (6)
				All ages	159.7[97.6–246.7] (20)

Heit[105]				15-19	30.1 (1)
continued		PE	Pregnancy and Postpartum	20-24	38.3 (5)
				25-29	36.9 (7)
USA-MN **				30-34	44.8 (5)
				≥35	168.5 (6)
				All ages	47.9[30.7–71.3] (24)
		All VTE	Whole pregnancy	15-19	240.7 (6)
				20-24	71.5 (7)
				25-29	56.2 (8)
				30-34	131.3 (11)
				≥35	149.8 (4)
				All ages	95.8 [67.1–132.7] (36)
			Postpartum	15-19	240.7 (2)
				20-24	490.1 (16)
				25-29	548.2 (26)
				30-34	429.8 (12)
				≥35	898.9 (8)
				All ages	511.2[393.7–652.8] (64)
			Pregnancy and Postpartum	15-19	240.7 (8)
				20-24	176.1 (23)
				25-29	179.2 (34)
				30-34	206.0 (23)
				≥35	337.1 (12)
				All ages	199.7[162.5–242.9](100)
			Pregnancy – 2nd Trimester	15-19	240.7 (2)
				20-24	91.9 (3)
				25-29	84.3 (4)
				30-34	143.3 (4)
				≥35	112.4 (1)
				All ages	111[61.1–187.6] (14)
			Pregnancy – 3rd Trimester	15-19	361.0 (3)
				20-24	122.5 (4)
				25-29	42.2 (2)
				30-34	214.9 (6)
				≥35	337.1 (3)
				All ages	143.8[85.2–227.2] (18)
			Postpartum week 1	15-19	3166.8 (2)
				20-24	1612.2 (4)
				25-29	4438.9 (16)
				30-34	3770.5 (8)
				≥35	5913.7 (4)
				All ages	3573.2[2474.6-4993.2](34)
			Postpartum week 2	15-19	0 (0)
				20-24	2821.4 (7)
				25-29	1109.7 (4)

				30-34	471.3 (1)
				≥35	2956.8 (2)
				All ages	1471.3[804.4–2468.6] (14)
ASIA	NONE				
AUSTRALIA/OCEAN	NONE				
EUROPE					
Sultan[106] UK *** Note: Exclusion pregnancy time period resulting in non-live birth (includes spontaneous abortions, terminations of pregnancy and stillbirths)	1987-2004	VTE	Antepartum: all trimesters	15-24	50 [32-80] (18)
				25-34	67 [52–86] (60)
				35-44	80 [49–130] (16)
				15-44	65 [52–79] (94)
			Antepartum: 1st Trimester	15-44	30[17–50]
			Antepartum: 2nd Trimester	15-44	40[25–63]
			Antepartum: 3rd Trimester	15-44	114[89–146]
			Postpartum days 1-90	15-24	138 [84–225]
				25-34	223 [176–281]
				35-44	379 [265–542]
				15-44	228 [189–273]
			Postpartum days 1-45	15-44	421[349–509]
			Postpartum days 46-90	15-44	35[18–67]
Virkus[107] Denmark *	1995-2005	VTE	Whole Pregnancy	15-19	104 [59–183] (12)
				20-24	96 [75–122] (65)
				25-29	108 [93–124] (185)
				30-34	109 [93–127] (161)
				35-39	114[88–147] (60)
				40-44	87[41–182] (7)
				45-49	268 [38–1902] (1)
			Pregnancy by weeks gestation	1-11	41 [32 – 52] (61)
				12-23	57 [46 – 72] (75)
				24-27	122 [93 – 159] (53)
				28-31	156[123 – 198] (68)
				32-35	174[139 – 218] (75)
				36	113[64 – 200] (12)
				37	232[155 – 346] (24)
				38	305[213 – 436] (30)
				39	386[274 – 543] (33)
				40+	593 [461 – 764] (60)
				All (1-40+)	107 (491)
				1	600 [472 – 764] (66)
				2	483 [369 – 632] (53)
				3	366 [268 – 499] (40)

			Weeks postpartum	4	15-49	156 [97 – 251] (17)
				5-6		107 [71 – 160] (23)
				7-8		52 [29 – 94] (11)
				9-12		21 [11 – 42] (8)
				All (1-12)		175 (218)

Salonen-Ros[108] Sweden * Note: also used secondary and tertiary diagnoses in cases in which diagnoses related to pregnancy or puerperium were noted as the primary diagnosis, such as in pregnancies complicated by stillbirth or preeclampsia	1987-1995	VTE	3rd Trimester (28 weeks gestation to 3 days before delivery)	12-29	110.8	(123)
				30-34	103.8	(46)
				35-55	91.9	(18)
			Peripartum (2 days before to 1 day after delivery)	12-29	1985.6	(99)
				30-34	2216.9	(46)
				35-55	4402.5	(42)
			Puerperium (2 days to 6 weeks after delivery)	12-29	274.3	(177)
				30-34	249.1	(67)
				35-55	265.6	(33)
			Postpartum weeks 7 - 52	12-29	8.8	(44)
				30-34	8.9	(19)
				35-55	7.0	(7)
		PE	3rd Trimester (28 weeks gestation to 3 days before delivery)	12-29	14.4	(16)
				30-34	18.1	(8)
				35-55	25.5	(5)
			Peripartum (2 days before to 1 day after delivery)	12-29	381.1	(19)
				30-34	626.5	(13)
				35-55	209.6	(2)
			Puerperium (2 days to 6 weeks after delivery)	12-29	41.8	(27)
				30-34	66.9	(18)
				35-55	136.8	(17)
			Postpartum weeks 7 - 52	12-29	4.2	(21)
				30-34	3.3	(7)
				35-55	8.0	(8)

TABLE 11A. Stroke in Pregnancy and Postpartum period. Incidence denominator expressed in deliveries or pregnancies. Case ascertainment method indicated after Country: * indicates diagnostic codes only; ** indicates diagnosis based on appropriate imaging study or confirmed physician diagnosis with appropriate signs and symptoms plus anticoagulation therapy; *** coded diagnosis supplemented by evidence of anticoagulation therapy. The duration of the puerperium is indicated in brackets in the Pregnancy Period column.

Country [reference]	Study years	Event	Pregnancy Period	Population (age in years)	Incidence rate per 100,000 Deliveries [95% confidence interval] (total cases)
AFRICA	NONE				
AMERICAs					
James[109] USA*	2000-2001	All stroke (includes hemorrhagic, ischemic stroke, CVT and pregnancy related cerebrovascular events)	Pregnancy and Puerperium[a]	<20	30.3 [25.0–35.6] (290)
				20-24	26.3[23.0–29.6] (535)
				25-29	26.3[23.3–29.4] (575)
				30-34	35.3[30.6–40.0] (697)
				35-39	58.1[51.4–64.8] (564)
				≥40	90.5[71.9–109.1] (190)
				Total	34.2[33.3–35.1] (2850)
Liu [110] Canada**	2003-2016	Ischemic stroke	Pregnancy and Puerperium (≤42 days post-delivery)	≥20	3.8 (149)
		CVT			0.6 (22)
ASIA					
Jeng[111] Taiwan**	1984-2002	Ischemic stroke	Pregnancy and Puerperium (Not defined)	15-40	16.0 [8.0-32.1] (7)
		CVT	Pregnancy and Puerperium (Not defined)		10.0 [4.2-24.1] (5)
Liang[112] Taiwan** Note: There were two stillbirths at 28 and 37 gestational weeks	1992-2004	All strokes	Pregnancy and the puerperium	23-38	38.9 (26)
		Cerebral Infarction			13.5 (9)
AUSTRALIA/OCEANIA		NONE			
EUROPE	NONE				
MIDDLE EAST	NONE				

[a] Antepartum: pregnancy-related code (ICD-9 codes 630 – 648) Delivery: delivery code (ICD-9 codes 74 for cesarean delivery and 72, 73, 75, v27, or 650 – 659 for vaginal delivery. Postpartum: ICD-9 codes 660 – 677.

Table 11B. Stroke in Pregnancy and Postpartum period. Incidence denominator expressed in person years. Case ascertainment method indicated after Country: * indicates diagnostic codes only; ** indicates diagnosis based on appropriate imaging study or confirmed physician diagnosis with appropriate signs and symptoms plus anticoagulation therapy; *** coded diagnosis supplemented by evidence of anticoagulation therapy. The duration of the puerperium is indicated in brackets in the Pregnancy Period column.

Country [reference]	Study years	Event	Pregnancy Period	Population (age in years)	Incidence rate per 100,000 woman years [95% confidence interval] (total cases)
AFRICA	NONE				
AMERICAs					
Weibers[113] MN-USA*	1955-1979	Cerebral Infarction	Whole pregnancy	15-39	5.1
ASIA	NONE				
AUSTRALIA/OCEANIA - NONE					
EUROPE					
Salonen-Ros[114] Sweden*[a]	1987-1995	Intracerebral Infarction	3rd Trimester (28 weeks gestation to 3 days before delivery	12-29	
				30-34	
				35-55	
			Peripartum (2 days before to 1 day after delivery)	12-29	2.7 (3)
				30-34	4.8 (2)
				35-55	0.0 (0)
			Puerperium (2 days to 6 weeks after delivery)	12-29	40.1 (2)
				30-34	144.6 (3)
				35-55	104.8 (1)
			Postpartum weeks 7 - 52	12-29	12.4 (8)
				30-34	14.9 (4)
				35-55	24.1 (3)
					3.0 (15)
					2.8 (6)
					3.0 (3)
Ban[115] England*[b]	1997-2014	Ischemic Stroke	Antepartum		4.2 [2.4–7.3] (13)
			Peripartum		60.4 [19.5–187.4] (<5)

			Postpartum: 0-45 days	15-49	30.8 [18.5–51.0] (15)
			Postpartum: 46-90 days		10.1 [4.2–24.3] (5)
Ban[116] Sweden* Note: included live birth or stillbirth	1992-2011	Ischemic Stroke	Antepartum (conception to 3 days before delivery)	15-49	3.3 [2.5–4.4] (48)
			1st trimester		1.9 [1.0–3.7] (9)
			2nd trimester		2.9 [1.8–4.8] (16)
			3rd trimester		5.4[3.6–8.1] (23)
			Peripartum (2 days pre- to 1 day post-delivery)		112.7[75.6–168.2] (24)
			Postpartum (2 days to 12 weeks post-delivery)		19.4[15.6–24.0] (84)
			Postpartum weeks 1-6		34.4[27.3–43.2] (73)
			Postpartum weeks 7-12		5.0[2.7–9.0] (11)
MIDDLE EAST	NONE				

[a]Used secondary and tertiary diagnoses for cases in which diagnoses related to pregnancy or puerperium were noted as the primary diagnosis, such as in pregnancies complicated by stillbirth or preeclampsia

[b] Note: included live birth or stillbirth defined as as a

APPENDIX 3.
Thrombosis and Thromboembolism Risk Factors

3.1 Thrombosis and Thromboembolism Risk Factors

It is beyond the scope of the Guide to provide a detailed summary of the many documented risk factors for thrombosis and thromboembolism. It is a complex topic with substantial overlap in risk factors for venous and arterial thrombosis as well as some unique risk factors for either, and for particular sites of thrombosis (lower or upper extremity, abdominal, cerebral, retinal veins or arteries) and thromboembolism (pulmonary embolus, ischemic stroke, myocardial infarction).[117-123] Venous thrombosis and thromboembolism (VTE) are clearly events related to aging especially after age 45 years.[124] In many cases there are multiple risk factors which may be a combination of triggering factors (hospitalization, surgery, prolonged immobility, trauma or pregnancy) with or without additional inherited (clotting factor mutations, anticoagulant deficiencies, ABO blood type, sickle cell trait or disease) or acquired risk factors (cancer, inflammatory or autoimmune disease, chronic liver disease, first VTE event).

The mechanisms linking risk factors to the pathologic outcome are also complex. The basis for VTE has long rested on Virchow's triad of changes in blood flow, vessel wall and blood composition.[1] More recently these have been reviewed and broadened to include stasis, low oxygen tension, activation of endothelium, platelets, innate and acquired immunity as well as the concentration and nature of microparticles (submicron vesicles shed from surface of intravascular cells including platelets, endothelial cells and leukocytes), pro- and anticoagulant proteins. [125]

In the tables included in this section, emphasis is on presenting some detail on risk factors that should be considered in the setting of thrombosis or thromboembolism when temporally associated with immunization. This would primarily relate to understanding the types of events that could lead to a coincidental occurrence in the post-immunization context and thus what types of investigation should be considered as discussed in Appendix 4.

Table 3.1 summarizes well established and frequently associated risk factors along with some that occur less frequently. Where possible distinction is made in terms of whether the risk factor applies to venous or arterial thrombotic events or both. References are provided to enable a more detailed review of specific risk factors, in particular the evidence for their role. Appendix 2 should also be consulted as it presents evidence on background incidence for both VTE, including DVT and PE (Tables 1-3), Cerebral venous thrombosis (Table 4), cerebral venous sinus thrombosis (Table 5), Stroke and cerebral infarction (Tables 6-8) and abdominal thromboses (Table 9). Incidence in pregnancy and the puerperium are presented separately (VTE - Tables 10A & 10B; Ischemic stroke - Tables 11A & 11B). Note: the incidence of Myocardial infarction is included in the Myocarditis and Pericarditis Companion Guide (give xenodo link) in Appendix 2 – Table 3.

Table 3.2 provides a more visual summary of risk factors by type (arterial or venous) and location.

Table 3.3 provides an overview of the evidence on risk factors for pediatric thrombosis and thromboembolism.

TABLE 1. Risk Factors for Thrombosis and Thromboembolism [117-155]

AGE	VTE and ischemic stroke may occur at all ages [117], but incidence increases with increasing age, especially for those ≥70 years old[123] (Also see appendix 2, background rates). Advanced age is also a risk factor for retinal vein thrombosus[122]
SEX	Females have higher rates than males until menopause when the incidence in males exceeds that of females[118]

PREGNANCY AND PUERPERIUM	• Higher risk for both venous and arterial thromboembolism (80% events venous)[126, 127]
	  ○ Relative risk for VTE 4 to 5 times higher than non-pregnant of same age; greatest risk during pregnancy is during the 3rd Trimester[105-7]; and in the early postpartum period [100,105-8] (See background incidence data in Appendix 2: Table 10A (Galambosi[100]) and Table 10B (Heit[105],Sultan[106], Virkus[107], Salonen-Ros[108])
	  ○ The risk for thrombus formation in rare sites, including hepatic venous thrombosis and CVT / CVST is also increased in pregnancy.[122]
	  ○ For Ischemic stroke the greatest risk is in the peripartum period from 2 days before to 1 day after delivery[114-6] (See background incidence Appendix 2, Table 11A, Salonin-Ross[114] and Ban[115,116]).
	• Thromboembolism contributes to about 15% of maternal deaths[127]
	• Increased risk attributed to multiple factors that contribute to a hypercoagulable state, including: increased concentration of coagulation factors (VII, VIII, X, TF); decreased levels of anticoagulants (protein S, activators of fibrinolysis); gravid uterus may compress pelvic vasculature; risk may be further enhanced by pregnancy complications such as multiple gestation, pre-eclampsia and eclampsia[127]

GENETICS	• Race: evidence supports a higher incidence of VTE in African Americans versus Caucasian or Hispanic populations and a lower incidence in Asian populations[128, 129] .(Also see background rates in Appendix 2, Table 1(Stein[9], White[13]), Table 2(Stein[9]) and Table 3(Martinez[37]). This observation is likely due to multifactorial differences in other recognized risk factors • Mutations in clotting factors (Factor V Leiden; Prothrombin 20210A) and anticoagulant deficiencies (Protein C, Protein S). All first detected in family studies but only confirmed in population based studies for Factor V Leiden and Prothrombin 20210A.[130] • ABO blood group: non-blood group O associated with higher incidence but not clear if it is due to blood type or associated differences in levels of vonWillebrand factor and clotting factor VIII[131] • Sickle cell trait[132] UK cohort study (1988-2013) using CPRD database compared incidence in sickle cell trait carriers versus non-carriers and found an increased risk of PE among carriers (2.27; 1.17-4.39) but not DVT (1.43; 0.79-2.59)
SEASON	• Winter versus other seasons In temperate climates, higher incidence seen in winter with peak in January[133] . May be related to prolonged immobility or to seasonal variation in coagulation factors and cholesterol but nothing proven.
BEHAVIORAL	• Current smoker or past history of smoking may increase risk of VTE but not clear to what extent it is independent of the many other risk factors[134] • Immobilization – especially if prolonged (bed rest, casts for fracture/post-op) • Prolonged travel (air, car, bus, train) especially if ≥10 hours[125] • Recreational drug use – check to see if in general refs; may delete
HOSPITAL CARE AND SURGERY	• Hospitalization for any reason is a long and well-established risk factor for thrombosis and thromboembolism. The greatest impact is associated with prolonged bed rest, immobilization such as after multiple fractures or other severe trauma[117] and orthopedic surgery (hip or knee replacement) where the risk period extends for 3 months post-op.[135] • Indwelling venous and arterial cathethers.[117] Deep vein thrombosis of the upper limb is rare but when it occurs is usually associated with an indwelling central venous catheter.

	Cancer – Active[135] especially gastric, pancreatic, ovarian, brain and lung; also lymphoma or cancer of kidney, bladder or testes

COMORBIDITIES INCLUDING UNDERLYING DISEASES	Cancer – Occult[136]: among patients with 'idiopathic' VTE (i.e., no identified risk or triggering factors), 10% develop clinically overt cancer during follow up. Population-based studies done in Europe and the USA found a significantly increased risk of a new cancer diagnosis within 4 months to 1 year after discharge for idiopathic VTE. Most commonly found cancers in these populations were AML, NHL, ovarian, pancreatic, stomach, lung and renal cell.
	Coeliac Disease[137] Systematic review and meta-analysis suggested a small increased risk of VTE (meta-analysis of 4 studies from Austria, England, Sweden and Denmark showed a pooled risk ratio of 1.25 (1.02-1.53). Basis for risk not established but likely multifactorial.
	Inflammatory Bowel Disease[138] (IBD; both Crohn's and Ulcerative Colitis): increase the risk of VTE but not clear if IBD itself increases risk or if it is a combination of need for hospitalization with or without surgery, associated nutritional deficiencies or ongoing inflammation
	Migraine: established association between migraine and arterial thromboembolism, including ischemic stroke, coronary artery disease, and peripheral obstructive arterial disease. (see reference 140, Peng at al, for references re the association). • Migraine with aura[139.] First evidence for association between migraine and VTE (DVT & PE). Taiwanese large national cohort follow-up controlled database study showed association with migraine with aura (Adjusted Hazard Ratio of 2.42; 95% Confidence Interval 1.4-4.19) but not migraine alone (0.81; 0.5-1.20) or unspecified migraine (1.07; 0.84-1.36)
	Obesity: independently associated with both arterial and venous thrombosis[140] with evidence for a significant linear relationship between body mass index (BMI) and risk of VTE.[141]
	Obstructive sleep apnea: a systematic review found evidence for an independent association, increasing risk for both a first and recurrent VTE[142]
	Vasculitis [143, 144] • Behcet's Disease, which affects vessels of different sizes is associated with venous thrombosis in the limbs, splanchnic veins and cerebral veins and venous sinuses. Small vessel vasculitides including Churg-Strauss Syndrome(CSS), Granulomatosis with Polyangiitis(GPA), Microscopic polyangiitis(MPA) and Polyarteritis Nodosa(PAN) have increased risk of splanchnic venous thrombosis and myocardial infarction. • Large vessel vasculitis including Takayasu arteritis(TAK) and Giant Cell Arteritis(GCA) are associated with an increased risk of arterial thrombosis primarily involving the brain.
INFECTION	• Localized infections, especially abscesses or chronic infectious processes, may contribute to the occurrence of venous as well as arterial thrombosis in the same area: e.g., intrabdominal infection and splanchnic venous thrombosis; intracranial infection and CVT/CVST. • DVT and PE may occur as complications of respiratory viral infections including COVID-19, SARS and influenza; Also may occur in CMV, EBV, VZV, HIV and Hepatitis A and Hepatitis C.[1,145,146] • COVID-19 has also been linked to unusual sites of thrombosis including portal and cerebral venous thrombosis as well as acute ischemic stroke.[1] Most of these have occurred in severely ill patients in ICU and thus may have been multifactorial in origin. • Chronic hepatitis C, especially in setting of liver cirrhosis may contribute to splanchnic venous thrombosis[145] • Ischemic stroke has been associated with acute and chronic infections infections[120, 145, 147] including: acute endocarditis, meningoencephalitis, VZV, HZ, HIV, respiratory tract infections; chronic periodontitis, bronchitis, Helicobacter pylori[147], Chlamydia pneumoniae. In endemic setting syphilis, tuberculosis, neurocysticercosis and Trypanasoma cruzi (Chagas) disease should be considered as potential causes.

MEDICATION	Oral contraceptives[117, 148] are a well established risk factor for VTE, especially for high estrogen content (50ug) prevalent in OC's until the early 1980's. More recently the risk is highest with newer generations of combined oral contraceptives (estrogen and progestogens). Beyond the scope of this document but excellent reviews available.[117, 148]
	IVIG[149] In their 2005 review, Paran noted 65 reports of thrombosis, the majority arterial (53 with 36 stroke, 13 MI, 2 stroke & MI, and 2 limb ischemia) but also some venous (15 with 12 DVT or PE, 2 retinal vein thrombosis and 1 CVST). Nearly half of the arterial events onset <4 hours after the infusion whereas 45% of venous events occurred 24 hr to 7 days after infusion. Many had comorbid conditions: hypertension, coronary artery disease or elderly for arterial events and immobility or obesity for venous events. The mechanism and particularly the role of coexisting risk factors is not yet clearly defined.
	Anti-depressants[150] A meta-analysis of 8 studies (4 European, 2 Taiwan, 1 Canada, 1 New Zealand) found that both depression and anti-depressant use were associated with an increased risk of VTE. The mechanisms are not clear and the authors noted the association may be an epi-phenomenon.
	Antipsychotics[151] Review article citing some evidence for an elevated risk for VTE and antipsychotic use, especially 2nd generation (clozapine, olanzapine) and low potency first generation (chlorpromazine, thioridazine) agents.
VACCINE	The Institute of Medicine (now called the National Academy of Medicine) published, in 2012, their review of the evidence for an association between Varicella Zoster Vaccine and stroke; inactivated influenza vaccine and stroke as well as myocardial infarction; and Human Papillomavirus vaccine and thromboembolic events as well as hypercoagulable states.[152] For all, they concluded that the evidence was inadequate to accept or reject a causal relationship with vaccine. For some this was due to the limited number of epidemiologic studies which are briefly described below: • VZV & stroke: Varicella infection can cause stroke at a frequency of 1/15,000 cases, and is caused by direct invasion of cerebral arteries. Thus it would theoretically be possible that a live viral vaccine could cause stroke. There were 2 reports of stroke following varicella vaccine but the evidence only supported a temporal association. There was a single epidemiologic study.[153] This was a retrospective cohort study which included ischemic stroke as an outcome within 12 months of varicella vaccination. Adjusted hazard rations were calculated for stroke occurrence within 1, 1-3, 3-6, 6-9 and 9-12 months after vaccination and no increased risk was found. • Influenza vaccine and stroke: A single epidemiology study was cited. This was a self-controlled case series involving patients enrolled in the U.K. GPRD for at least 1 year with a diagnosis of stroke 6 months or more after enrollment.[154] A total of 19,063 patients were included in the analysis which not only showed no association between vaccination and stroke but also a reduced incidence of stroke during the month following vaccination. There was a single case report of ischemic stroke after influenza immunization but the evidence only supported a temporal association. • Influenza vaccine and MI: The single epidemiologic study done for stroke, also examined the age-adjusted rate of a first MI at 1-3, 4-7, 8-14, 15-28 and 29-91 days following influenza immunization[154]. Individuals ≥18 years old, enrolled in the GPRD for ≥1 year from 1987 through 2001 and with an MI ≥6 months after enrollment. The risk periods for MI were applied to each dose of influenza vaccine if multiple doses were given. A total of 20,486 patients were included in the analysis. There was no increased risk of first MI at the specified risk periods after immunization and a decreased risk of first MI within 1 month following influenza vaccine. There were no other epidemiologic data and only a single case report of MI following immunization but the evidence only supported a temporal association.

- HPV & Thromboembolic events: the committee cited 2 reports from passive surveillance systems and 2 case reports of thromboembolic events following HPV vaccine. They dismissed all 4 as non-contributory to any conclusions regarding causality.
- HPV & Hypercoagulable states: the committee identified no epidemiologic or case reports related to this association.

Dudley et al[155] did a systematic search through July 2018 for evidence supporting a causal relationship between vaccines routinely recommended by the Advisory Committee on Immunization Practices for use in the general U.S. population and 46 specified adverse events of interest including MI and stroke. No such association was found.

Dudley et al[156] summarized the evidence for vaccine – adverse event associations based on their systematic search noted above[155] as well as the IOM report[152] and the 2014 report by the Agency for Healthcare Research and Quality (AHRQ).[157] There were no proven associations between routinely recommended U.S. vaccines and MI, or stroke. In some cases vaccines protected against the adverse outcome. The main findings are briefly summarize below:

- Seasonal influenza vaccine and:
  - MI: reduced risk[158-162] or no increased risk[163]
  - Stroke: reduced risk[164-7], or reduced risk of death due to stroke[168] or no increased risk[163]
- HPV vaccine and stroke: no association in 9-16 yr olds[169]; no increase in background rate incidence over 9 years following HPV vaccine programme introduction (2006-15)[170]
- Pneumococcal vaccine and:
  - MI: no increased risk [158,171,172]
  - Coronary syndrome: risk decreased (polysaccharide vaccine)[173,174]
  - Stroke: no association[164,171,175]
- VZV vaccine and MI: no association[176]
- HZ vaccine and stroke or CV events: no association [177]
- DTaP-IPV for 4-6 yr olds and stroke: no association[178]
- Routine childhood vaccination: protective against stroke[179]

The Case Definition working group cited two additional relevant studies, not cited above:

- VZV vaccine and acute ischemic stroke[180] This was a Canadian cohort study of children born between January 1, 2006 and December 31, 2013. Of 368,992 children in the cohort, 325,729 received varicella vaccine between 11 and 23 months of age. The incidence of acute ischemic stroke in the 12 months following varicella vaccine (7.8/100,000 person years; 95% CI 4.8-10.9) was not significantly different than the rate among non-vaccinated children (6.8/100,000 person years; 95% CI 1.3-12.2). Controlling for known risk factors for acute ischemic stroke the adjusted Hazard Ratio for ischemic stroke among vaccinated children was 1.6 (95% CI 0.7-3.7) for the 12 months following immunization and 1.7 (95% CI 05-4.9) for 30 days after immunization suggesting no associated increased risk due to vaccine. Results of this study are similar to those reported by Donahue et al[153] and cited as the single (at the time) contributory epidemiologic study in the 2012 IOM report.
- HZ vaccine and stroke[181] A US study compared the incidence of stroke among 1,603,406 Medicare beneficiaries aged ≥66 years with no history of stroke who received live Herpes Zoster vaccine (Zostavax®)between 2008 and 2014 to a similar number of propensity score-matched unvaccinated beneficiaries. All were followed through December 31, 2017. Adjusted hazard ratios comparing vaccinated to unvaccinated for all stroke, acute ischemic stroke and

	hemorrhagic stroke were respectively: 0.84(95% CI 0.83-0.85), 0.83 (0.82-0.84) and 0.88 (0.85-0.91) suggesting that vaccination lowered the incidence of stroke.
OTHER	Remnant cholesterol (defined as total cholesterol minus LDL and HDL cholesterol): Copenhagen general population study involving 20-100 years recruited (completed questionnaire, physical exam and blood sample at intake) and followed for ischemic stroke outcome. Analysis showed that a stepwise increase in remnant cholesterol concentration was directly associated with a stepwise higher risk of ischemic stroke[182]
	Copenhagen General Population Study[183] involving otherwise healthy Caucasians found an association between: • High platelet count and 1.8 fold increased risk of ischemic stroke; • High hematocrit and 1.5 fold increased risk of myocardial infarction. Detailed discussion of this study beyond the scope of the guide. The authors review other studies on platelet count and hematocrit with inconsistent findings. They provide an excellent discussion on why their findings vary from previous work.
	Elevated resting heart rate[184] Large American cohort study of over 6000, aged 45-84 years, free of clinical cardiac disease or cancer and followed a median of 14 years with clinic visits every 2-3 years for determining resting heart rate and performing a 12 lead ECG. Outcome was an incident case of VTE. In a subset of participants plasma haemostatic factors and endothelial markers measured. Study conducted in multiple states and include Caucasian, Black, Hispanic and Chinese populations. The VTE incidence (95% Confidence Interval) varied with resting heart rate: ≤60: 2.72 (2.19-3.37); 60-69: 2.36 (1.88-2.96); 70-79: 3.71 (2.83-4.87); ≥80: 6.16 (4.20-9.05). As a possible explanation for the observed association, they also showed a significant positive correlation between resting heart rate and the following inflammatory/coagulation factors: high sensitivity CRP, IL-6, fibrinogen, D-dimer, von Willebrand factor, Factor VIII, PAP(plasmin-antiplasmin), PAI-1 (plasminogen activator inhibitor-1), E-selectin and ICAM-1 (Intercellular adhesion molecule 1).
RECENT HISTORY OF A VTE EVENT	A first symptomatic VTE event in hospital is associated with a risk of recurrence following discharge: around 3% by 30 days, 8% by 6 months and 13% by 21 months.[123] A prospective cohort study, using UK CPRD data, followed 783 patients with an index VTE event for 8 years showing recurrence rates after 1, 2, 3, 4 and 5 years to be 7%, 12%, 15%, 17.9% and 21.5%.[185] Martinez et al used the UK Clinical Practice Research Database to determine the incidence of first and recurrent VTE.[37] The age- and sex- specific incidence of first VTE is shown in Appendix 2, Table 3. The rates/100,000 person years for a first VTE among 18-29 year olds were 22.3 for males and 43.2 for females. When looking at recurrent VTE among those with a first VTE the highest recurrence rates across all ages were for DVT among 18-29 year old males (just over 7/100 person years) and females (just under 4/100 person years).

TABLE 3.2. Summary of key risk factors by type (Venous vs Arterial) and location of thrombosis and thromboembolism [117, 119,120-123,186-198]

Location	Common risk factor(s)	Less common risk factor(s)
Arterial [120, 186-9]	Ischemic stroke and myocardial infarction • Increasing Age • Cardiovascular disease (hypertension, coronary artery disease, congestive heart failure, valvular disease, atrial fibrillation, intracardiac tumors, cardiomyopathy, sick sinus syndrome, recent MI, prior MI with akinesia, Left ventricle or atrial thrombus, Congenital heart disease) • Diabetes mellitus • Smoking • Dyslipidemia • Thrombophilia – genetic* ad acquired	Ischemic stroke • Large vessel vasculitis (GCA, TAK) • Elevated remnant cholesterol • High platelet count • Migraine • Pregnancy – especially peripartum period • Patent foramen ovale (in younger persons) • Alcohol / Illicit drugs (in younger persons) • Inherited monogenic disorders (in younger persons) Myocardial infarction • Small vessel vasculitis (GPA, MPA, CSS, PAN) • Elevated resting HR (esp >80)
VTE (DVT & PE) [117,119,123,190-192]	• Increasing age • History of past VTE • Recent hospitalization especially if included surgery • Trauma • Cancer: Solid (especially gastric, pancreatic, ovarian, brain, lung, bladder, testicular) or myeloproliferative • Prior central venous catheter • Prolonged immobilization (>4days) / travel (>4hours) • Pregnancy / puerperium • Hormone use (OC, replacement, HRT) • Infection • Heart or respiratory failure • Obesity	• Anti-phospholipid syndrome • Obstructive sleep apnea • Coeliac disease • Migraine with aura (especially for PE) • Polycythemia vera • Paroxysmal nocturnal hemoglobinuria • Paraproteinemia • Systemic Lupus Erythematosus, Rheumatoid arthritis • Inflammatory bowel disease • Nephrotic syndrome • Thrombophilia – genetic* and acquired • Smoking • Varicose veins

CVT/CVST[122, 193-198]	• Oral Contraception or Hormone replacement therapy
	• Pregnancy
	• Thrombophilia (62.8% of CVST in India[Kalita 2016]:
	  ○ Genetic*
	  ○ Acquired: nephrotic syndrome, dehydration
		• Local infection (mastoiditis, otitis, sinusitis, meningitis)-now uncommon cause in high income countries but may cause up to 20% of cases in low- and middle-income countries[195]
		• Cancer especially myeloproliferative neoplasms
		• Behcet disease
		• IBD

Table 2 (continued)

Location	Common risk factor(s)	Less common risk factor(s)
Portal vein[121,122]	• Liver cirrhosis • 1° hepatobiliary cancer • Myeloproliferative and solid cancer	• Infection / inflammation • Vasculitis – Behcet's, GPA, MPA, CSS • Antiphopholipid syndrome

	• Metastatic cancer • Abdominal surgery	
Hepatic vein[121,122] (Budd Chiari Syndrome, refers to any obstruction of hepatic venous outflow)	• Myeloproliferative cancer • Anti-phospholipid syndrome • Genetic* thrombophilia • Paroxysmal Nocturnal Hemaglobinuria • Systemic inflammatory disease (Behcet disease, IBD, connective tissue disorder)	• OC or hormonal replacement • Pregnancy
Splenic vein[121,122]	Pancreatic disorders: pancreatitis (acute & chronic), cancer, abscess, pseudocysts,	
Mesenteric vein[121,122]	• Portal hypertension • Solid cancer • Pancreatitis • Severe heart failure • Morbid obesity	• IBD
Renal vein[122]	• Malignancy • Nephrotic syndrome	
DVT – arm[122]	• Indwelling venous catheter (80% of cases)	Strenuous arm exercise (Paget-Schroetter syndrome)
Retinal vein[122]	• Age>80	

* Genetic causes of thrombophilia include: Factor V Leiden mutation; Prothrombin 20210A mutation; natural anticoagulant deficiencies (Protein C, Protein S, antithrombin), non-O blood group, sickle cell disease and sickle cell trait.

TABLE 3. Summary of key risk factors for thrombosis and thromboembolism in children.[117,1199-201]

Location	Risk Factors
Ischemic stroke [187]	• Thrombophilia – genetic (Factor V Leiden) • Focal cerebral arteriopathy of childhood • Heart disease – congenital and acquired • Hematologic diseases • Metabolic diseases (mitochondrial myopathy, lactic acidosis) • Vasculitis • Sickle cell disease • Infection (Varicella Zoster Virus) • Trauma
DVT-leg[117]	• Indwelling venous catheter • Surgery • Local infection • Trauma • Immobilization
PE[199]	• Central venous catheters • Inflammation (SLE, IBD) • Systemic infection • Anti-phospholipid syndrome • Acquired thrombophilia
CVT/CVST [200,201]	Neonate: • acute systemic illness • infection • fluid/electrolyte abnormalities Previously healthy infants / children: • Head and neck infections • Acute illness with dehydration • Iron deficiency anemia • Inherited thrombophilia Chronically ill children • IBD • Cancer • Autoimmune disorders • Nephrotic syndrome • Chronic kidney disease • Behcet disease • Leukemia, l-asparaginase therapy • Sickle cell disease • Beta-thalassemia major

APPENDIX 4

Thrombosis and Thromboembolism Case Definition Key Caveats for Diagnosis, Data Analysis and Presentation

Thrombosis and Thromboembolism Case Definition[1] Key Caveats for Diagnosis, Data Analysis and Presentation

4.1 Key elements of Case Definition (CD)

- There are 3 levels of diagnostic certainty. For the most specific (Level 1, definite case), there must be proof of the presence of thrombus or thromboembolism via diagnostic imaging, pathologic examination of a biopsy or from an autopsy, or surgical evidence as would be the case if thrombectomy is performed. The case definition working group recommended first line and alternate investigations for documenting thrombosis or thromboembolism based on the anatomic location.[1] These have been reproduced in Table 4.1.

- The intermediate degree of diagnostic certainty (Level 2, probable case) relies on a physician report of a specific thrombus or thromboembolism.syndrome or presence of signs and symptoms consistent with one of the syndromes along with supportive diagnostic tests (both elevated D-dimer and at least 1 supportive finding (based on chest x-ray, chest MRI or transthoracic echocardiogram).

- The lowest level of diagnostic certainty (Level 3, possible case) relies only on clinical diagnosis of a specific thrombus or thromboembolism syndrome or signs and symptoms consistent with one of the syndromes (same as level 2). No lab or radiologic testing is required to reach level 3.

- Presence of an alternative diagnosis for the clinical presentation required to meet level 2 or level 3, would change the classification to level 5: Not a case. This is not applicable to level 1, since there is definitive proof of the presence of a thrombus or thromboembolism.

4.2 Guidance on data collection, analysis and presentation.

- Most cases of thrombosis and thromboembolism have multiple risk factors. See Appendix 3, Tables 3.1 and 3.2 for lists of relevant risk factors. When assessing an AEFI report of thrombosis or thromboembolism it is important to do a thorough history for presence of risk factors at the time of immunization and several months prior to immunization. In clinical studies where subjects are enrolled prospectively history of any prior occurrence of VTE should be sought since this is strongly correlated with a risk of recurrence. [37] It is also important to look for a history of recent hospitalization or surgery, especially orthopedic surgery as the risk for VTE can extend for several months beyond the time in hospital.

- All cases of thrombosis and thromboembolism should be classified in one of 5 groups:
    - Meets the case definition at: 1. Level 1 of certainty; 2. Level 2 of certainty; 3. Level 3 of certainty
    - Does not meet the case definition because: 4. Data collected were insufficient to meet any of the 3 levels of certainty; 5. An alternate diagnosis was found to explain the clinical illness, and thus it is Not a case. It is important to note that cases classified in the 4th category may eventually be able to meet the case definition if additional data are gathered as part of follow-up investigation.

- For data to be comparable across different settings and clinical trials it is very important to use consistent categories for time to onset following immunization. The case definition Working Group has recommended that the data be analyzed and presented in the following categories of interval from immunization to presentation:
    - ≤4 days after immunization
    - 5-14 days after immunization
    - 15-28 days after immunization
    - 29-42 days after immunization
    - >42 days after immunization.

Recommendations for real time assessment

Investigation can help confirm the level of certainty of the diagnosis of thrombosis and thromboembolism and may also contribute to assessing vaccine – event causality versus coincidental occurrence. Table 4.1 provides the most common presenting signs and symptoms for each of the thrombosis and thromboembolism syndromes along with recommendations for confirming the presence of thrombus or thromboembolism and suggested workup for cases where there are no known risk factors. This is not meant to be an exhaustive listing. The citations for each section can be consulted for further recommendations.

TABLE 4.1 Typical clinical presentation of thrombosis and thromboembolism by location and suggested investigations. The recommendations for 1st line and alternate investigations to confirm thrombus or thromboembolism are from the case definition working group. [1]

Site	Clinical presentation	Suggested investigation to confirm thrombosis or thromboembolism	In absence of known risk factors, consider
DVT – leg	• Calf pain, redness, warmth • Ankle swelling	• 1st line: Compression ultrasonagraphy with or without doppler • Alternate: MR or CT venography	Consider screening for genetic causes of thrombophilia if there has been a history of a first VTE[125] • Factor V Leiden; prothrombin G20210A; ABO blood group rs8176719; FGG C10034T; factor XI rs2036914
PE [192]	• Pleuritic pain with hemoptysis • Circulatory collapse syndrome (usually massive PE with cor pulmonale, distended neck veins, hypotension) • Uncomplicated dyspnea syndrome	• 1st line: CT pulmonary angiography • Alternate: V/Q scan, contrast-enhanced MR angiography; digital subtraction or conventional angiography • Supportive: Chest-xray or CT. Not definitive but may provide supportive information (included as one of the criteria to reach level 2 LOC): o wedge shaped density; o pleural effusion o prominent proximal pulmonary artery with reduction in peripheral vessel markings	

Splanchnic veins[121,122] (portal, splenic, mesenteric)	• acute sudden onset abdominal pain most common and sometimes only symptom; also fever, nausea, vomiting,	• Portal and hepatic VT: Doppler ultrasonography • Mesenteric VT: CT or MRI angiography	• Pregnancy test • Anticardiolipin and Beta 2 glycoprotein IgG and IgM • Flow cytometry for PNH • Lupus anticoagulant
Hepatic vein (Budd-Chiari) [121,122]	Typical triad: • Abdominal pain • Ascites • Hepatomegaly	CT liver; Doppler ultrasound; venography and same as above for splanchnic VT	Same as for Splanchnic VT
Renal vein [121]	• Flank pain • Hematuria	CT abdomen: 24 hour urine collection for protein; serum albumin;	
Retinal vein[122]	• Acute painless loss of vision, unilateral	Complete eye exam	
Cerebral vein / venous sinus [193,195]	• Sudden onset of headache which may be the only symptom. Typically persistent over hours to days, worse on coughing or bending over. • Focal neurologic deficits • Seizure(s)	• First line: MR venography with contrast • Alternate: CT venography	• Anticardiolipin and Beta 2 glycoprotein IgG and IgM • Screen for genetic causes of thrombophilia • antiPF4 antibodies
Ischemic stroke [120, 186,187]	• Headache, • Focal neurologic deficits	• First line: contrast CT if able to do it within 6 hours of presentation • Alternate: CT or MR angiography	• CBC lipid panel, blood glucose, kidney function • Inflammatory workup • Urine screen for illicit drugs • Screen for genetic / acquired thrombophilia • Anticardiolipin and Beta-2 glycoprotein IgG and IgM • 12 lead eCG – for occult Atrial Fibrillation Also see Putaala[186] and Koptya[187] for extensive discussion of mono-genic disorders causing stroke in younger adults and children

APPENDIX 5

Thrombosis and Thromboembolism Data Abstraction and Interpretation Forms With Algorithms for Assessing Level of Certainty

5.1. Thrombosis and Thromboembolism Data

Instructions are provided with each table. The focus is on the specific data needed to meet and/or exclude Thrombosis and Thromboembolism based on the Brighton case definition.[1] This form will be most applicable to situations where a hospital/other institutional chart is available and used retrospectively to gather the information needed to validate that a case coded as Thrombosis and Thromboembolism meets or does not meet the Brighton case definition. It may also serve as a guide for the type of data to be collected and investigations to be done at the time a possible case is identified or reported during a clinical trial or active surveillance for cases as part of pharmacovigilance.

Four tables are included in the form.

- Table 5.1 is a guide to likely sources of information for the key case definition clinical and laboratory criteria.
- Table 5.2 is the main data abstraction form. Use it to record data from the chart. Space is limited and additional paper can be used as appropriate to capture key clinical and laboratory data.
- Table 5.3 is a guide for assigning a Yes (Y), No (N) or Unknown (U) value for each of the case definition criteria. For selected criteria the possible values may be limited to 2 options: e.g., Y or N/U; Y or N.
- Table 5.4 provides space to summarize the final criterion values determined in Table 3.
- Table 5.5 provides the formulae to convert the final criterion values recorded in Table 4 to a case definition level of certainty. Depending on the available data a case can 'Meet the case definition' at Level 1, 2 or 3 of certainty; OR 'not meet the case definition' because of missing or uncertain information (Level 4) or because there is an alternate diagnosis for the clinical illness (Level 5 – Not a case).
- Figure 5.1 provides a pictorial algorithm as an alternate tool for determining the level of certainty.

TABLE 1. Thrombosis and Thromboembolism KEY CASE DEFINITION CRITERIA, LIKELY AND ACTUAL SOURCES OF INFORMATION

Criterion	Criterion category	Likely sources of information	Actual sources of information

A	Confirmation of presence of thrombosis or thromboembolism	• A-1 Histopathology report(s) from:
		  • autopsy or
		  • biopsy tissue sample
		• A-2 Inpatient/outpatient surgical report of procedure confirming thrombus
		• A-3 Radiologic imaging report(s) including: CT, MRI, ultrasound, doppler, venography, angiography, V/Q scan	

B	Clinical evidence for presence of thrombosis or thromboembolism (B-1 diagnosis of clinical thrombus or thromboembolism syndrome; B-2 clinical signs or symptoms suggestive of thrombus or thromboembolism syndrome)	• Emergency report • Hospital admission history/exam, • Consultation reports, • ICU admission notes • Hospital discharge summary • Admitting / Discharge Diagnoses	
C	Biologic marker of thrombosis	Lab report: D-dimer measurement(s)	
D	Imaging studies that support but don't confirm presence of thrombus or thromboembolism	• Radiology reports: CXR or CT • Transthoracic Echocardiogram report	
X	Alternate etiology	• Hospital discharge diagnosis and discharge summary • Subspecialty Consultant reports l • Laboratory investigations • Follow-up visits to specialty clinics, • Readmission to hospital	

TABLE 5.2. THROMBOSIS AND THROMBOEMBOLISM DATA ABSTRACTION FORM: Record specific information, to the extent possible, for 1-4 below

1. Date of illness onset:	
2. Date of hospital admission:	
3. Admitting diagnosis:	
4. Discharge diagnosis:	

THROMBOSIS AND THROMBOEMBOLISM DATA ABSTRACTION FORM (continued):

Record specific information, to the extent possible, for all rows in the table below. The red font identifies specific criteria related to the thrombosis / thromboembolism case definition.

5. Criterion A Confirmation of Thrombosis or Thrombo-embolism	A-1 Pathologic findings from autopsy or biopsy	Check the one best answer and provide details as appropriate: ☐ 1. Biopsy showed presence of thrombosis or thromboembolism (describe location and results) ☐ 2. Autopsy showed presence of thrombosis or thromboembolism: (give date of autopsy and brief description in terms of the pathologic proof of thrombosis or thromboembolism or both if present) ☐ 3. Biopsy or autopsy done but showed neither thrombosis nor thromboembolism ☐ 4. No biopsy or autopsy done, unknown if done, or done but results unavailable.
	A-2 Surgical procedure	Check the one best answer and provide added details as appropriate: ☐ 1. Thrombectomy performed* ☐ 2. Other procedure done that confirmed presence of thrombosis or thromboembolism* ☐ 3. No surgical procedure done; or, done but either did not confirm presence of thrombosis or thromboembollism or findings unknown; or unknown if done * If 1 or 2 checked describe procedure, location and finding:
	A-3 Imaging studies confirmed the presence of thrombosis or thrombo-embolism	A-3.1 Choose the one best answer ☐ 1. ≥1 imaging study was done and confirmed thrombosis or thromboembolism (if yes answer A-3.2 below) ☐ 2. ≥1 Imaging study was done but didn't confirm thrombosis or thromboembolism ☐ 3. No imaging studies done, unknown if done, or done but results unknown
		A-3.2 If option 1 chosen for A-3.1, which studies confirmed thrombosis or thromboembolism? Check all that apply ☐ 1. Compression ultrasonography (for limb DVT) ☐ 2. CT pulmonary angiography (for pulmonary embolus) ☐ 3. Ventilation-Perfusion (V/Q) scan (for pulmonary embolus) ☐ 4. CT or MR angiography (for arterial thrombosis) ☐ 5. CT or MR venography (for venous thrombosis) ☐ 6. CT or MRI (with or without contrast enhancement) ☐ 7. Echocardiogram (for thromboembolisms in heart or pulmonary artery) ☐ 8. Conventional angiography or digital subtraction angiography ☐ 9. Abdominal ultrasound with doppler (for portal vein thrombosis) ☐ 10. Other – Describe:
		A-3.3 Describe location(s) of thrombosis/thromboembolism based on imaging study:

THROMBOSIS AND THROMBOEMBOLISM DATA ABSTRACTION FORM (continued):

6. Criterion B: Clinical evidence for presence of thrombosis or thromboembolism	B-1.1 Reported thrombosis or thromboembolism syndrome	Choose the one best answer: ☐ 1. ≥1 syndrome of thrombosis or thromboembolism was reported. (If yes, answer B-1.2 below) ☐ 2. There was no report of a recognized thrombosis or thromboembolism syndrome ☐ 3. It is unknown if there was a report of a thrombosis or thromboembolism syndrome	
	B-1.2 Specific type(s) of thrombosis or thromboembolism syndrome DVT = deep vein thrombosis	Check all that apply: ☐ 1. Cerebral venous thrombosis ☐ 2. Cerebral venous sinus thrombosis ☐ 3. Lower extremity DVT ☐ 4. Upper extremity DVT ☐ 5. Pulmonary Embolism ☐ 6. Portal vein thrombosis ☐ 7. Hepatic vein thrombosis or Budd-Chiari syndrome ☐ 9. Mesenteric vein thrombosis	☐ 10. Splenic vein thrombosis ☐ 11. Retinal vein thrombosis ☐ 12. Other venous thrombosis: specify site(s): ☐ 13. Non-Hemorrhagic stroke ☐ 14. Myocardial infarction ☐ 15. Other arterial thrombosis: specify site(s):
	B-2 New onset clinical symptoms or signs that could suggest thrombosis or thromboembolism	Check all that apply: ☐ 1. Sudden onset headaches ☐ 2. Severe headaches that persist ☐ 3. Sudden painless loss of vision ☐ 4. Loss of, or change in, level of consciousness ☐ 5. Seizure(s) ☐ 6. Focal neurologic abnormalities (e.g., facial paralysis, difficulty with speech, ataxic gait, hemiparesis, abnormal eye movements, blurred vision or seeing double) ☐ 7. Calf pain or tenderness ☐ 8. Ankle swelling or pitting edema ☐ 9. Absent pulses in legs or arms ☐ 10. Redness, warmth or pain in one or more extremities	☐ 11. Sudden shortness of breath, at rest or on exertion ☐ 12. Pleuritic chest pain (sudden, sharp or stabbing, worse on breathing or coughing or sneezing or laughing) ☐ 13. Crushing central chest pain (cardiac angina) ☐ 14. Tachypnea ☐ 15. Tachycardia ☐ 16. Cyanosis ☐ 17. Hypotension ☐ 18. Sudden onset abdominal pain ☐ 19. Sudden unexpected death ☐ 20. None of the above were present or it is unknown if any of 1-19 were present.

7. Criterion C D-Dimer	Choose the one best answer: ☐ 1. D-dimer exceeded test lab's upper limit of normal. What was the highest measured value: If known please indicate the test lab's upper limit of normal: ☐ 2. D-dimer tested and was within test lab's range of normal ☐ 3. D-dimer not tested, or tested but results unknown or not available

8. Criterion D: Imaging studies supported but did not confirm the presence of thrombosis or thromboembollism	D-1 Chest radiograph (CXR)	Choose the one best answer: ☐ 1. CXR done and showed ≥1 of the following: wedge shaped opacity; pleural effusion; prominent proximal pulmonary artery with reduction in peripheral vessel markings ☐ 2. CXR done and was normal or had none of the findings listed in choice 1 above ☐ 3. Unknown if CXR was done or CXR done but results unknown
	D-2 Transthoracic Echocardiogram (T-Echo)	Choose the one best answer ☐ 1. T-Echo was done and showed ≥1 of the following: right heart dilation; tricuspid regurgitation; interventricular septal compression; or right ventricular hypokinesia. ☐ 2. T-echo was done and was normal or had none of the findings listed in choice 1 above ☐ 3. Unknown if T-echo was done or T-echo done but results unknown.
	D-3 Non-contrast computed tomography (CT)	Choose the one best answer: ☐ 1. Non-contrast chest CT was done and showed ≥1 of the following: wedge shaped opacity; pleural effusion; prominent proximal pulmonary artery with reduction in peripheral vessel markings ☐ 2. Other regional non-contrast CT done and was suggestive of thrombosis. If yes describe the findings including body location: ☐ 3. Non-contrast CT was done and was normal or had none of the findings listed in choice 1. ☐ 4. Non-contrast CT not done, or done but results unknown.
9. Criterion X: Alternative diagnosis	Choose the one best answer ☐ 1. An alternative diagnosis was found that explained the acute illness: describe- ☐ 2. No alternative diagnosis was found to explain the acute illness	

TABLE 3. Based on the information recorded in Table 2 above, record the status for each of the listed criteria

CRITERIA	CRITERION OPTIONS			Criterion Value
	Criterion=YES (Y) IF:	Criterion=NO (N) IF:	Criterion=UNKNOWN (U) IF:	
Thrombosis or thromboembolism: A-1: Confirmed by pathology	__A-1 = 1 or 2	__ A-1 = 3	__ A-1 = 4	A-1 = Y N U
A-2: Confirmed by surgery	__A-2 = 1 or 2	__ A-2 = 3		A-2 = Y N/U
A-3: Confirmed by imaging.	__A-3.1 = 1 and A-3.2 = ≥1 of (1-8)	__A3.1 = 2	__ A-3.1 = 3	A-3 = Y N U
B-1: Thrombosis or thromboembolism syndrome reported	__B-1.1 = 1 AND B-1.2 = ≥1 of (1-15)	__B-1.1 = 2	__ B-1.1 = 3	B-1 = Y N U
B-2: ≥1 non-specific clinical symptom or sign	__B-2 = ≥1 of (1-19)	__ B-2 = 19		B-2 = Y N/U
C. D-Dimer >test lab's upper normal limit	__C = 1	__C = 2	__C = 3	C = Y N U
D. Imaging studies supported but couldn't confirm thrombosis or thromboembolism	__(D-1 = 1) or (D-2 = 1) or D-3 = (1 or 2)	__(D-1 = 2 or 3) and (D-2 = 2 or 3) and (D-3 = 3 or 4)		D = Y N/U
X. Alternative diagnosis	__X = 1	__X = 2	Not applicable	X = Y N

TABLE 4. Record the final value for each Criterion from Table 3 into Table 4

Criterion	A-1	A-2	A-3	B-1	B-2	C	D	X
Final Value								

TABLE 5 Based on the values for the Criteria in table 3 above, circle the corresponding value in the table below to determine the highest achievable level of certainty (LOC) for Thrombosis and Thromboembolism

Level of Certainty	
Level 1	A-1 OR A-2 OR A-3 = YES
Level 2	[B-1 or B-2 = YES] AND [C AND D = YES] AND X = NO
Level 3	[B-1 or B-2 = YES] AND X = NO
Level 4	Reported as a case of Thrombosis or thromboembolism but fails to meet any level of certainty
Level 5	An alternative diagnosis to account for the clinical illness was found (X = YES)

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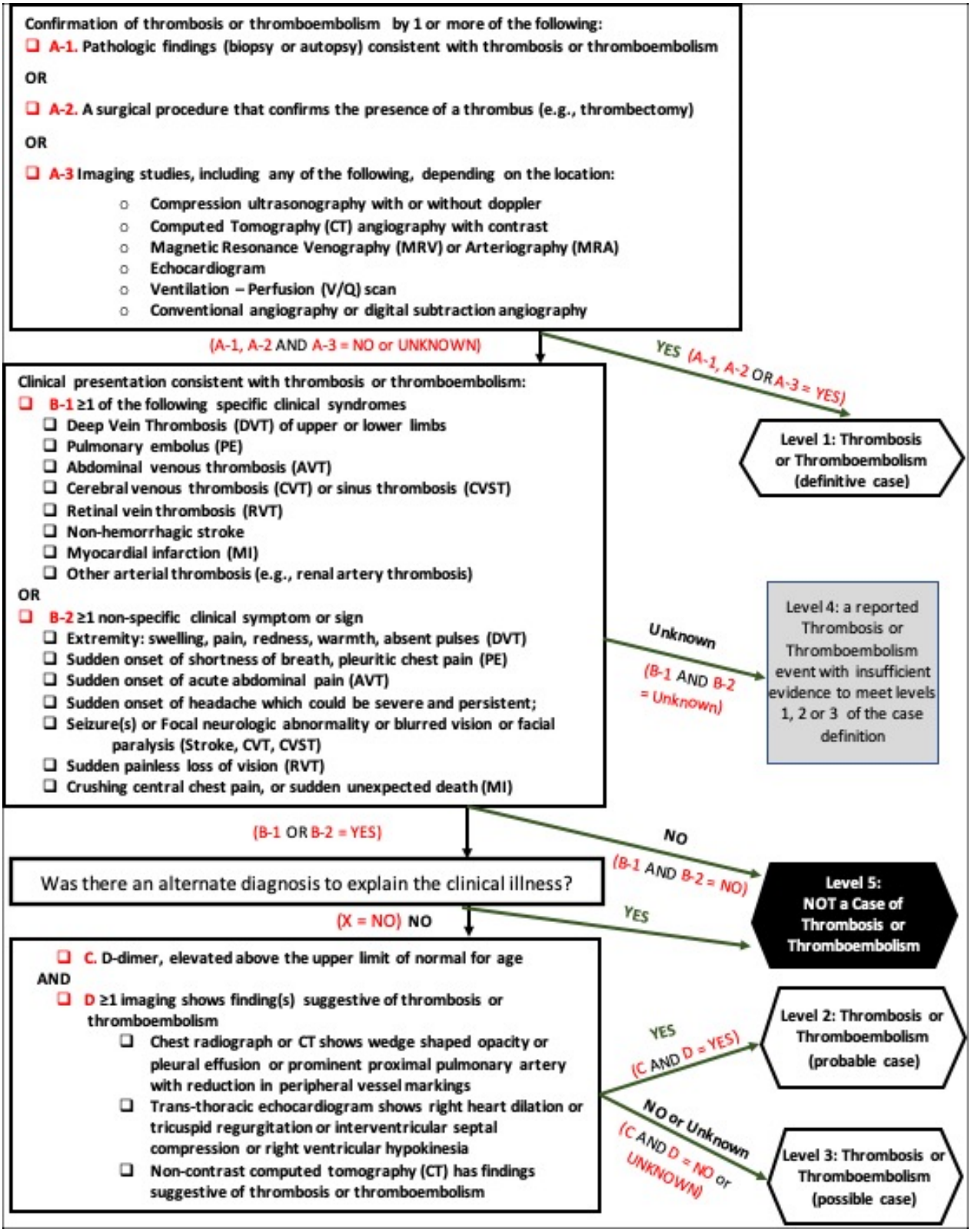
Figure 5.1. Pictorial algorithm for determining level of certainty for Thrombosis and Thromboembolism



APPENDIX 6.

Methodology: Brief Summary

6.1. Thrombosis and Thromboembolism ICD-9/10-CM and MedDRA Codes [2-6]

An initial set of codes were retrieved through the Codemapper tool that was developed in the IMI-ADVANCE project. Subsequently they were reviewed and classified into narrow or broad codes by the authors.

CodeMapper[2] builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.[3] Codemapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9 CM, ICD-10 CM, and MedDRA.[4,5] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[6] Of note, while SPEAC focused on ICD-9/10-CM and MedDRA codes, the CodeMapper concepts shown in the table can be used to search for codes in other systems including SNOMED-CT, MeSH, ICPC-2 and Read-CTv3.

CodeMapper has three screens.

1. The first displays the free text entered by the user – in this case the Brighton case definition. Medical concepts are automatically identified in the text and highlighted inline.
2. The second displays the mapping as a table with one row for each medical concept, and one column for each targeted vocabulary. Each cell contains the names of the codes that are used to represent the medical concept of the row in the targeted vocabulary of the column. The codes are displayed when the names are hovered over with the mouse. Several user operations are available for revising the mapping. The user can remove concepts from the mapping, search and add concepts, or retrieve more general and more specific concepts. The retrieved concepts are shown in a list and can be selected by the user for inclusion in the mapping. The user can also add or remove vocabularies that should be targeted by the mapping. After every operation, the codes are automatically updated and displayed in the table.
3. The third shows a list of all operations that have been made, for later traceability of the mapping process. When the user saves the mapping, he has to provide a summary of the modifications, which is incorporated into the mapping history. The user can download the mapping as a spreadsheet file to incorporate the codes into extraction queries. The spreadsheet file comprises the original free-text case definition, the concepts of the mapping, the codes for the targeted vocabulary, and the full history of the mapping process.

Codemapping was conducted by MS. The output of the Codemapper concepts was reviewed by a medical expert (BL) familiar with the Anaphylaxis Brighton case definitions for all Tier 1 AESI. The concepts identified for Anaphylaxis were considered relevant for background incidence rate determination as well as to study hypotheses related to Anaphylaxis as a vaccine-product related reaction.

For a more detailed description of methodology see SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes which is available in the CEPI Developers' Toolbox and at the Brighton Collaboration website.

6.2. Thrombosis and Thromboembolism Background Incidence

A systematic literature search to estimate the incidence of acute Thrombosis and Thromboembolism in the population was conducted using the following search strategy:

"Thromboembolism"[Mesh:noexp] OR "thromboembolic"[ti] OR "thromboembolism"[ti] OR "thrombosis"[ti] OR "thromboses"[ti] OR "thrombotic"[ti] OR "Pulmonary embolism"[Mesh] OR "pulmonary embolus"[ti] OR "pulmonary embolism"[ti] OR "pulmonary thrombosis"[ti] OR "pulmonary thromboses"[ti] OR "pulmonary artery occlusion"[ti] OR "Sinus Thrombosis, Intracranial"[Mesh] OR "sinus thrombosis"[ti] OR "sinus thromboses"[ti] OR "Ischemic Stroke"[Mesh] OR "Ischemic Stroke"[ti] OR "Ischemic Strokes"[ti] OR "Cerebral artery occlusion"[ti] OR "Ischemic Cerebrovascular Accident"[ti] OR "Ischemic Cerebrovascular Accidents"[t

AND ("Incidence"[Mesh:noexp] OR "incidence"[tiab])

AND English[lang]

AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT])

AND ("Observational Study"[Publication Type] OR "Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type])

NOT ("animals"[Mesh:noexp] NOT "humans"[Mesh:noexp])

NOT ("Coronavirus"[Mesh:noexp] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti])

NOT ("therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti] OR "drug"[ti] OR "drugs"[ti] OR "trial"[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti] OR "prevents"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti])

Articles had to meet the following criteria:

1. Original research/meta-analysis
2. Population-based study (selecting the entire population or using probability-based sampling methods)
3. Reported an incidence estimate (or raw numbers that allowed the calculation of an estimate).

If multiple articles reported data from the same study population, the most comprehensive data were used. When studies reported on different data collection years or subgroups (sex, age), efforts to include all nonoverlapping data were made. Age, sex, study location, sources of ascertainment, and definitions/diagnostic

criteria for Anaphylaxis were extracted. Anaphylaxis incidence estimates, raw numbers, and confidence intervals (CIs) (when provided) were recorded along with any stratified results by age, sex, or year of data collection.

Articles were screened by a single medical reviewer. Screened in articles were reviewed and relevant data abstracted for inclusion in the background rate table (MRV) when novel articles were found from systematic reviews, these were included. The spreadsheet with all extracted background incidence data is available in the CEPI Developers' Toolbox and on the Brighton Collaboration website.

6.3. Thrombosis and Thromboembolism Risk Factors

A risk factor is "an exposure, behavior, or attribute that, if present and active, clearly alters the occurrence of a particular disease compared with an otherwise similar group of people who lack the risk factor". According to James Last dictionary of epidemiology version 4, a risk factor is an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with health-related condition(s) considered important to prevent. The term risk factor is rather loosely used, with any of the following meanings:

1. An attribute or exposure that is associated with an increased probability of a specified outcome, such as the occurrence of a disease. Not necessarily a causal factor. A RISK MARKER.
2. An attribute or exposure that increases the probability of occurrence of disease or another specified outcome. A DETERMINANT.
3. A determinant that can be modified by intervention, thereby reducing the probability of occurrence of disease or other specified outcomes. To avoid confusion, it may be referred to as a modifiable risk factor.

Risk factors can include infection, medication, diet, surgical or medical procedure, environmental location, stress, toxins, trauma and vaccine. Attributes includes genetic makeup, age, gender, ethnicity, social status, occupation. Behavior includes smoking, drinking, other substance abuse, sexual practices, level of physical activity. A standard tabular format, as shown in the appendices was used to summarize the key known risk factors for each AESI. Risk factors are only included if there is evidence for an association with the AESI.

The published Brighton Case definition[1] for Thrombosis and Thromboembolism was reviewed for evidence related to associated risk factors. In addition, a systematic search was conducted to identify evidence for risk factors using the same search strategy shown for background incidence in section 6.2 above. The same expert (BL) screened all retrieved articles and set aside and reviewed all that pertained to the epidemiology of thrombosis and thromboembolism. Additional articles were retrieved by a hand search of the article citations. The included articles were used not only to inform the Risk factor table(s) in Appendix 3, but also guidance on real time investigation in Appendix 4.

6.4. Thrombosis and Thromboembolism Case Definition key caveats for diagnosis, data analysis and presentation [1]

The published Brighton case definition[1] was reviewed and key aspects identified with particular relevance to real time assessment of cases of Thrombosis and Thromboembolism in the context of a clinical trial outcome or where it is reported as an AEFI. In addition, the guideline section of the published case definition was reviewed, and key recommendations identified for data collection, analysis and presentation.

For a more detailed description of methodology see SO1-D2.7 Guidance for CEPI Developers which is available in the CEPI Developers' Toolbox.

6.5. Tabular Checklist and Algorithms for Level of Certainty Determination [1]

The Brighton Collaboration case definition for Thrombosis and Thromboembolism[1] was thoroughly and repeatedly reviewed by one individual (BL) to identify all clinical, laboratory and other criteria (e.g., temporal course of disease) used to define each and every case definition level of certainty.

The Thrombosis and Thromboembolism criteria were displayed in a tabular format to enable recording of all relevant clinical data (based on history, physical examination, laboratory investigation and temporal criteria as relevant to each case definition) needed to meet each criterion.

Algorithms were developed for each level of diagnostic certainty based on the values of each criterion as described in the published case definition.[1] Two types of algorithm were developed for the case definition: a tabular presentation with formulae based on the logic in the case definition which were put into tables with each row representing a level of certainty; a more visual decision tree algorithm.

For a more detailed description of methodology see Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation which is available in the CEPI Developers' Toolbox.