Peripheral Artery Disease Mortality: Systematic Review with ☸SAIMSARA.

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Abstract: This paper aims to synthesize recent evidence on peripheral artery disease mortality, identifying key risk factors, prognostic indicators, and the impact of various interventions, as extracted and structured by a multilayer AI research agent. The review utilises 2149 studies with 15723713 total participants (naïve ΣN). The median 30-day mortality rate for patients with peripheral artery disease (PAD) or undergoing PAD-related procedures is 4.3%, highlighting the substantial and variable early mortality risk in this population. This risk is compounded by numerous comorbidities and can be mitigated by effective medical therapies. The reliance on diverse study designs and inconsistent outcome reporting is a significant limitation affecting the certainty of aggregated findings. A critical next step is to conduct large-scale prospective comparative effectiveness trials with standardized mortality endpoints to better inform clinical decision-making.

Keywords: Peripheral Artery Disease; Mortality; Cardiovascular Mortality; All-Cause

Review Stats

- Generated: 2026-01-30 21:36:38 CET
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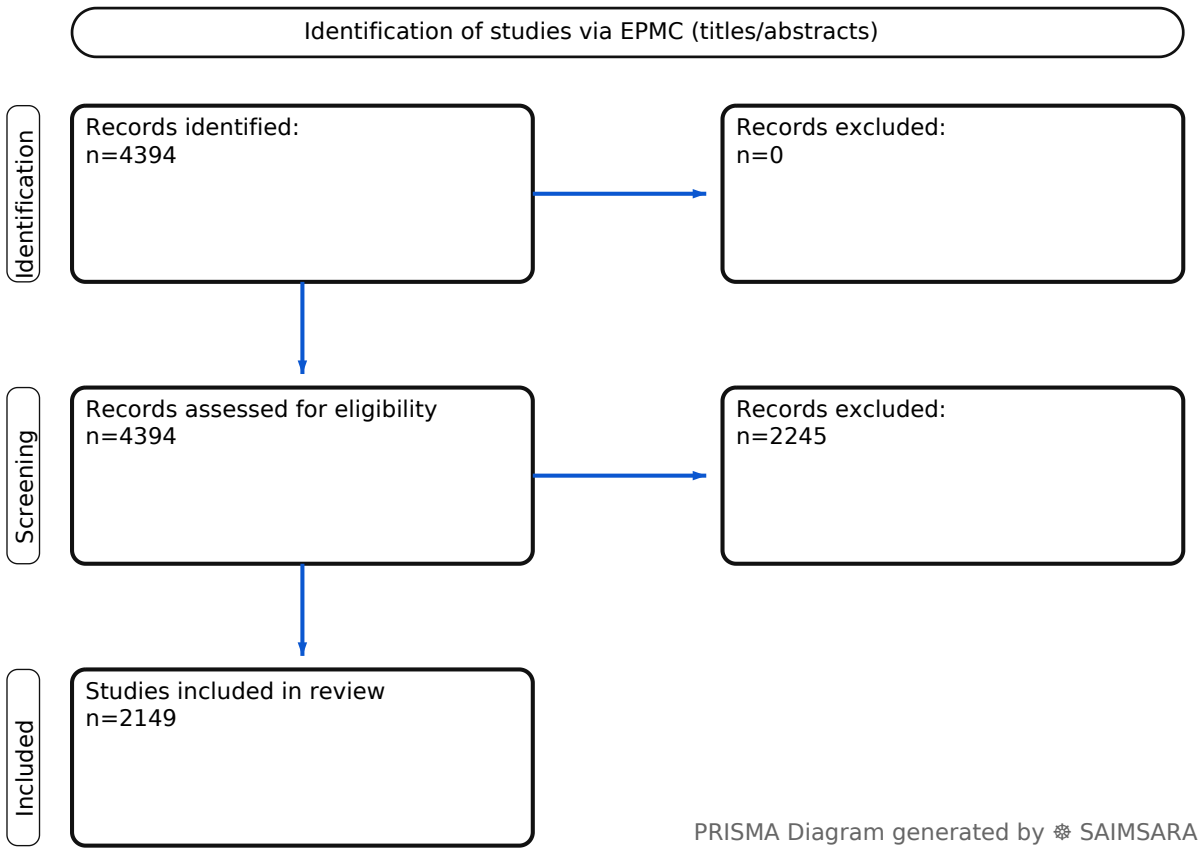
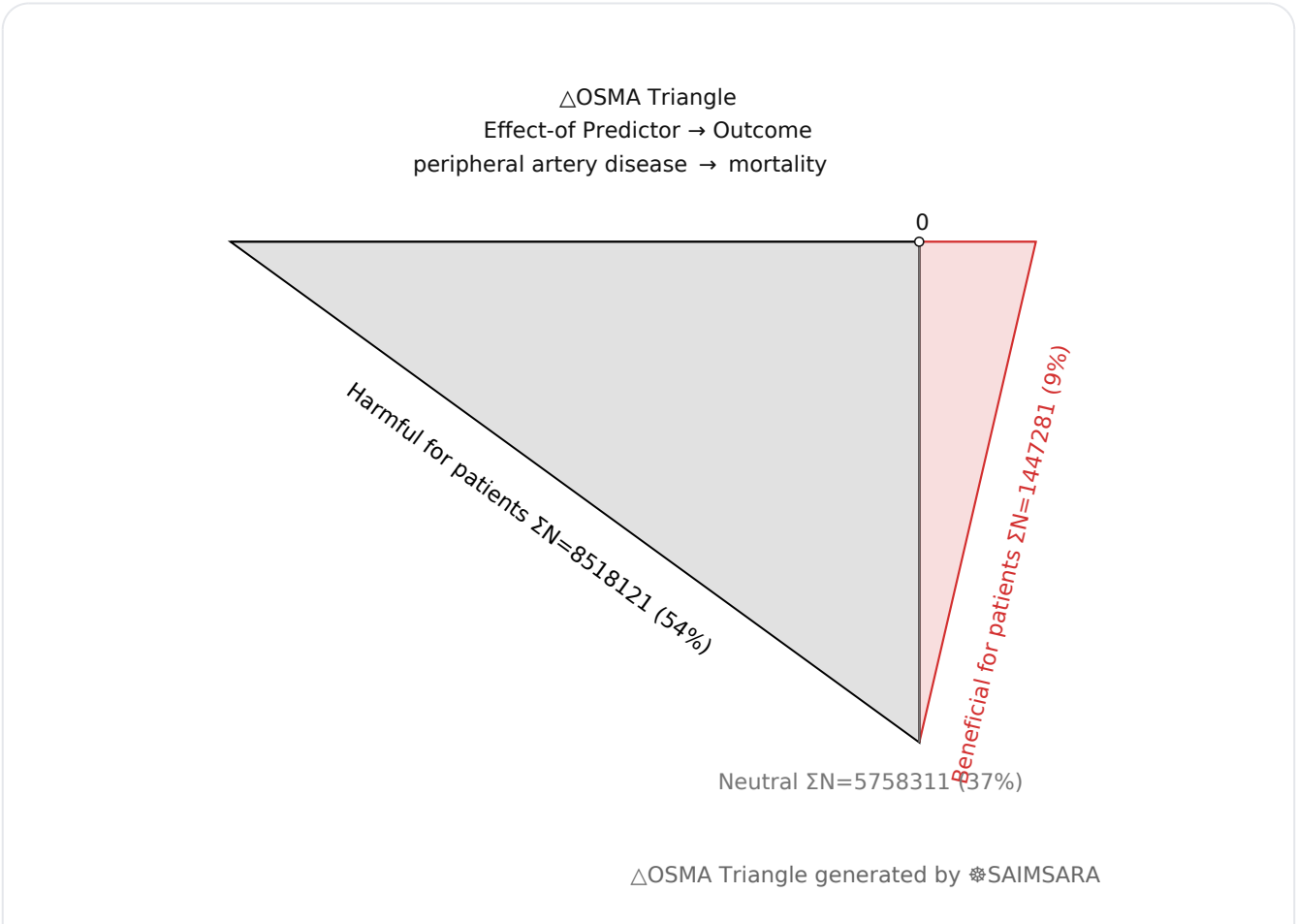
- Source: Europe PMC
- Scope: Titles/Abstracts (tiab)
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
- Total Abstracts/Papers: 4394
- Downloaded Abstracts/Papers: 4394
- Included original Abstracts/Papers: 2149
- Total study participants (naïve ΣN): 15723713


Identification of studies via EPMC (titles/abstracts)
Identification
Records identified:
n=4394
Records excluded:
n=0
Screening
Records assessed for eligibility
n=4394
Records excluded:
n=2245
Included
Studies included in review
n=2149
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
peripheral artery disease → mortality
0
Harmful for patients ΣN=8518121 (54%)
Beneficial for patients ΣN=1447281 (9%)
Neutral ΣN=5758311 (37%)
△OSMA Triangle generated by ☸SAIMSARA

Outcome-Sentiment Meta-Analysis (OSMA): *(LLM-only)*

Frame: Effect-of Predictor → Outcome • *Source*: Europe PMC

Outcome: mortality Typical timepoints: peri/post-op, 1-y. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: mortality, complications, survival.

Predictor: peripheral artery disease — exposure/predictor. Doses/units seen: 1.0 mg, 30 mg, 100 mg. Routes seen: iv, oral, sc, intramuscular. Typical comparator: women, nonpremature pad, diabetic subjects, individuals with only pad….

- **1) Beneficial for patients** — mortality with peripheral artery disease — [9], [15], [17], [18], [25], [43], [46], [102], [119], [125], [128], [134], [150], [152], [154], [156], [161], [174], [179], [185], [189], [196], [198], [210], [212], [217], [223], [249], [279], [281], [282], [285], [298], [329], [331], [340], [343], [344], [363], [383], [386], [409], [418], [423], [439], [445], [466], [470], [472], [498], [500], [512], [513], [520], [523], [540], [597], [610], [615], [659], [683], [684], [687], [691], [705], [711], [715], [731], [743], [750], [755], [757], [763], [765], [769], [777], [788], [801], [814], [819], [823], [836], [843], [853], [858], [880], [891], [907], [910], [917], [928], [943], [947], [951], [989], [992], [994], [1013], [1026], [1036], [1104], [1107], [1115], [1116], [1123], [1190], [1193], [1194], [1199], [1246], [1248], [1313], [1320], [1325], [1339], [1350], [1389], [1395], [1442], [1468], [1489], [1574], [1633], [1635], [1637], [1660], [1665], [1668], [1709], [1710], [1717], [1783], [1790], [1791], [1797], [1800], [1804], [1890], [1894], [1895], [1980], [1981], [1983], [1984], [1986], [1988], [1997], [2040], [2043], [2125] — ΣN=1447281
- **2) Harmful for patients** — mortality with peripheral artery disease — [1], [2], [3], [4], [6], [7], [8], [10], [11], [13], [14], [16], [19], [20], [21], [22], [23], [24], [27], [30], [32], [34], [36], [39], [42], [44], [45], [48], [49], [50], [78], [91], [92], [93], [95], [96], [100], [101], [103], [104], [107], [108], [109], [111], [113], [118], [121], [122], [124], [126], [135], [143], [148], [151], [157], [158], [159], [160], [162], [163], [165], [166], [167], [170], [171], [172], [173], [175], [176], [177], [181], [183], [186], [187], [188], [190], [191], [192], [195], [197], [199], [200], [201], [202], [203], [204], [205], [208], [211], [214], [215], [218], [219], [220], [222], [224], [225], [226], [228], [229], [230], [231], [232], [235], [236], [237], [238], [239], [241], [243], [246], [250], [276], [277], [278], [280], [283], [284], [286], [287], [288], [289], [290], [292], [293], [295], [296], [297], [299], [300], [326], [328], [330], [332], [334], [336], [337], [339], [342], [346], [347], [348], [349], [350], [351], [352], [354], [356], [357], [358], [359], [360], [361], [362], [365], [366], [367], [368], [371], [375], [376], [380], [381], [382], [384], [390], [392], [395], [399], [400], [404], [406], [408], [410], [411], [412], [415], [419], [420], [421], [425], [426], [427], [428], [433], [437], [438], [440], [441], [442], [443], [444],

[446], [448], [449], [451], [452], [453], [454], [455], [458], [459], [460], [461], [463], [464], [465], [467], [468], [469], [471], [474], [475], [478], [479], [480], [483], [484], [485], [486], [487], [489], [490], [492], [493], [495], [496], [497], [499], [502], [504], [505], [506], [508], [509], [510], [515], [516], [517], [519], [521], [522], [524], [525], [527], [528], [530], [531], [533], [534], [535], [536], [537], [538], [539], [541], [542], [543], [546], [547], [548], [549], [550], [578], [579], [583], [584], [585], [587], [588], [589], [590], [592], [593], [594], [595], [596], [598], [600], [601], [603], [605], [609], [612], [616], [617], [619], [620], [622], [623], [624], [626], [633], [634], [637], [642], [643], [644], [645], [646], [648], [649], [652], [653], [655], [656], [658], [660], [661], [662], [663], [666], [667], [668], [669], [670], [671], [672], [673], [674], [675], [678], [681], [685], [686], [688], [689], [690], [693], [694], [697], [698], [699], [700], [701], [702], [703], [706], [710], [712], [713], [717], [718], [719], [721], [722], [723], [724], [725], [726], [727], [728], [729], [730], [732], [733], [735], [737], [738], [740], [741], [744], [745], [746], [747], [748], [751], [752], [754], [756], [758], [759], [760], [761], [764], [767], [768], [770], [771], [772], [773], [775], [778], [779], [780], [781], [782], [784], [786], [789], [791], [793], [794], [795], [796], [797], [798], [799], [803], [805], [806], [810], [812], [818], [825], [827], [830], [831], [833], [838], [839], [841], [845], [847], [851], [852], [854], [856], [857], [859], [860], [866], [867], [868], [870], [871], [873], [874], [876], [877], [878], [879], [882], [885], [886], [887], [889], [892], [893], [895], [896], [899], [901], [902], [905], [906], [908], [909], [911], [912], [913], [915], [916], [918], [919], [924], [925], [926], [929], [931], [932], [934], [935], [936], [939], [941], [945], [946], [948], [949], [950], [952], [953], [954], [955], [956], [957], [958], [959], [960], [961], [963], [964], [965], [966], [967], [968], [969], [970], [971], [972], [973], [976], [978], [979], [982], [985], [986], [990], [991], [993], [995], [996], [997], [998], [999], [1000], [1001], [1002], [1003], [1004], [1006], [1007], [1008], [1009], [1010], [1011], [1012], [1016], [1017], [1018], [1019], [1020], [1021], [1025], [1027], [1028], [1029], [1031], [1040], [1042], [1043], [1044], [1048], [1049], [1050], [1101], [1102], [1103], [1105], [1106], [1108], [1109], [1110], [1111], [1112], [1113], [1114], [1117], [1118], [1119], [1121], [1122], [1124], [1125], [1151], [1152], [1153], [1154], [1156], [1159], [1160], [1161], [1162], [1165], [1170], [1172], [1173], [1175], [1177], [1178], [1179], [1180], [1191], [1196], [1198], [1200], [1228], [1229], [1233], [1234], [1236], [1240], [1244], [1245], [1249], [1250], [1301], [1302], [1305], [1307], [1308], [1309], [1310], [1311], [1314], [1316], [1317], [1321], [1322], [1323], [1324], [1326], [1327], [1328], [1329], [1330], [1331], [1332], [1334], [1335], [1336], [1337], [1338], [1340], [1341], [1342], [1343], [1344], [1345], [1346], [1351], [1353], [1355], [1356], [1357], [1359], [1361], [1363], [1364], [1366], [1372], [1373], [1375], [1376], [1377], [1382], [1383], [1385], [1386], [1387], [1388], [1391], [1393], [1397], [1400], [1405], [1406], [1417], [1419], [1421], [1422], [1424], [1425], [1426], [1427], [1428], [1430],

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- **3) No clear effect** — mortality with peripheral artery disease — [5], [12], [26], [28], [29], [31], [33], [35], [37], [38], [40], [41], [47], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [72], [73], [74], [75], [76], [77], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [94], [97], [98], [99], [105], [106], [110], [112], [114], [115], [116], [117], [120], [123], [127], [129], [130], [131], [132], [133], [136], [137], [138], [139], [140], [141], [142], [144], [145], [146], [147], [149], [153], [155], [164], [168], [169], [178], [180], [182], [184], [193], [194], [206], [207], [209], [213], [216], [221], [227], [233], [234], [240], [242], [244], [245], [247], [248], [251], [252], [253], [254], [255], [256], [257], [258],

[259], [260], [261], [262], [263], [264], [265], [266], [267], [268], [269], [270], [271], [272], [273], [274], [275], [291], [294], [301], [302], [303], [304], [305], [306], [307], [308], [309], [310], [311], [312], [313], [314], [315], [316], [317], [318], [319], [320], [321], [322], [323], [324], [325], [327], [333], [335], [338], [341], [345], [353], [355], [364], [369], [370], [372], [373], [374], [377], [378], [379], [385], [387], [388], [389], [391], [393], [394], [396], [397], [398], [401], [402], [403], [405], [407], [413], [414], [416], [417], [422], [424], [429], [430], [431], [432], [434], [435], [436], [447], [450], [456], [457], [462], [473], [476], [477], [481], [482], [488], [491], [494], [501], [503], [507], [511], [514], [518], [526], [529], [532], [544], [545], [551], [552], [553], [554], [555], [556], [557], [558], [559], [560], [561], [562], [563], [564], [565], [566], [567], [568], [569], [570], [571], [572], [573], [574], [575], [576], [577], [580], [581], [582], [586], [591], [599], [602], [604], [606], [607], [608], [611], [613], [614], [618], [621], [625], [627], [628], [629], [630], [631], [632], [635], [636], [638], [639], [640], [641], [647], [650], [651], [654], [657], [664], [665], [676], [677], [679], [680], [682], [692], [695], [696], [704], [707], [708], [709], [714], [716], [720], [734], [736], [739], [742], [749], [753], [762], [766], [774], [776], [783], [785], [787], [790], [792], [800], [802], [804], [807], [808], [809], [811], [813], [815], [816], [817], [820], [821], [822], [824], [826], [828], [829], [832], [834], [835], [837], [840], [842], [844], [846], [848], [849], [850], [855], [861], [862], [863], [864], [865], [869], [872], [875], [881], [883], [884], [888], [890], [894], [897], [898], [900], [903], [904], [914], [920], [921], [922], [923], [927], [930], [933], [937], [938], [940], [942], [944], [962], [974], [975], [977], [980], [981], [983], [984], [987], [988], [1005], [1014], [1015], [1022], [1023], [1024], [1030], [1032], [1033], [1034], [1035], [1037], [1038], [1039], [1041], [1045], [1046], [1047], [1051], [1052], [1053], [1054], [1055], [1056], [1057], [1058], [1059], [1060], [1061], [1062], [1063], [1064], [1065], [1066], [1067], [1068], [1069], [1070], [1071], [1072], [1073], [1074], [1075], [1076], [1077], [1078], [1079], [1080], [1081], [1082], [1083], [1084], [1085], [1086], [1087], [1088], [1089], [1090], [1091], [1092], [1093], [1094], [1095], [1096], [1097], [1098], [1099], [1100], [1120], [1126], [1127], [1128], [1129], [1130], [1131], [1132], [1133], [1134], [1135], [1136], [1137], [1138], [1139], [1140], [1141], [1142], [1143], [1144], [1145], [1146], [1147], [1148], [1149], [1150], [1155], [1157], [1158], [1163], [1164], [1166], [1167], [1168], [1169], [1171], [1174], [1176], [1181], [1182], [1183], [1184], [1185], [1186], [1187], [1188], [1189], [1192], [1195], [1197], [1201], [1202], [1203], [1204], [1205], [1206], [1207], [1208], [1209], [1210], [1211], [1212], [1213], [1214], [1215], [1216], [1217], [1218], [1219], [1220], [1221], [1222], [1223], [1224], [1225], [1226], [1227], [1230], [1231], [1232], [1235], [1237], [1238], [1239], [1241], [1242], [1243], [1247], [1251], [1252], [1253], [1254], [1255], [1256], [1257], [1258], [1259], [1260], [1261], [1262], [1263], [1264], [1265], [1266], [1267], [1268], [1269], [1270], [1271], [1272], [1273], [1274], [1275], [1276],

[1277], [1278], [1279], [1280], [1281], [1282], [1283], [1284], [1285], [1286], [1287], [1288], [1289], [1290], [1291], [1292], [1293], [1294], [1295], [1296], [1297], [1298], [1299], [1300], [1303], [1304], [1306], [1312], [1315], [1318], [1319], [1333], [1347], [1348], [1349], [1352], [1354], [1358], [1360], [1362], [1365], [1367], [1368], [1369], [1370], [1371], [1374], [1378], [1379], [1380], [1381], [1384], [1390], [1392], [1394], [1396], [1398], [1399], [1401], [1402], [1403], [1404], [1407], [1408], [1409], [1410], [1411], [1412], [1413], [1414], [1415], [1416], [1418], [1420], [1423], [1429], [1431], [1433], [1434], [1435], [1438], [1439], [1440], [1441], [1443], [1451], [1453], [1456], [1459], [1462], [1463], [1464], [1466], [1469], [1472], [1473], [1474], [1483], [1487], [1494], [1498], [1499], [1507], [1509], [1518], [1525], [1526], [1529], [1532], [1534], [1543], [1548], [1550], [1552], [1553], [1564], [1572], [1573], [1578], [1580], [1581], [1585], [1586], [1588], [1589], [1595], [1597], [1601], [1602], [1603], [1604], [1605], [1606], [1607], [1608], [1609], [1610], [1611], [1612], [1613], [1614], [1615], [1616], [1617], [1618], [1619], [1620], [1621], [1622], [1623], [1624], [1625], [1626], [1629], [1630], [1631], [1640], [1645], [1647], [1651], [1658], [1662], [1663], [1669], [1671], [1676], [1677], [1679], [1680], [1681], [1682], [1684], [1685], [1688], [1690], [1694], [1695], [1697], [1699], [1703], [1713], [1715], [1718], [1719], [1723], [1724], [1727], [1729], [1737], [1739], [1741], [1744], [1745], [1746], [1747], [1748], [1751], [1752], [1753], [1754], [1755], [1756], [1757], [1758], [1759], [1760], [1761], [1762], [1763], [1764], [1765], [1766], [1767], [1768], [1769], [1770], [1771], [1772], [1773], [1774], [1775], [1776], [1778], [1779], [1781], [1782], [1784], [1786], [1788], [1792], [1796], [1798], [1799], [1802], [1803], [1805], [1806], [1808], [1809], [1811], [1812], [1813], [1815], [1818], [1819], [1822], [1823], [1824], [1826], [1827], [1828], [1829], [1830], [1831], [1832], [1833], [1834], [1835], [1836], [1837], [1838], [1839], [1840], [1841], [1842], [1843], [1844], [1845], [1846], [1847], [1848], [1849], [1850], [1851], [1852], [1853], [1854], [1855], [1856], [1857], [1858], [1859], [1860], [1861], [1862], [1863], [1864], [1865], [1866], [1867], [1868], [1869], [1870], [1871], [1872], [1873], [1874], [1875], [1878], [1880], [1883], [1884], [1887], [1888], [1889], [1892], [1899], [1900], [1901], [1902], [1903], [1904], [1905], [1906], [1907], [1908], [1909], [1910], [1911], [1912], [1913], [1914], [1915], [1916], [1917], [1918], [1919], [1920], [1921], [1922], [1923], [1924], [1925], [1926], [1927], [1928], [1929], [1932], [1933], [1934], [1936], [1940], [1941], [1942], [1943], [1944], [1945], [1947], [1950], [1951], [1953], [1956], [1957], [1958], [1959], [1961], [1962], [1965], [1967], [1970], [1971], [1973], [1992], [2001], [2002], [2003], [2004], [2005], [2006], [2007], [2008], [2009], [2010], [2011], [2012], [2013], [2014], [2015], [2016], [2017], [2018], [2019], [2020], [2021], [2022], [2023], [2024], [2025], [2027], [2030], [2031], [2034], [2035], [2036], [2039], [2044], [2046], [2048], [2052], [2053], [2055], [2059], [2060], [2064], [2066], [2067], [2068], [2069], [2071], [2077], [2079], [2080], [2082], [2083], [2084], [2086], [2088], [2089],

[2091], [2093], [2094], [2095], [2097], [2098], [2099], [2107], [2108], [2109], [2110], [2112], [2113], [2114], [2115], [2116], [2119], [2123], [2127], [2128], [2130], [2131], [2135], [2137], [2138], [2140], [2142], [2146], [2147] — ΣN=5758311

1) Introduction

Peripheral artery disease (PAD) is a prevalent manifestation of systemic atherosclerosis, characterized by narrowed arteries that reduce blood flow to the limbs. It is a significant public health concern, strongly associated with increased cardiovascular morbidity and mortality [39, 674, 1859]. The global burden of PAD, including its associated mortality and disability-adjusted life years, continues to rise, particularly in specific demographic and geographic regions [67, 130, 1817]. Understanding the multifaceted factors influencing mortality in PAD patients is crucial for improving patient outcomes and guiding targeted therapeutic strategies.

2) Aim

This paper aims to synthesize recent evidence on peripheral artery disease mortality, identifying key risk factors, prognostic indicators, and the impact of various interventions, as extracted and structured by a multilayer AI research agent.

3) Methods

Systematic review with multilayer AI research agent: keyword normalization, retrieval & structuring, and paper synthesis (see SAIMSARA About section for details).

- **Bias:** Qualitatively inferred from study design fields. The included studies primarily consist of cohort designs, with a mix of prospective and retrospective approaches, and some randomized controlled trials (RCTs). This introduces a risk of selection bias and confounding, particularly in observational studies. Case series and mixed-design studies further contribute to heterogeneity in evidence strength.

4) Results

4.1 Study characteristics

The studies predominantly employed cohort designs, including both prospective and retrospective analyses, with some randomized controlled trials and mixed-design studies. Populations varied widely, encompassing patients with sonographically confirmed PAD, individuals from national health surveys, specific disease cohorts (e.g., type 2 diabetes, chronic kidney disease, severe aortic

stenosis, COVID-19), and those undergoing various revascularization procedures or amputations. Follow-up periods ranged from in-hospital mortality to long-term assessments spanning 5 to 10 years, with some projections extending to 2040.

4.2 Main numerical result aligned to the query

For 30-day mortality rates specifically reported for PAD patients or procedures where PAD was a primary indication or significant comorbidity, the median rate was 4.3% [275, 78, 5, 84, 85, 23, 36, 79, 88, 514, 546, 1199, 1771, 2145, 1826, 1935, 2052, 2123, 2132, 2143, 1993]. The range for 30-day mortality in these contexts was from 0.03% to 29% [1199, 2132]. This wide range reflects the diverse patient populations, procedural risks, and study settings.

4.3 Topic synthesis

- **Comorbidities as Mortality Predictors:** Coexisting conditions significantly elevate mortality risk. Chronic kidney disease (CKD) or end-stage renal disease (ESRD) with PAD is associated with substantially elevated risks of all-cause and cardio-cerebrovascular disease (CCD) mortality (adjusted HR 3.25 for all-cause, 4.76 for CCD) [4], and higher in-hospital mortality [1244, 186, 238, 366]. Type 2 diabetes (T2D) with PAD increases all-cause and cardiovascular mortality (adjusted HR 1.12 and 1.13, respectively) [16, 208, 325, 1328, 1652, 1773, 2092, 2096, 1016, 700, 721], particularly if uncontrolled (HbA1c >10.0%) [1326]. Depression in PAD patients is linked to increased all-cause mortality (HR 1.24) [91, 1455, 1467] and highest mortality risk when combined with T2D (HR 2.209) [22]. Coronary artery disease (CAD) is a strong predictor of mortality in PAD patients [192, 270, 754, 931, 1931, 1934, 1968, 1975, 1988, 1999, 1819, 1920, 1897, 2080, 2056, 2069, 2123], with PAD independently associated with worse outcomes after acute myocardial infarction (AMI) (adjusted OR 1.25 for in-hospital mortality) [93, 113, 352, 721, 868, 899, 1173, 1820, 1648]. Heart failure (HF) and atrial fibrillation (AF) also increase mortality risk in PAD patients [1338, 454, 517, 689, 790, 662, 1593, 1142, 1606, 1608, 1732, 365]. Chronic obstructive pulmonary disease (COPD) is associated with higher in-hospital mortality (OR 1.16) [1161, 360, 1787]. Frailty and malnutrition are significant predictors of mortality (HR 2.11 for frailty, HR 4.02 for low LBMI) [143, 290, 202, 733, 186].
- **Biomarkers for Risk Stratification:** Several biomarkers show promise for predicting mortality. Leucine-rich α-2 glycoprotein 1 (LRG1) is an independent predictor of 10-year all-cause (HR 3.12) and cardiovascular (HR 2.58) mortality in PAD patients [2]. Elevated cardiac troponins on admission are associated with increased all-cause mortality (HR 2.85) [100, 191, 328]. Inflammatory markers like hs-CRP and C-reactive protein-to-albumin ratio (CAR) are linked to increased all-cause mortality (HR 3.11 for high CAR) [48, 49, 740, 542, 887]. FGF-23 (HR 1.35) [107] and urinary Galectin-3 (uGal-3/cr) (HR 1.71) [175] predict all-cause

mortality. Elevated plasma trimethylamine N-oxide (TMAO) (HR 2.06) [356] and YKL-40 (HR 1.66) [241] are also associated with increased mortality.

- **Impact of Interventions and Therapies:** Guideline-directed medical therapy (GDMT) is associated with lower mortality (adjusted HR 0.329) [25]. Statin therapy reduces all-cause mortality (HR 0.87 for women) [102, 318, 743, 1266, 1830, 2003, 917] and cardiovascular death [318, 917]. Dual pathway inhibition with low-dose rivaroxaban plus aspirin reduces overall (HR 0.82) and cardiovascular (HR 0.78) mortality [156, 413, 498, 520, 769, 1077, 1214, 1218]. GLP-1 receptor agonists are beneficial in PAD, reducing revascularization and all-cause mortality (OR 0.55) [125, 150, 174, 258]. Surgical revascularization for lower extremity artery disease (LEAD) is associated with decreased adjusted mortality rates compared to percutaneous transluminal angioplasty (PTA) [344, 885]. However, some studies show no significant difference in mortality between endovascular therapy and vein bypass [31, 110] or between paclitaxel-coated and uncoated devices [18, 155, 180, 209, 333, 843, 1034, 1144, 736, 476, 398, 245]. Exercise-based rehabilitation is fundamental for reducing high cardiovascular mortality rates [66, 540, 1509].
- **Prognostic Tools and Scores:** The CHA2DS2-VASc score is independently associated with adverse long-term outcomes and mortality in PAD patients [148, 1117]. Machine learning models can predict in-hospital mortality in PAD patients with adequate predictability [82, 668, 870], and also predict future mortality in general PAD populations [544]. The Hospital Frailty Risk Score (HFRS) predicts mortality in ESRD patients with PAD [186].
- **Demographic and Geographic Disparities:** PAD mortality is projected to increase in Brazil by 10.99% by 2040, with a notable rise among women [12]. Sub-Saharan Africa (SSA) has seen sharp increases in PAD burden and mortality, contrasting with global declines [87, 508]. Globally, while the burden remains substantial, age-standardized mortality rates are projected to decline, yet disparities persist across regions [130, 89]. Women with PAD often face higher mortality risks in specific contexts, such as after open abdominal aortic aneurysm repair (OR 3.96) [78], lower extremity peripheral vascular intervention (OR 1.21) [486, 723, 741], or CABG [2145, 1627]. Older age is consistently identified as a risk factor for mortality [97, 191, 1058, 1067, 1118, 1205, 1341, 1488, 1849, 1993, 2133, 1771].
- **Specific PAD Manifestations and Severity:** Chronic limb-threatening ischemia (CLTI), the most severe form of PAD, is associated with significant amputation and mortality risk [72, 672, 680, 835, 1530, 1642, 511, 492, 204]. A higher number of leg arteries with PAD is associated with a progressively higher risk of mortality [190]. High ankle-brachial pressure index (ABI >1.4) is associated with elevated cardiovascular and all-cause mortality, similar to PAD [21]. Lower ankle systolic blood pressure (SBP) quartiles predict higher mortality [20].
- **Perioperative and Procedural Risks:** Concurrent abdominal stoma is associated with increased postoperative mortality after open lower extremity revascularization (LER) [23].

Acute limb ischemia (ALI) after percutaneous coronary intervention (PCI) is associated with a 1.6 times greater risk of in-hospital mortality, with PAD being the strongest predictor of post-PCI ALI [30, 352]. PAD is independently associated with increased mortality in patients undergoing transcatheter aortic valve replacement (TAVR) [6, 42, 69, 205, 275, 712, 1028, 1366, 1428, 1788, 1803, 1826, 549, 923]. Major amputations are associated with high mortality rates [36, 231, 300, 52, 546]. Postoperative delirium is associated with increased mortality after lower extremity bypass (HR 2.0) [877]. Pre-admission opioid use is linked to higher all-cause mortality after revascularization [181]. High inflammation-related biomarkers (e.g., NLR) are associated with increased mortality after PCI for PAD [188, 437, 348].

5) Discussion

5.1 Principal finding

The median 30-day mortality rate for patients with peripheral artery disease (PAD) or undergoing PAD-related procedures is 4.3% [275, 78, 5, 84, 85, 23, 36, 79, 88, 514, 546, 1199, 1771, 2145, 1826, 1935, 2052, 2123, 2132, 2143, 1993], with a wide observed range from 0.03% to 29% [1199, 2132], underscoring the significant and variable risk of early mortality associated with this condition and its management.

5.2 Clinical implications

- **Aggressive Comorbidity Management:** Clinicians should prioritize aggressive screening and management of comorbidities like CKD, T2D, CAD, and depression in PAD patients, given their strong association with increased mortality [4, 16, 22, 91, 93, 113, 1338].
- **Biomarker-Guided Risk Stratification:** Incorporating emerging biomarkers such as LRG1, cardiac troponins, and inflammatory markers (hs-CRP, CAR) can enhance early risk stratification and guide intensified interventions for high-risk PAD patients [2, 100, 49, 191, 328, 740].
- **Optimized Therapeutic Strategies:** Adherence to guideline-directed medical therapy (GDMT), including statins and dual antiplatelet therapy (DAPT), and considering GLP-1 receptor agonists, is crucial for reducing mortality in PAD patients [25, 102, 125, 150, 156, 318, 891].
- **Enhanced Perioperative Surveillance:** Patients undergoing PAD-related surgical or endovascular interventions, especially those with additional risk factors like frailty, malnutrition, or hostile vascular access, require heightened perioperative monitoring for complications that directly impact mortality [23, 143, 202, 205, 290].

- **Addressing Health Disparities:** Awareness of demographic and geographic disparities in PAD burden and mortality, such as higher rates in women and specific regions, should inform targeted screening and intervention programs [12, 78, 87, 486, 723, 741].

5.3 Research implications / key gaps

- **Standardized Mortality Reporting:** Develop standardized definitions and reporting timepoints for PAD-related mortality across studies to enable more robust meta-analyses and comparisons [e.g., 30-day, 1-year, 5-year all-cause and cardiovascular mortality].
- **Prospective Comparative Effectiveness:** Conduct large-scale prospective comparative effectiveness research comparing surgical and endovascular revascularization strategies in diverse PAD populations, with long-term mortality as a primary endpoint [e.g., 31, 110, 344, 885].
- **Biomarker Integration Algorithms:** Develop and validate clinical algorithms that integrate novel biomarkers (e.g., LRG1, uGal-3, TMAO, YKL-40, TFF3, GDF15) with established risk factors to improve mortality prediction in PAD patients [e.g., 2, 107, 175, 356, 241, 337, 447].
- **Intervention for Depression in PAD:** Investigate the impact of targeted depression screening and treatment interventions on all-cause and cardiovascular mortality in PAD patients through randomized controlled trials [e.g., 22, 91, 1455].
- **Impact of Socioeconomic Factors:** Explore the causal pathways through which socioeconomic factors and health literacy contribute to PAD mortality disparities, informing public health interventions [e.g., 428, 538, 605, 606, 807].

5.4 Limitations

- **Heterogeneous Study Designs** — The varied study designs (cohort, RCT, mixed) and methodologies limit direct comparability and the strength of aggregated conclusions.
- **Inconsistent Outcome Definitions** — Mortality endpoints, follow-up durations, and reported statistics are not uniform, making quantitative synthesis challenging.
- **Observational Data Reliance** — A significant portion of the evidence is observational, which inherently carries risks of confounding and bias, impacting causal inference.
- **Geographic and Demographic Specificity** — Many findings are specific to certain populations or regions, limiting generalizability to a global or broader PAD patient cohort.
- **Missing Data and Unspecified Factors** — Several summaries lack details on specific study characteristics, such as directionality, or comprehensive reporting of all relevant

covariates, potentially obscuring important associations.

5.5 Future directions

- **Standardize Outcome Reporting:** Implement core outcome sets for PAD mortality studies.
- **Conduct Large RCTs:** Evaluate interventions with long-term mortality endpoints.
- **Validate Novel Biomarkers:** Test new biomarkers in diverse PAD cohorts.
- **Develop Integrated Risk Models:** Combine clinical, imaging, and biomarker data.
- **Investigate Health Equity:** Research interventions to reduce disparities.

6) Conclusion

The median 30-day mortality rate for patients with peripheral artery disease (PAD) or undergoing PAD-related procedures is 4.3% [275, 78, 5, 84, 85, 23, 36, 79, 88, 514, 546, 1199, 1771, 2145, 1826, 1935, 2052, 2123, 2132, 2143, 1993], highlighting the substantial and variable early mortality risk in this population. This risk is compounded by numerous comorbidities and can be mitigated by effective medical therapies. The reliance on diverse study designs and inconsistent outcome reporting is a significant limitation affecting the certainty of aggregated findings. A critical next step is to conduct large-scale prospective comparative effectiveness trials with standardized mortality endpoints to better inform clinical decision-making.

References

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Figure 1. Publication-year distribution of included originals

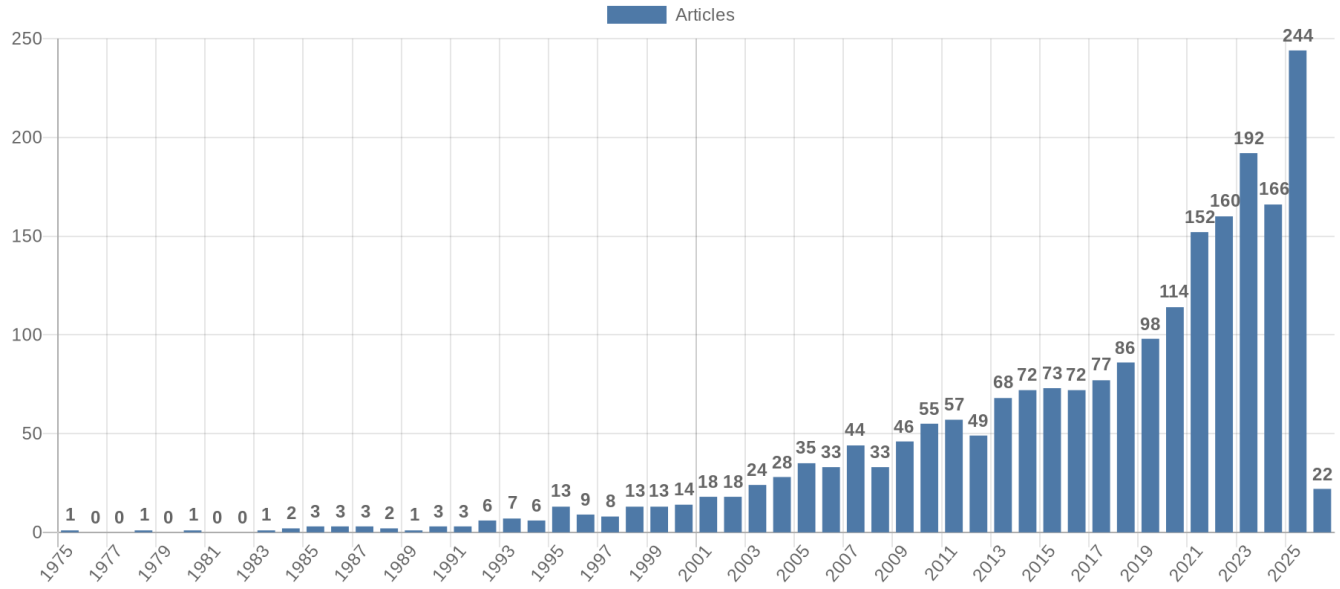

Figure 2. Study-design distribution of included originals

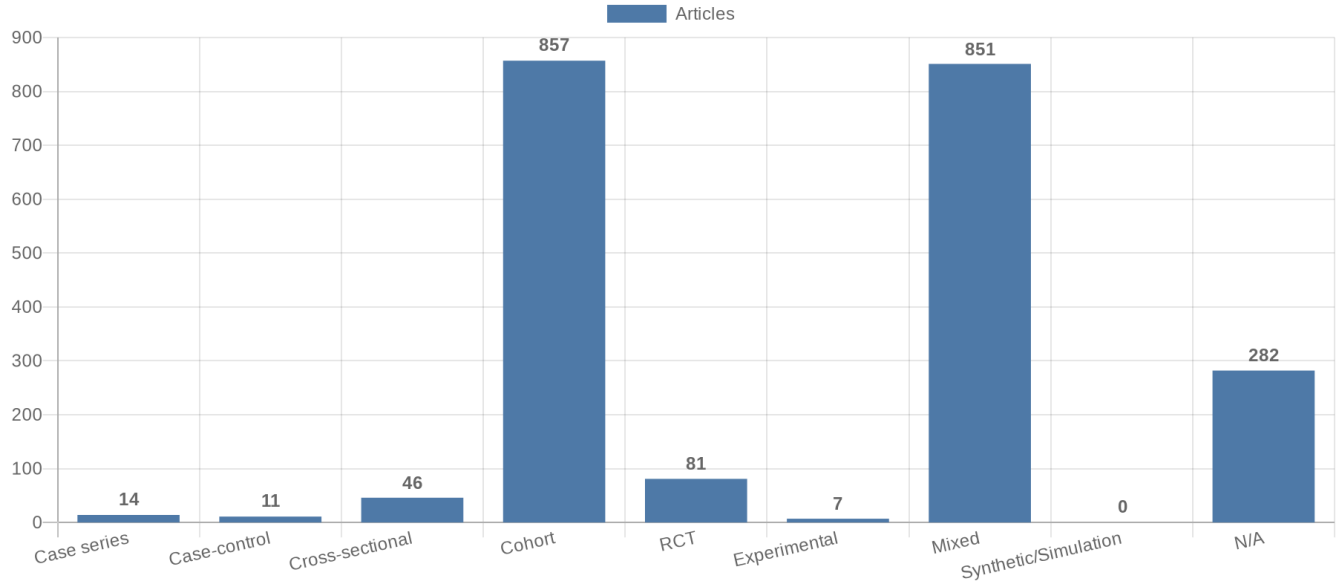

Figure 3. Study-type (directionality) distribution of included originals

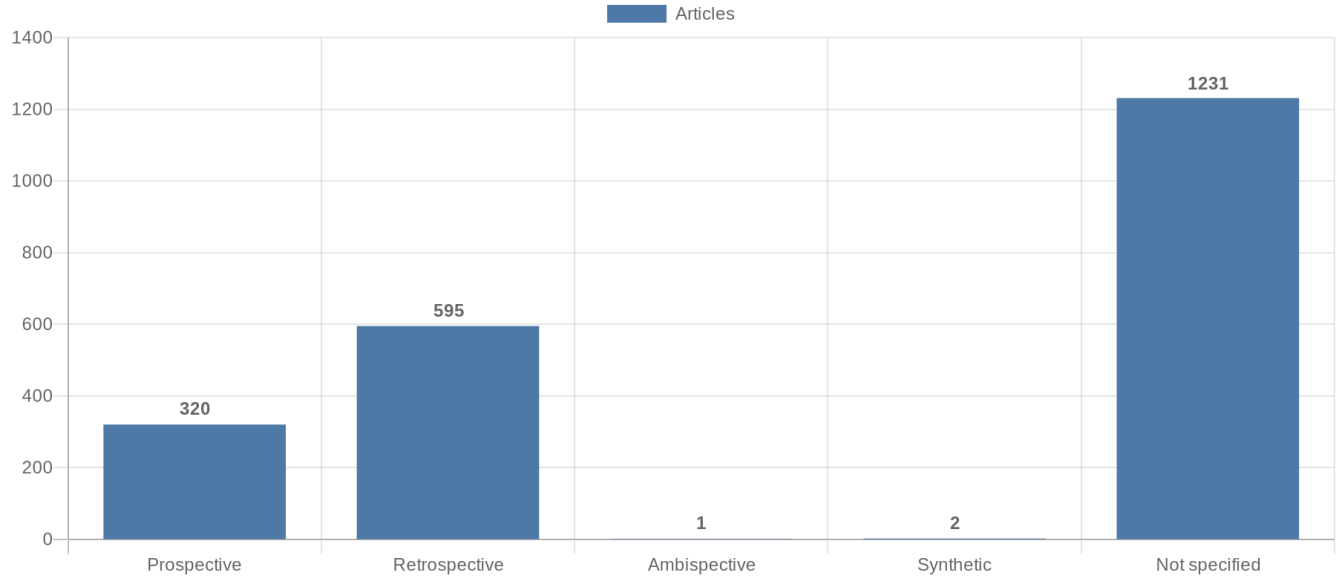

Figure 4. Main extracted research topics

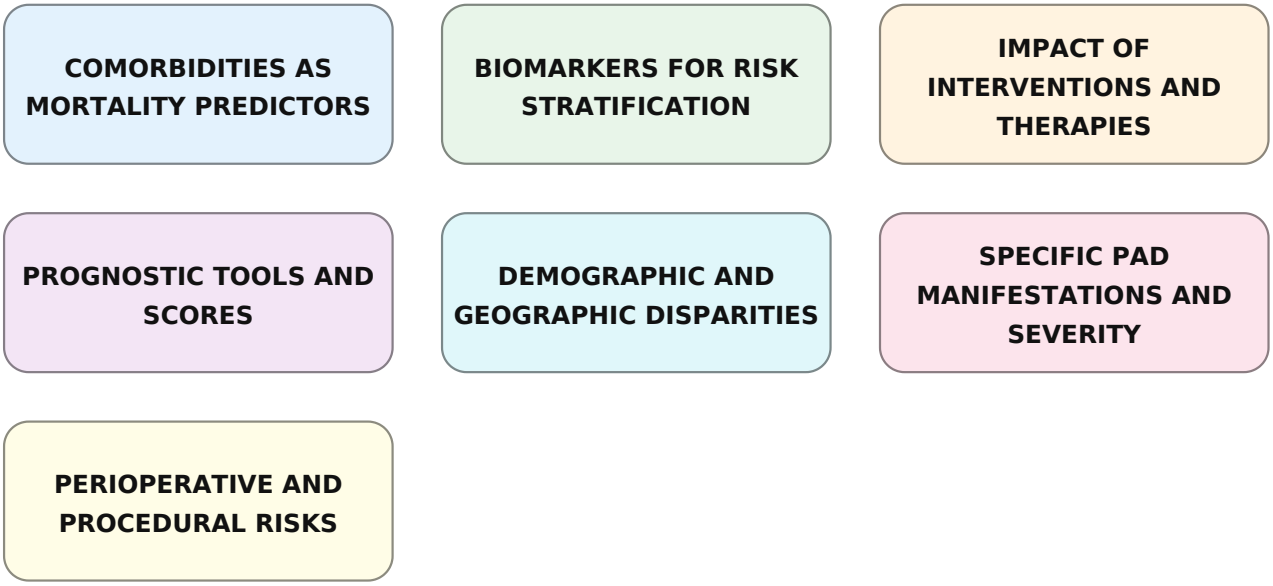

Figure 5. Limitations of current studies (topics)

Figure 6. Future research directions (topics)