

ORIGINAL ARTICLE

The Influence of Primary Atherosclerotic Diseases on the Occurrence of Secondary Disease

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Abstract

Background: Atherosclerosis is a condition in which fats, cholesterol, fibrin, and other substances accumulate into plaque on the arterial walls. Plaque can harden and narrow the arteries, in turn limiting the blood flow and resulting in diseases, such as acute myocardial infarction (AMI), ischemic stroke (IS), or peripheral arterial disease (PAD). There is a fairly high risk of a secondary atherosclerotic event if patients are not treated after the primary episode.

Objective: To calculate the statistical probability of developing AMI, IS, or PAD after treating the primary disease.

Methods: Data for statistical probability studies included 507,690 patients with primary atherosclerotic disease, who were in treatment during the study period and who did or did not develop a secondary atherosclerotic disease event.

Result: Statistical probability data indicate that few AMI patients can develop IS (2.99%) or PAD (2.86%) as a secondary disease. Patients with primary diagnoses of IS showed a 5.07% risk of developing PAD and a 0.95% risk of developing AMI; however, PAD patients showed a higher probability for both AMI (9.17%) and IS (8.79%).

Conclusion: Secondary atherosclerotic disease episodes after IS, AMI, and PAD were confirmed by statistical probability and are consistent with data from the literature. The study revealed that a primary PAD event leads to high rates of secondary episodes, and special attention should be given to the diagnosis and treatment of PAD in order to decrease the occurrence of secondary events.

Keywords: Peripheral Arterial Disease; Amputation; Myocardial Ischemia; Cerebrovascular Disease; Lower Extremity; Aging; Diabetes Mellitus.

Introduction

Atherosclerosis is a multifactorial inflammatory disease, often asymptomatic, which affects 10% of the world population and starts with a vascular endothelial dysfunction.¹ Its progression leads to the formation of fat plaques on the internal walls of vessels,² in several types of arteries, resulting in pathologies such as acute myocardial infarction (AMI), ischemic stroke (IS), and peripheral artery disease (PAD).

Acute myocardial infarction is responsible for 15 million deaths a year worldwide; most deaths occur within the first few hours after the symptoms appear, and about 80% in the first 24 h.³

Ischemic stroke is one of the most important causes of deaths and neurological events around the world.⁴ The mortality associated with the IS is about 10% in the first month and about 40% at the end of the first year after the onset of the disease. The consequences are irreversible, reducing the quality of life of patients; 70% of the patients do not return to work, and 30% require walking support.⁵

Peripheral artery disease affects 20% of the people over 70 years of age and 3-6% of the people under 60 years of age.⁶ Approximately 70% of the patients are asymptomatic⁷ or the symptoms can be confused with other pathologies and neglected, leading to late diagnosis, and amputation.² In addition, the high prevalence of PAD is associated with both coronary artery disease and cerebrovascular disease.⁸

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Several studies report the association of these atherosclerotic pathologies. Most of them report the association of AMI with IS, showing the results of the incidence of one after the other one either during hospitalization or within the first year of monitoring. However, to the best of our knowledge, no reports can be found in the literature, showing the relationship of these three diseases – AMI, IS, and PAD – and the probability of their occurrence. Moreover, rare studies report PAD as a primary disease and as the risk factor for the development of AMI and IS. In this light, the present study describes the probability of occurrence of these three diseases over a five-year period after the primary diagnosis. The study was carried out using clinical diagnoses based on imaging tests, and the relationship among them was calculated using statistical probability.

Methods

Search in the database

This study's search was conducted in the Web of Science and PubMed electronic databases in October 2020 in order to identify the studies published from 1995 to 2020 that were relevant for this proposal. The search was carried out using the subject headings (acute coronary disease) OR (myocardial infarction) OR (coronary artery disease) OR (cardiovascular disease) OR (diagnosis of myocardial infarction) OR (ischemic stroke) OR (cerebral artery disease) OR (cerebrovascular disease) OR (diagnosis of ischemic stroke) OR (peripheral arterial disease) OR (diagnosis of peripheral arterial disease) OR (peripheral obstructive arterial disease) OR (peripheral arterial ischemia).

Inclusion criteria

The papers were selected after reading the titles and the abstracts. Only English language studies were included and evaluated. In the first inclusion criteria, the studies were included if the results of the clinical diagnosis were confirmed by imaging techniques for at least one of following atherosclerotic diseases: Acute Myocardial Infarction, Ischemic Stroke, or Peripheral Arterial Disease.

The papers included in the first inclusion criterion were evaluated using the second inclusion criterion, which correspond to treated patients who have developed at least one of the atherosclerotic diseases

that form part of the first inclusion criteria. The diseases identified in the first and second inclusion criteria were called primary and secondary diagnoses, respectively.

The papers that reported the occurrence of the disease, but that did not report the confirming diagnosis, were excluded. The papers that did not report the occurrence of secondary disease were excluded. The collected data included the full reference of the article, study size, and the number of people who experienced the atherosclerotic diseases. The papers that met the inclusion criteria were in full.

Data extraction

The total number of patients who participated in the study shown in each paper, the number of patients who developed the primary disease, and the number of patients who developed the secondary disease were used to construct the tables, and were then analyzed for statistical treatments. The papers used in this study did not reveal the patients who developed a re-incidence of the primary disease. The set of patients reported in the papers used in this study were those who were treated or were under treatment at the moment of the secondary disease.

Statistical analysis

The statistical treatment was carried out to determine two sets of analysis: *i*) the probability of developing a secondary disease after each primary disease, and *ii*) the probability of developing a specific secondary disease after the specific primary disease.

The data for the first set of analysis included *(i)* the total number of patients found in the papers and were separated into three groups as follows: **Group 1 (G1)** – Patients who developed the primary disease AMI; **Group 2 (G2)** – Patients who developed the primary disease IS; **Group 3 (G3)** – Patients who developed the primary disease PAD. The statistical probability was calculated using the following equations:

$$P(A) = \frac{n_A}{N_{G1}} \quad (1)$$

$$P(B) = \frac{n_B}{N_{G1}} \quad (2)$$

$$P(C) = \frac{n_C}{N_{G2}} \quad (3)$$

$$P(D) = \frac{n_D}{N_{G2}} \quad (4)$$

$$P(E) = \frac{n_E}{N_{G3}} \quad (5)$$

$$P(F) = \frac{n_F}{N_{G3}} \quad (6)$$

Wherein:

P = Probability of Group (1, 2, or 3) patients to develop the secondary disease IS or PAD or AMI

n = Number of patients of G1 or G2 or G3 who developed the secondary disease IS or PAD or AMI, respectively

N = Total number of patients with primary disease AMI or IS or PAD

A = Number of patients of G1 who developed the secondary disease IS

B = Number of patients of G1 who developed the secondary disease PAD

C = Number of patients of G2 who developed the secondary disease AMI

D = Number of patients of G2 who developed the secondary disease PAD

E = Number of patients of G3 who developed the secondary disease AMI

F = Number of patients of G3 who developed the secondary disease IS

The data for the second set of analysis (ii) included only patients who have developed a secondary disease and were separated into three groups as follows: **Group 4** – Patients who developed the primary disease AMI and at least one secondary disease; **Group 5** – Patients who developed the primary disease IS and at least one secondary disease; and **Group 6** – Patients who developed the primary disease PAD and at least one secondary disease. The statistical probability was calculated using the following equations:

$$P(A) = \frac{n_A}{N_{G4}} \quad (1)$$

$$P(B) = \frac{n_B}{N_{G4}} \quad (2)$$

$$P(C) = \frac{n_C}{N_{G5}} \quad (3)$$

$$P(D) = \frac{n_D}{N_{G5}} \quad (4)$$

$$P(E) = \frac{n_E}{N_{G6}} \quad (5)$$

$$P(F) = \frac{n_F}{N_{G6}} \quad (6)$$

P(A) = Probability of the patient to develop IS as the secondary disease, given that the patient has developed AMI

n_A = Number of patients of G1 who developed the secondary disease IS

N_{G4} = Patients with primary disease AMI who developed at least one secondary disease

P(B) = Probability of the patient to develop PAD as the secondary disease, given that the patient has developed AMI

n_B = Number of patients of G1 who developed the secondary disease PAD

N_{G4} = Patients with primary disease AMI and at least one secondary disease

P(C) = Probability of the patient to develop AMI as the secondary disease, given that the patient has developed IS

n_C = Number of patients of G2 who developed the secondary disease AMI

N_{G5} = Patients with primary disease IS and at least one secondary disease

P(D) = Probability of the patient to develop PAD as the secondary disease, given that the patient has developed IS

n_D = Number of patients of G2 who developed the secondary disease PAD

N_{G5} = Patients with primary atherosclerotic disease IS and at least one secondary disease

P(E) = Probability of the patient to develop AMI as the secondary disease, given that the patient has developed PAD

n_E = Number of patients of G3 who developed the secondary disease AMI

N_{G6} = Patients with primary atherosclerotic disease PAD and at least one secondary disease

P(F) = Probability of the patient to develop IS as the secondary disease, given that the patient has developed PAD

n_F = Number of patients of G3 who developed the secondary disease IS

N_{G6} = Patients with primary atherosclerotic disease PAD and at least one secondary disease

Results

Studies included

The literature search resulted in 8,320 papers, which were selected according to the inclusion criteria. Duplicate papers were eliminated, resulting in 6,840 papers, which were analyzed according to the first inclusion criterion, resulting in 180 relevant papers for the study. The full text analysis led to the exclusion of 131 papers; therefore, 49 papers were used for data extraction and for the statistical treatment. The primary atherosclerotic disease diagnosis AMI was identified in 18 papers, IS in 14 papers, and PAD in 17 papers, as shown in the scheme of Figure 1.

The detailed data of the studies displayed in each evaluated paper are depicted in Tables 1, 2, and 3. The

data were organized (in the) according to the groups described in item 2.4., in which the number of patients diagnosed with the primary atherosclerotic disease is Group 1, Group 2, or Group 3.

In Table 1, Group 1 displays 83,804 patients diagnosed with AMI as the primary atherosclerotic disease, extracted from 18 papers; 2,508 patients diagnosed with IS, extracted from 14 papers; and 2,402 patients with PAD as the secondary atherosclerotic disease, extracted from 17 papers. Group 2 displays 385,756 patients diagnosed with IS as the primary atherosclerotic disease; 3,694 patients diagnosed with AMI; and 19,562 patients with PAD as the secondary atherosclerotic disease. Group 3 displays 38,130 patients diagnosed with PAD as the primary atherosclerotic

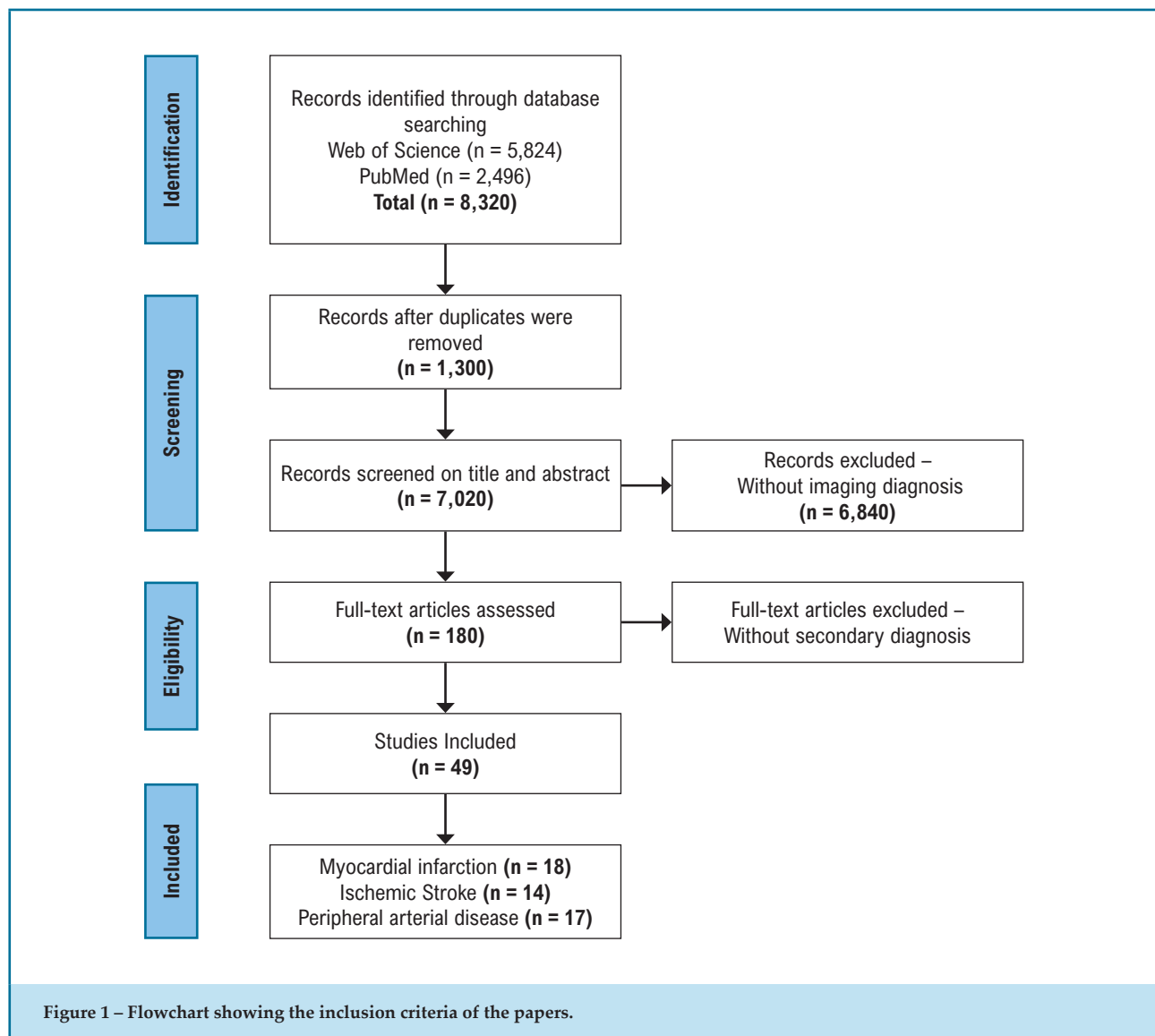


Table 1 – Patients diagnosed with the primary atherosclerotic disease groups, considering Group 1, AMI, Group 2, IS, and Group 3, PAD, and their corresponding secondary diseases

| GROUP 1 | | | | |
|-------------------|---------------------|--------------|------------------------|------------------|
| Primary Diagnosis | Secondary Diagnosis | | Only Primary Diagnosis | |
| AMI | IS | PAD | AMI | |
| 384 | 6 | 4 | 374 | ESCOSTEGUY, 2003 |
| 583 | 44 | 48 | 491 | ABBOTT, 2007 |
| 274 | 1 | 5 | 269 | BIANCHINI, 2018 |
| 592 | 10 | 7 | 575 | YILDIZ, 2019 |
| 903 | 47 | 38 | 818 | ABBOTT, 2007 |
| 144 | 3 | 1 | 140 | GERBER, 2012 |
| 528 | 7 | 10 | 511 | MATSUZAWA, 2013 |
| 1,022 | 61 | 42 | 919 | ABOYANS, 2005 |
| 5,446 | 333 | 166 | 4,947 | DALÉN, 2019 |
| 153 | 0 | 27 | 126 | OTOMO, 2013 |
| 4,077 | 45 | 0 | 4,032 | ASCIONE, 2002 |
| 2,985 | 48 | 0 | 2,937 | FILSOUFI, 2007 |
| 16,184 | 743 | 0 | 15,441 | BUCERIUS, 2003 |
| 19,224 | 270 | 2,054 | 16,900 | JOHN, 2000 |
| 1,779 | 29 | 0 | 1,750 | RICOTTA, 1995 |
| 1,760 | 52 | 0 | 1,708 | GUARAGNA, 2006 |
| 4,862 | 149 | 0 | 4,713 | MAGEDANZ, 2016 |
| 22,904 | 660 | 0 | 22,244 | FERREIRA, 2018 |
| Total | 83,804 | 2,508 | 2,402 | 78,894 |
| GROUP 2 | | | | |
| Primary Diagnosis | Secondary Diagnosis | | Only Primary Diagnosis | |
| IS | AMI | PAD | IS | Reference |
| 797 | 7 | 0 | 790 | TAKASUGI, 2017 |
| 204 | 7 | 0 | 197 | LIESIROVA, 2018 |
| 169 | 2 | 0 | 167 | DUCCI, 2016 |
| 45 | 3 | 11 | 31 | ASCIONE, 2002 |
| 729 | 5 | 0 | 724 | WEIMAR, 2008 |
| 465 | 2 | 0 | 463 | NEDELTCHEV, 2010 |
| 233 | 33 | 74 | 41 | DIAMOND, 2018 |
| 421 | 303 | 0 | 118 | HYSING, 2007 |
| 138 | 5 | 2 | 131 | KHATIB, 2018 |
| 366,551 | 2,785 | 19,176 | 344,590 | LICHTMAN, 2009 |

| | | | | | |
|----------------|--------------------------|----------------------------|---------------|-------------------------------|------------------|
| | 7,114 | 247 | 185 | 6,682 | HASSAN, 2012 |
| | 6,685 | 282 | 110 | 6,293 | HASSAN, 2012 |
| | 2,082 | 4 | 0 | 2,078 | ARBOIX, 2010 |
| | 120 | 9 | 4 | 107 | ABREU, 2020 |
| Total | 385,756 | 3,694 | 19,562 | 362,412 | |
| GROUP 3 | | | | | |
| | Primary Diagnosis | Secondary Diagnosis | | Only Primary Diagnosis | |
| | PAD | AMI | IS | PAD | Reference |
| | 3,096 | 93 | 71 | 2,932 | CACOUB, 2009 |
| | 237 | 13 | 5 | 219 | ARMSTRONG, 2014 |
| | 502 | 28 | 11 | 463 | ARMSTRONG, 2014 |
| | 16,440 | 1,563 | 1,589 | 13,288 | CARO, 2005 |
| | 756 | 33 | 22 | 701 | SMOLDEREN, 2015 |
| | 1,770 | 6 | 6 | 1,758 | FASHANDI, 2018 |
| | 2,155 | 19 | 19 | 2,117 | FASHANDI, 2018 |
| | 239 | 16 | 9 | 214 | SZCZEKLIK, 2018 |
| | 29 | 1 | 0 | 28 | BAUMHAKEL, 2018 |
| | 509 | 34 | 34 | 441 | VAINAS, 2005 |
| | 102 | 4 | 2 | 96 | SARKADI, 2015 |
| | 118 | 110 | 110 | 8 | STONE, 2014 |
| | 98 | 4 | 0 | 94 | BOTO, 2016 |
| | 117 | 2 | 1 | 114 | KALS, 2014 |
| | 461 | 57 | 26 | 378 | GOESSENS, 2007 |
| | 11,234 | 1,496 | 1,446 | 8,292 | BUDTZ-LILY, 2015 |
| | 267 | 18 | 3 | 246 | HUANG, 2007 |
| Total | 38,130 | 3,497 | 3,354 | 31,389 | |

AMI: acute myocardial infarction; IS: stroke; PAD: peripheral arterial disease.

disease; 3,497 patients diagnosed with AMI; and 3,354 patients with IS as the secondary atherosclerotic disease. The results of the probability calculation (Table 2) indicated that 2.99% of the patients with AMI as the primary atherosclerotic disease developed IS and 2.86% developed PAD, during or after treatment. The patients diagnosed with IS as the primary atherosclerotic disease show a 0.95% risk for developing AMI and a 5.07% risk for developing PAD. The patients diagnosed with PAD as the primary atherosclerotic disease show an 8.79% risk for developing IS and a 9.17% risk for AMI, as the secondary atherosclerotic disease.

Table 3 displays the number of patients who had the primary disease and at least one secondary disease. These data were used to calculate the probabilities of the occurrence of the specific secondary diseases for the patients who developed the secondary disease.

The data shown in Table 4 indicated that the probability of a primary AMI patient developing IS or PAD is about 50%; similar probabilities were found for PAD primary patients, which developed AMI or IS with about a 50% risk for each. An interesting result was found for primary IS patients, for whom the probability of developing PAD was about 84% and

Table 2 – Contingency table group of patients with the primary and secondary diagnoses

| PRIMARY DIAGNOSIS | SECONDARY DIAGNOSIS | | |
|-------------------|---------------------|---------------|----------------|
| | AMI | IS | PAD |
| AMI Group 1 | - | P(A) = 0.0299 | P(B) = 0.0286 |
| IS Group 2 | P(C) = 0.0095 | - | P(D) = 0.05071 |
| PAD Group 3 | P(E) = 0.0917 | P(F) = 0.0879 | - |

AMI: acute myocardial infarction; IS: stroke; PAD: peripheral arterial disease.

AMI, 16%. For all of the studies, the time necessary to contract the secondary disease was not calculated or evaluated.

Discussion

All of the patients in the studied papers were followed up after the primary atherosclerotic pathology. The secondary atherosclerotic disease was developed during the treatment. The diagnoses of all the diseases were proven by clinical imaging exams. The total number of patients (507,690) and the number of patients who developed the secondary atherosclerotic disease were used to calculate the statistical probability of the occurrence. When the primary atherosclerotic disease was AMI, the secondary was IS or PAD; when the primary disease was IS, the secondary was AMI or PAD; and when the primary disease was PAD, the secondary was AMI or IS.

The results of the statistical probability of the patients with AMI as the primary atherosclerotic disease indicated a low risk of occurrence of IS and PAD, namely 2.99% and 2.86%, respectively. Many published studies show that when the primary atherosclerotic disease is AMI, the prevalent secondary disease is IS. For instance, the data from a recent meta-analysis showed that the incidence of IS in patients within 30 days after myocardial infarction was about 10.9%, while within 31–180 days, it decreased to 2.3%. The study suggests that the reduction of the risk for the secondary disease was associated with the

use of statins and P2Y12 inhibitors.⁹ Another meta-analysis showed that 1.1% of the strokes occur during hospitalization, 1.2% at 30 days, and 2.1% at one year after the myocardial infarction.¹⁰ Another study showed that the incidence of ischemic stroke during the first month after an acute myocardial infarction indicated that the odds ratios ranged from 1.5 to 3.5% within one month, and 50% of them up to 5 days after the infarction.¹¹ Another report followed hospitalized patients in a 25-year study (1986 - 2011). The results indicated that 1.4% of the patients experienced an acute, first-ever stroke during hospitalization for acute myocardial infarction, and 10.8% died during hospitalization.¹² These data are in agreement with our results, indicating that the rates of IS after AMI were kept in recent decades.

Few results directly related to the development of PAD after AMI have been reported. The study published in 2010 showed that 5.9% of the patients with acute myocardial infarction which underwent primary percutaneous coronary intervention had been diagnosed with PAD within one year after the intervention.¹³ Another study reported that 4.9% of the patients suffered incident symptomatic PAD events during the follow-up period (two years) after cardiovascular events; however, the cardiovascular event was not specifically myocardial infarction.¹⁴ Interestingly, another study showed that 8.2% of the patients who developed PAD after myocardial infarction were older patients, who had co-morbidities and were less likely to be prescribed aspirin or a beta-blocker. The results showed that the number of patients that developed PAD was higher than the treated patients.¹⁵

The analysis of the patients with IS who developed AMI as the secondary disease was 0.95% and those who developed PAD was 5.07%. A meta-analysis using data until 2015 showed that 3% of the patients with ischemic stroke and with no cardiac history are at risk of developing AMI within one year.¹⁶ Sun et al.,¹⁷ studied patients admitted for ischemic stroke and showed that 2.9% of these patients presented AMI within 4.5 hours, the time window for thrombolysis. Liao,¹⁸ reported that 2.3% of the patients suffer a myocardial infarction during hospitalization following acute ischemic stroke, 64.9% of whom died or were severely disabled in the hospital; the mortality rate at one year after the ischemic stroke was 56.4% (in patients with myocardial infarction). Naito et al.,¹⁹

Table 3 – Group of patients diagnosed with the primary disease (AMI, IS, and PAD) who developed the secondary disease

| G4 | | | | |
|-------------------|--------------|---------------------|------------------|--|
| Primary Diagnosis | | Secondary Diagnosis | | |
| AMI | IS | PAD | Reference | |
| 10 | 6 | 4 | ESCOSTEGUY, 2003 | |
| 92 | 44 | 48 | ABBOTT, 2007 | |
| 6 | 1 | 5 | BIANCHINI, 2018 | |
| 17 | 10 | 7 | YILDIZ, 2019 | |
| 85 | 47 | 38 | ABBOTT, 2007 | |
| 4 | 3 | 1 | GERBER, 2012 | |
| 17 | 7 | 10 | MATSUZAWA, 2013 | |
| 103 | 61 | 42 | ABOYANS, 2005 | |
| 499 | 333 | 166 | DALÉN, 2019 | |
| 27 | 0 | 27 | OTOMO, 2013 | |
| 45 | 45 | 0 | ASCIONE, 2002 | |
| 48 | 48 | 0 | FILSOUFI, 2007 | |
| 743 | 743 | 0 | BUCERIUS, 2003 | |
| 2,324 | 270 | 2,054 | JOHN, 2000 | |
| 29 | 29 | 0 | RICOTTA, 1995 | |
| 52 | 52 | 0 | GUARAGNA, 2006 | |
| 149 | 149 | 0 | MAGEDANZ, 2016 | |
| 660 | 660 | 0 | FERREIRA, 2018 | |
| Total | 4,910 | 2,508 | 2,402 | |
| G5 | | | | |
| Primary Diagnosis | | Secondary Diagnosis | | |
| IS | AMI | PAD | Reference | |
| 7 | 7 | 0 | TAKASUGI, 2017 | |
| 7 | 7 | 0 | LIESIROVA, 2018 | |
| 2 | 2 | 0 | DUCCI, 2016 | |
| 14 | 3 | 11 | ASCIONE, 2002 | |
| 5 | 5 | 0 | WEIMAR, 2008 | |
| 2 | 2 | 0 | NEDELTCHEV, 2010 | |
| 107 | 33 | 74 | DIAMOND, 2018 | |
| 303 | 303 | 0 | HYSING, 2007 | |
| 7 | 5 | 2 | KHATIB, 2018 | |
| 21,961 | 2,785 | 19,176 | LICHTMAN, 2009 | |

| | | | | |
|---|--------------------------|--------------|----------------------------|------------------|
| | 432 | 247 | 185 | HASSAN, 2012 |
| | 392 | 282 | 110 | HASSAN, 2012 |
| | 4 | 4 | 0 | ARBOIX, 2010 |
| | 13 | 9 | 4 | ABREU, 2020 |
| Total | 23,256 | 3,694 | 19,562 | |
| G6 | | | | |
| | Primary Diagnosis | | Secondary Diagnosis | |
| | PAD | AMI | IS | Reference |
| | 164 | 93 | 71 | CACOUB, 2009 |
| | 18 | 13 | 5 | ARMSTRONG, 2014 |
| | 39 | 28 | 11 | ARMSTRONG, 2014 |
| | 3,152 | 1,563 | 1,589 | CARO, 2005 |
| | 55 | 33 | 22 | SMOLDEREN, 2015 |
| | 12 | 6 | 6 | FASHANDI, 2018 |
| | 38 | 19 | 19 | FASHANDI, 2018 |
| | 25 | 16 | 9 | SZCZEKLIK, 2018 |
| | 1 | 1 | 0 | BAUMHAKEL, 2018 |
| | 68 | 34 | 34 | VAINAS, 2005 |
| | 6 | 4 | 2 | SARKADI, 2015 |
| | 118 | 110 | 110 | STONE, 2014 |
| | 4 | 4 | 0 | BOTO, 2016 |
| | 3 | 2 | 1 | KALS, 2014 |
| | 83 | 57 | 26 | GOESSENS, 2007 |
| | 21 | 18 | 3 | HUANG, 2007 |
| Total | 6,851 | 3,497 | 3,354 | |
| <i>AMI: acute myocardial infarction); IS: stroke; PAD: peripheral arterial disease.</i> | | | | |

showed that 20.1% of the stroke patients had PAD, but only 32.5% of them were symptomatic. However, this does not mean that they had developed PAD after IS.

In the set of analyses in which PAD was the primary diagnosed disease, one a few in-depth studies were reported, as described below. It was found that 8.79% of the patients developed IS as the secondary disease, while 9.17% of them developed AMI.

Yang et al.,²⁰ followed PAD patients for 60 months and concluded that 9.4% of them evolved to IS. Kolls et al.,²¹ monitored PAD patients for 30 months and showed that 2.3% of them developed IS as the secondary disease. Another study, following the PAD

patients from 2003 to 2012 revealed that 3.8% of them, which were treated with anticoagulants, developed IS within 2.8 years. The study also revealed that 10% of these patients had developed AMI within the same period of time. In this study the patients were treated with antiplatelet drugs when they developed the diseases.²² Another study, conducted from 2009 to 2012, followed PAD patients and showed that 8.0% of them developed cardiovascular events, including AMI, while 1.8% of them developed IS within 19.0 ± 9.5 months of monitoring.²³ Olivier et al.,²⁴ followed PAD patients for 30 months and showed that 4.9% of them evolved to AMI.

Table 4 – Results of the statistical probability of the patients to develop the specific secondary disease or who clearly developed the secondary disease

| PRIMARY DIAGNOSIS | SECONDARY DIAGNOSIS | | |
|-------------------|--------------------------------------|-------------------------------------|---------------------------------------|
| | AMI | IS | PAD |
| AMI | - | 2,508/4,910 P(A) = 0.5107943 | 2,402/4,910 P(B) = 0.4892057 |
| IS | 3,694/23,256 P(C) = 0.15884073 | - | 19,562/23,256 P(D) = 0.84115927 |
| PAD | 3,497/6,851 P(E) = 0.51043643 | 3,354/6,851 P(F) = 0.48956357 | - |

AMI: acute myocardial infarction; IS: stroke; PAD: peripheral arterial disease.

Another interesting study, conducted with PAD patients who developed IS, was carried out from 1997 to 2015, with 1,000 patients/year. The cumulative incidence of IS was 2.71%, 2.71%, 1.95%, and 1.81%, for the groups corresponding to the periods of time from 1997 to 2000, 2001 to 2005, 2006 to 2010, and 2011 to 2015, respectively. They attributed the decrease of cases to the use of drugs to control the blood lipid rate and anticoagulants.²⁵

Finally, a comparative study of 400 PAD patients and 400 no-PAD patients showed that 12.1% of the PAD group and only 7.2% of the no-PAD group developed AMI.²⁶ The increased risk of developing a secondary disease in PAD patients may be the result of non-specific treatment for lipid control, blood pressure, among other conditions.

With respect to the patients who developed the secondary disease and then developed another (secondary disease), to the best of our knowledge, no data similar to this finding were identified in the literature. Thus, these data may represent preliminary results and can open a new source of research in the field.

The study limitations may be related to the data about the patients who developed a re-incidence of the primary disease, which were not found in the documents. In addition, the search method and the sets

of words used in the search were unable to reveal all the papers in the field that could be included in the study.

Conclusion

The statistical analysis affirmed the secondary atherosclerotic diseases after the diagnosis of the primary atherosclerotic disease during the treatment period. The results suggest that the IS patients were monitored and treated to avoid AMI, and the results indicated a low probability for the secondary disease. Similar behavior was indicated by the AMI patients; however, the results of the PAD patients indicated a higher incidence of secondary atherosclerotic diseases after the diagnosis, suggesting that deep studies and monitoring of PAD patients is necessary, mainly because PAD can be asymptomatic. Thus, if diagnosed and treated early, secondary diseases can be avoided.

Author contributions

Conception and design of the research, obtaining financing and writing of the manuscript: Picoli PMC, Trovatti E; acquisition of data: Picoli PMC; analysis and interpretation of the data: Picoli PMC, Amaral CST, Trovatti E; statistical analysis: Amaral CST; critical revision of the manuscript for intellectual content: Amaral CST, Trovatti E.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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