Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____

Sheharyar Minhas

Sex differences in the prevalence of coronary artery aneurysms and mortality among those with the disease among hospitalized patients in the United States, 2016 to 2018

By

Sheharyar Minhas
Executive Master of Public Health

Applied Epidemiology

_____

Roberd M. Bostick. MD, MPH
Committee Chair

_____

Laura M. Gaydos, PhD
Committee Member

Sex differences in the prevalence of coronary artery aneurysms and mortality among those with the disease among hospitalized patients in the United States, 2016 to 2018

By

Sheharyar Minhas

M.D., St. Georges University, 2012

Thesis Committee Chair: Roberd M. Bostick, MD, MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of Master of Public Health in Applied Epidemiology
2021

Abstract

Sex differences in the prevalence of coronary artery aneurysms and mortality among those with the disease among hospitalized patients in the United States, 2016 to 2018

By Sheharyar Minhas

Coronary artery aneurysms (CAAs) are rare and often discovered incidentally during coronary angiography or other cardiac imaging. There are no known differences in CAA prevalence across age groups; however, possible sex differences remain unclear. Accordingly, we investigated possible sex differences in CAA prevalence and of all-cause mortality among CAA patients. We conducted a cross-sectional analysis of publicly available, de-identified, 2016 to 2018 data from approximately 8 million inpatients in the United States multi-center National Inpatient Sample (NIS) database. Our primary exposure of interest was sex. We also included data on age, race, income, hospital division, and diagnoses of hyperlipidemia, diabetes mellitus, and hypertension as potential confounding and effect-modifying variables. A total of 7,326,573 individual inpatients (3,174,632 male and 4,151,941 female), of whom 607 (0.008%, or 8.3/100,000) had a CAA diagnosis (427 male [0.013%], 180 [0.004%] female), were included for analysis. Overall, cases were more likely to be male (70.4% vs. 43.3%; $P<0.0001$). In the multivariable analysis, females relative to males, had less than half the odds of having a CAA diagnosis: odds ratio (OR) 0.40; 95% confidence interval (CI) 0.33-0.48. Among patients with a CAA diagnosis, there were 24 deaths (14 among males, and 10 among females). The adjusted association of sex (females relative to males) with all-cause mortality among CAA patients was not statistically significant (OR 1.38; 95% CI 0.50-3.77). In conclusion, our findings taken together with those of previous studies, suggest that men are more likely to be diagnosed with CAA than are women.

Sex differences in the prevalence of coronary artery aneurysms and mortality among those with the disease among hospitalized patients in the United States, 2016 to 2018

By

Sheharyar Minhas

M.D., St. Georges University, 2012

Thesis Committee Chair: Roberd M. Bostick, MD, MPH

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health in Applied Epidemiology
2021

Table of Contents

CHAPTER I: BACKGROUND

First described in 1761, coronary artery aneurysms (CAAs) are a rare but important cause of short- and long-term morbidity and mortality (1). CAAs are defined as dilation of the coronary artery exceeding 50% of the reference vessel diameter or a focal artery segment dilation at least 1.5 times larger than adjacent normal segments. Further classification is based on aneurysm shape, composition (true vs. false/pseudo), size, and overall involvement (2-4). Aneurysms can be fusiform (transverse aspect < longitudinal) or saccular (longitudinal aspect < transverse) (5). CAA can be called giant if the diameter is > 8 mm in diameter (children) or > 20-150 mm in diameter in adults (4,6). Involvement can be diffuse with 2-3 vessels (Type I), diffuse in one vessel and focal in another (Type II), diffuse only in one vessel (Type III), or localized/segmental dilation (Type IV) (7). Although these are often asymptomatic, symptomatic CAA can manifest with dyspnea, angina, myocardial infarction, congestive heart failure, or sudden cardiac death. CAA can be complicated by thromboembolism, arteriovenous fistulization, spasm, rupture, hemopericardium, and tamponade (8). Short-term complications include aneurysmal rupture with hemopericardium and cardiac tamponade, and vessel compression. Long-term complications include arteriovenous fistualization, distal embolization with myocardial infarction, coronary artery disease, and death (9).

CAAs can be diagnosed at any age, though those related to Kawasaki disease are predominately diagnosed in children, primarily among Asians (19-20). In adults, atherosclerosis is an established risk factor for CAA due to lipid deposition, calcification, and fibrosis, which reduce the vessel's tolerance to intraluminal pressure leading to dilation and aneurysm formation (21).

Some studies suggest that atherosclerosis accounts for over 80% of CAAs, with CAA just being a variant of coronary artery disease (3,13,21). Interestingly, CAA has been implicated after coronary intervention (e.g., stents and angioplasty) at a rate of 0.3% to 6%, with the first reported case as early as the early 1980s (22-24). Risk factors for CAA are similar to those for coronary artery disease, including tobacco use, hyperlipidemia, diabetes, perivascular/aortic disease, lupus, and inflammatory/connective tissue disorders (2, 25-27). CAA associated with atherosclerosis appears later in life than CAA associated with congenital conditions (e.g., 9p 21.3 allele variants) (28-29). Atherosclerotic CAAs are often multiple and involve more than one coronary artery. In contrast, those related to congenital or traumatic CAAs are usually single (30). CAA occurs most commonly in the proximal half of the right coronary artery (68%), left circumflex (50%), and left main stem (0.1%), but these estimated distributions have differed across study populations (3,27,31). Despite knowledge of these risk factors, the overall pathogenesis of CAA is still poorly understood due to the heterogeneity of the disease (32).

The diagnosis of CAA can be through noninvasive techniques such as echocardiography, CT, and MRI; however, invasive coronary angiography remains the gold standard since it details the location, shape, size, co-existing anomalies, and the possibility of surgical resection. Coronary CT is the noninvasive test of choice and is used for follow-up of CAA. Coronary magnetic resonance angiography is a noninvasive alternative to coronary CT which avoids considerable radiation exposure. Intravascular ultrasound has become the preferred alternative as it can help differentiate true from false aneurysms caused by plaque rupture. The management of CAA is not well established and provides a significant challenge depending on the clinical presentation (size, expansion history, pathophysiology, and symptoms). Treatment can consist of medical

management to prevent thromboembolic complications through antiplatelets and anticoagulants, surgical resection, or stent placement (33).

While there are no recognized differences in CAA prevalence across age groups, sex differences in prevalence and mortality due to the disease are less well characterized. CAA occurs uncommonly, with prevalence estimated to be between 0.37-2.53% (2, 10-12). CAA was also found postmortem in 1.4% of all autopsied individuals (13). One of the most striking and consistent findings is a stable prevalence of CAA at any age, and there is no specific age predilection. Previous studies that addressed the possible prevalence of CAA overall and by sex, generally were small, angiography-based clinical series studies. The largest of these studies was the multi-center Coronary Artery Aneurysm Registry (CARR), which involved 32 hospitals across 9 countries (Canada, Cuba, Czech Republic, Germany, Italy, Netherlands, Spain, United States and Uruguay) and included 436,467 consecutive adult patients who underwent invasive coronary angiograms from 2004 to 2016 (14). Of these patients, 1,561 (of whom 78.5% were males, and 21.5% were females) fulfilled criteria for at least one coronary aneurysm, indicating an overall prevalence of 0.35%, with a nearly 4:1 male to female ratio, in the adult coronary angiography population. In another study, the US multi-institutional Coronary Artery Surgery Study (CASS), of 20,087 patients who underwent coronary arteriography for clinically suspected coronary artery disease at 15 participating clinical centers between July 1975 and May 1979, a total of 978 patients, representing 4.9% of the total registry population, was identified as having CAA (13). Among these 978 patients with CAA, relative to the remaining 15,249 patients, the percentage of males was statistically significantly greater (75.3% vs. 62.2%). Of 6,100 patients who underwent coronary angiography at an academic center in Eskisehir, Turkey, 36 were

diagnosed with CAA; CAA prevalence among men and women in that study population was estimated to be 0.7% and 0.5%, respectively, although the difference was not statistically significant ($P = 0.09$) (15). In that study, when CAA and coronary artery ectasia (CAE) were combined, the estimated aneurysm prevalence among men and women was 6.9% and 4.5%, respectively ($P =<0.01$) (9). Of 4,993 adult inpatients who had coronary angiograms at a single tertiary care hospital in Middlesex, UK from 1976 to 1982, 3,299 had coronary artery disease (16); of those who had coronary artery disease, 39 (1.2%) had a CAA. Of the 1,051 female patients in that study, 414 (39%) had clinically significant coronary artery disease, and only 12 (2.9%) had a CAA; of the 3,942 men, 2,885 (73%) had clinically significant coronary artery disease, and 27 (0.9%) had a CAA. In a series of 390 consecutive patients who underwent coronary tomography coronary angiography (CTCA) from 2007 to 2015 at an Italian hospital, nine (2.3%) were found to have CAA (6 men and 3 women) (17). Finally, a population-based case-control study in Taiwan used data from the National Health Insurance Research Database (NHIRD), which included adult inpatient and outpatient medical records. A total of 1,397 inpatients and outpatients with a diagnosis of CAA were identified between January 1, 2005 and December 31, 2011. Of these CAA cases, 957 (68.5%) were men and 31.5% were women (18).

To clarify possible sex differences in CAA prevalence, herein we report the results of a cross-sectional study, among patients hospitalized for any reason, of sex differences in CAA prevalence and of all-cause mortality among CAA patients in the largest study of CAA prevalence and mortality to date.

CHAPTER II: MANUSCRIPT

Sex differences in the prevalence of coronary artery aneurysms and mortality among those with the disease among hospitalized patients in the United States, 2016 to 2018

By

Sheharyar Minhas

ABSTRACT

Coronary artery aneurysms (CAAs) are rare and often discovered incidentally during coronary angiography or other cardiac imaging. There are no known differences in CAA prevalence across age groups; however, possible sex differences remain unclear. Accordingly, we investigated possible sex differences in CAA prevalence and of all-cause mortality among CAA patients. We conducted a cross-sectional analysis of publicly available, de-identified, 2016 to 2018 data from approximately 8 million inpatients in the United States multi-center National Inpatient Sample (NIS) database. Our primary exposure of interest was sex. We also included data on age, race, income, hospital division, and diagnoses of hyperlipidemia, diabetes mellitus, and hypertension as potential confounding and effect-modifying variables. A total of 7,326,573 individual inpatients (3,174,632 male and 4,151,941 female), of whom 607 (0.008%, or 8.3/100,000) had a CAA diagnosis (427 male [0.013%], 180 [0.004%] female), were included for analysis. Overall, cases were more likely to be male (70.4% vs. 43.3%; $P<0.0001$). In the multivariable analysis, females relative to males, had less than half the odds of having a CAA

diagnosis: odds ratio (OR) 0.40; 95% confidence interval (CI) 0.33-0.48. Among patients with a CAA diagnosis, there were 24 deaths (14 among males, and 10 among females). The adjusted association of sex (females relative to males) with all-cause mortality among CAA patients was not statistically significant (OR 1.38; 95% CI 0.50-3.77). In conclusion, our findings taken together with those of previous studies, suggest that men are more likely to be diagnosed with CAA than are women.

INTRODUCTION

Coronary artery aneurysms (CAA) are a rare but important cause of short- and long-term morbidity and mortality. These complications are exceedingly rare. Short-term complications include aneurysmal rupture with hemopericardium and cardiac tamponade, and vessel compression. Long-term complications include arteriovenous fistualization, distal embolization with myocardial infarction, coronary artery disease, and death (34).

CAA occurs uncommonly in the general population. Even among patients referred for coronary artery angiography, reported CAA prevalence estimates range from 0.2% to 5.3% (35-36). CAA are often unsuspected and discovered incidentally during diagnostic evaluations performed for other reasons. The vast majority of CAA are discovered during coronary angiography or computed tomography (32). One of the most striking and consistent findings is a stable prevalence of CAA at any age, without evidence of a specific age predilection (37). While there are no recognized differences in CAA prevalence across age groups, sex differences in prevalence and mortality due to the disease are less well characterized. Several primarily small, angiography-based clinical series studies suggested that CAA maybe more common among males than females (38).

To clarify possible sex differences in CAA prevalence, herein we report the results of a cross-sectional study, among patients hospitalized for any reason, of sex differences in CAA prevalence and of all-cause mortality among CAA patients in the largest study of CAA prevalence and mortality to date.

MATERIALS AND METHODS

Data source and study population

We conducted cross-sectional analyses of de-identified, publicly available 2016 to 2018 data from the multi-center National Inpatient Sample (NIS). The NIS, developed in part by the Healthcare Cost and Utilization Project (HCUP) of the Agency of Healthcare Research and Quality in Rockville, MD, is the largest publicly available all-payer hospitalization database in the United States. With over 1,000 hospitals participating in the HCUP, the NIS contains inpatient data from approximately 8 million hospital stays annually and represents a more than 20% stratified sample of all nonfederal hospitals in the United States. The NIS inpatient data are cataloged into clinically purposeful categories using the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM).

Outcomes

We defined our primary outcome as all inpatients with a diagnosis of CAA (ICD-10-CM code I25.41) between 2016 and 2018. Patients in the NIS database were diagnosed with CAA via computed tomography (CT), echocardiography, magnetic resonance imaging (MRI), coronary angiography, or cardiac catheterization. CAA was defined as a localized dilatation of the coronary vascular lumen with diameter > 1.5 times the reference coronary artery. Patients with coronary ectasia—diffuse dilatation of the coronary vessels—were not included as CAA cases. For our analyses, we counted patients with more than one hospitalization only once. If someone

had more than one hospitalization, if they had a CAA diagnosis, we used data only from their most recent hospitalization for which a CAA diagnosis was listed; similarly, among those with more than one hospitalization who did not have a CAA diagnosis, we used data only from their most recent hospitalization. Our secondary outcome was all-cause mortality among hospitalized CAA patients during the same time period.

Exposures

Our primary exposure of interest was sex (male/female). We also included data on age, race, income, hospital division, and diagnoses of hyperlipidemia, diabetes mellitus, and hypertension as potential confounding and effect-modifying variables. The hospital divisions included in the NIS are the nine U.S. Census Bureau Census Divisions (New England, Middle Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain, Pacific). For income, we assigned patients the average income of the population in their residential zip code, and categorized income according to quartiles of the income distribution in the study population. Hyperlipidemia, diabetes mellitus, and hypertension were ascertained and categorized using the Elixhauser Comorbidity Index, which is a method to dichotomize patients' co-morbidities based on ICD codes. A history of hyperlipidemia was defined using ICD-10 codes E781, E782, and E785; a history of diabetes mellitus using ICD-10 codes E08, E09, E10, E11, E1122, and E13; and a history of hypertension using ICD-10 codes I10, I11, I12, I13, I15, and I16.

Statistical analyses

Data were weighted as provided by the HCUP in order to generate nationally representative estimates. We categorized age into five categories (>20, 20–39, 40–59, 60–79, >80 years). As noted above, all other exposure variables were categorical. Accordingly, we summarized the characteristics of the study participants, by CAA status, among men and women separately and combined, using frequencies as percentages, and compared them using chi-square tests. To estimate associations of sex with a CAA diagnosis and all-cause mortality among those with a CAA diagnosis, we used unconditional multivariable logistic regression models to calculate odds ratios (OR) and their 95% confidence intervals (CI). Covariates for the models included all of the available demographic and medical factors described above. We also investigated sex differences in associations of the above-described risk factors with CAA two ways. First, starting with all potential covariates, we conducted forward stepwise logistic regression using a cut off for covariate retention of $P <= 0.10$, followed by backward stepwise selection of the variables retained in the forward procedure, using a cut off for covariate retention of $P <= 0.05$, by sex, to assess potential sex differences in the best 'predictive' models. Second, we investigated associations of all the above-described risk factors with CAA, stratified by sex, using unconditional multivariable logistic regression models.

We conducted all analyses using SAS software, version 9.4 (SAS Institute, North Carolina, US). We considered a *P*-value <= 0.05 or a 95% confidence interval that excluded 1.0 statistically significant.

RESULTS

Patient characteristics

A total of 7,326,573 individual patients (3,174,632 male and 4,151,941 female), of whom 607 (0.008%, or 8.3/100,000) had a CAA diagnosis (427 male [0.013%], 180 [0.004%] female), were included in the present analyses. The characteristics of the hospitalized patients with and without CAA, overall and by sex, are summarized in **Table 1**. Overall, cases were more likely to be male (70.4% vs. 43.3%; P <0.0001). Also, although the proportions of cases and non-cases were similar across most age categories, cases were less likely to be in the 20 – 39-year-old and more likely to be in the 60 – 79-year-old categories. Cases were also more likely to have hyperlipidemia and hypertension. The cases and non-cases did not differ substantially by race, income, hospital division, or diabetes status. The distributions of the participant characteristics, by case/non-case status, did not differ substantially by sex, although the prevalence of both hyperlipemia and hypertension among female cases and non-cases was slightly less than among male cases and non-cases.

Association of sex with CAA

In the multivariable analysis, females relative to males, had statistically significantly less than half the odds of having a CAA diagnosis (OR 0.40 [95% CI 0.33, 0.48]) (**Table 2**).

Associations of demographic/medical factors with CAA, by sex

The estimated associations of the demographic and medical factors described above with CAA were similar by sex (**Table 3**). Furthermore, the forward/backward model selection procedures to select the most 'predictive' models for each sex yielded the same final model covariates (diabetes mellitus, hyperlipidemia, hypertension, age, race).

Association of sex with all-cause mortality among CAA cases

There were only 24 deaths (14 among males, and 10 among females) among hospitalized patients with CAA during 2016 – 2018. In the crude and adjusted analyses for the association of sex with all-cause mortality among CAA cases (**Table 4**), the estimated associations, neither of which were statistically significant, were OR 1.74 (95% CI 0.76-3.98) and OR 1.38 (95% CI 0.50-3.77), respectively.

DISCUSSION

Our findings suggest that, among hospitalized patients in the US, men are more likely to have or be diagnosed with CAA than are women. Although our preliminary analysis of all-cause mortality risk among hospitalized patients with CAA suggested the possibility of higher mortality risk among men, the sample size for this analysis was too small to yield stable/statistically significant estimated associations. Although this is by far the largest study of

CAA prevalence to date, a much larger study would be needed to yield stable estimates of mortality risk among CAA patients.

Previous studies that addressed the possible prevalence of CAA overall and by sex, generally were small, angiography-based clinical series studies, but like our study, estimated a higher prevalence among men. The largest of these studies was the multi-center Coronary Artery Aneurysm Registry (CARR), which involved 32 hospitals across 9 countries (Canada, Cuba, Czech Republic, Germany, Italy, Netherlands, Spain, United States and Uruguay) and included 436,467 consecutive adult patients who underwent invasive coronary angiograms from 2004 to 2016 (14). Of these patients, 1,561 (of whom 78.5% males, and 21.5% were females) fulfilled criteria for at least one coronary aneurysm, indicating an overall prevalence of 0.35%, with a nearly 4:1 male to female ratio, in the adult coronary angiography population. In another study, the US multi-institutional Coronary Artery Surgery Study (CASS), of 20,087 patients undergoing coronary arteriography for clinically suspected coronary artery disease at 15 participating clinical centers between July 1975 and May 1979, a total of 978 patients, representing 4.9% of the total registry population, was identified as having CAA (13). Among these 978 patients with CAA, relative to the remaining 15,249 patients, the percentage of males was statistically significantly greater (75.3% vs. 62.2%). Of 6,100 patients who underwent coronary angiography at an academic center in Eskisehir, Turkey, 36 were diagnosed with CAA; CAA prevalence among men and women in that study population was estimated to be 0.7% and 0.5%, respectively, although the difference was not statistically significant ($P = 0.09$) (15). In that study, when CAA and coronary artery ectasia (CAE) were combined, the estimated aneurysm prevalence among men and women was 6.9% and 4.5%, respectively ($P =<0.01$) (15).

Of 4,993 adult inpatients who had coronary angiograms at a single tertiary care hospital in Middlesex, UK from 1976 to 1982, 3,299 had coronary artery disease (16); of those who had coronary artery disease, 39 (1.2%) had a CAA. Of the 1,051 female patients in that study, 414 (39%) had clinically significant coronary artery disease, and only 12 (2.9%) had a CAA; of the 3,942 men, 2,885 (73%) had clinically significant coronary artery disease, and 27 (0.9%) had a CAA. In a series of 390 consecutive patients who underwent coronary tomography coronary angiography (CTCA) from 2007 to 2015 at an Italian hospital, nine (2.3%) were found to have CAA (6 men and 3 women) (17). Finally, a population-based case-control study in Taiwan used data from the National Health Insurance Research Database (NHIRD), which included adult inpatient and outpatient medical records. A total of 1,397 inpatients and outpatients with a diagnosis of CAA were identified between January 1, 2005 and December 31, 2011. Of these CAA cases, 957 (68.5%) were men and 31.5% were women (18).

Unfortunately, no study to date has been able to ascertain whether or not sex differences in CAA diagnoses represent true sex differences or detection bias (i.e., men may have been more likely to have a procedure at which CAA was an incidental finding). However, the risk factor most strongly associated with becoming diagnosed with a CAA is atherosclerosis (8,13-15). Vasculitis without atherosclerosis causes coronary artery aneurysms in young children with Kawasaki disease. CAA is associated with coronary artery disease (6,16), but it is unclear whether CAD directly causes CAA. Thrombosis and distal embolization are the most probable causes of the acute coronary syndrome-like presentation of patients with CAA without underlying coronary artery obstruction/atherosclerosis (17-18). A higher incidence of diagnosed coronary artery disease among men than among women may explain the higher prevalence of a

CAA diagnosis among men (39). CAD is under-diagnosed among women because of a higher frequency of atypical symptoms among women as well as a persistent attitude that CAD predominately affects men (40). Typical symptoms of chest pain are less common among women, who often present with non-specific symptoms such as fatigue and sleep disturbances (41-42).

Our study had several limitations and strengths. Many, if not most, non-cases likely did not have imaging procedures that would have detected an asymptomatic CAA, so the true prevalence of CAA, overall and by sex, among the hospitalized US population remains unknown, but likely is higher than estimated in the present study. Further, CAA diagnoses were not made using standardized methods, and all data on CAA diagnoses were claims-based and did not differentiate between coronary aneurysms and ectasia, which may have affected our prevalence estimates. The claims-based source for CAA diagnoses did not include specific information on aneurysm features, such as shape, location, size, degree of stenosis, and number of aneurysms, thus prohibiting analyses on categories of CAA. Our study population was limited to US hospitalized patients, and thus may not be generalizable to the general US population. We had no data on whether or not diagnosed CAAs were symptomatic or merely incidental diagnoses. We also had no data on individual exposures, such as dietary and lifestyle habits and family history, thus prohibiting etiologic analyses. We were unable to investigate urban-rural differences in CAA diagnoses; however, we did investigate differences across the nine U.S. Census Bureau Census Divisions included in the NIS, and found no evidence of differences across these diverse regions, overall or by sex. Finally, despite our large underlying study population, the number of deaths among CAA patients was too small for meaningful estimates of

all-cause and CAA-specific mortality risk. Despite the limitations of our study, we included all reported CAA diagnoses among hospitalized patients in the largest study of CAA in the US or elsewhere to date, giving a clearer indication that CAA may be more prevalent among men than women, thus supporting future studies more specifically designed to assess potential sex differences in incidence, prevalence, etiology, clinical presentations, and mortality risk.

In conclusion, our findings taken together with those of previous studies, suggest that men are more likely to be diagnosed with CAA than are women. Given that most CAA diagnoses are incidental, and men are more likely to be diagnosed with coronary artery disease, the possibilities for the observed male/female differences include coronary artery disease—which may be more common among men—causing CAA, detection bias, or unknown biological mechanisms. Given the apparent rarity of CAA, a general population-based study in which all participants would be tested for CAA would have to be so large as to be prohibitive. However, a large, nationwide prospective cohort study of patients diagnosed with CAA to investigate all-cause and CAA-specific mortality risk may be feasible and would help elucidate the clinical importance of CAA, overall and among males and females separately.

CHAPTER III: SUMMARY

Our study suggests that among hospitalized patients in the United States, women are less likely to have or be diagnosed with CAA than are men. Our findings also raised the possibility that men with CAA may be at higher risk for all-cause mortality risk; however, the sample size for this analysis was too small to yield a statistically significant result. Although our study by far is the largest study of CAA prevalence to date, a much larger study would be needed to yield stable estimates of mortality risk among CAA patients.

It is likely that many asymptomatic CAA were not detected in our study since cardiac imaging procedures are generally only done if clinically indicated. To determine the true prevalence of CAA, overall and by sex, among the hospitalized US population, conducting imaging procedures such as computed tomography (CT), echocardiography, magnetic resonance imaging (MRI), and coronary angiography, would have to be done on all, or a large, representative sample of the hospitalized population. In the latter scenario, standardized methods to differentiate between coronary aneurysms and ectasia would be preferable. Conducting such research on a general population would yield the truest prevalence estimates, but likely would be cost prohibitive. Future research should also include specific information on 1) aneurysm features, such as shape, location, size, degree of stenosis, and number of aneurysms, thus allowing analyses on categories of CAA; 2) whether diagnosed CAAs were symptomatic or incidentally discovered; and 3) geographic and urban/rural residence. Research to clarify the etiology of CAA would require more extensive collection of individual exposure information than was available in the present study; such information would include dietary and lifestyle habits and family history. CAA is

extremely rare, and despite our large underlying study population of over 7 million patients, the number of deaths among CAA patients was too small for meaningful estimates of all-cause and CAA-specific mortality risk. To address this, future research in this area would require a substantially larger sample size than was available for the present study. An optimal study design to assess mortality risk among CAA patients would be a large, nationwide prospective cohort study of CAA patients.

REFERENCES

1. Taskesen T, Osei K, Ugwu J, Hamilton R, Tannenbaum M, Ghali M. Coronary artery aneurysm presenting as acute coronary syndrome: two case reports and a review of the literature. Journal of Thrombosis and Thrombolysis. 2021:1-6.
2. Luo Y, Tang J, Liu X, et al. Coronary artery aneurysm differs from coronary artery ectasia: angiographic characteristics and cardiovascular risk factor analysis in patients referred for coronary angiography. Angiology. 2017;68(9):823-830.
3. Sheikh AS, Hailan A, Kinnaird T, Choudhury A, Smith D. Coronary artery aneurysm: evaluation, prognosis, and proposed treatment strategies. Heart views: the official journal of the Gulf Heart Association. 2019;20(3):101.
4. Díaz-Zamudio M, Bacilio-Pérez U, Herrera-Zarza MC, et al. Coronary artery aneurysms and ectasia: role of coronary CT angiography. Radiographics. 2009;29(7):1939-1954.
5. Indolfi C, Achille F, Tagliamonte G, Spaccarotella C, Mongiardo A, Ferraro A. Polytetrafluoroethylene stent deployment for a left anterior descending coronary aneurysm complicated by late acute anterior myocardial infarction. Circulation. 2005;112(5):e70-e71.
6. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease: a 10-to 21-year follow-up study of 594 patients. Circulation. 1996;94(6):1379-1385.
7. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-β receptor. New England Journal of Medicine. 2006;355(8):788-798.
8. Johnson PT, Fishman EK. CT angiography of coronary artery aneurysms: detection, definition, causes, and treatment. American Journal of Roentgenology. 2010;195(4):928-934.
9. Díaz-Zamudio M, et al. Coronary artery aneurysms and ectasia: Role of coronary CT angiography. RadioGraphics. 2009;29:1939–54.

10. Hartnell G, Parnell B, Pridie R. Coronary artery ectasia. Its prevalence and clinical significance in 4993 patients. Heart. 1985;54(4):392-395.
11. Robertson T. Prognostic significance of coronary artery aneurysm and ectasia in the Coronary Artery Surgery Study (CASS) registry. Prog Clin Biol Res. 1987;250:325.
12. Abou Sherif S, Ozden Tok O, Taşköylü Ö, Goktekin O, Kilic ID. Coronary artery aneurysms: a review of the epidemiology, pathophysiology, diagnosis, and treatment. Frontiers in cardiovascular medicine. 2017;4:24.
13. Swaye PS, Fisher LD, Litwin P, et al. Aneurysmal coronary artery disease. Circulation. 1983;67(1):134-138.
14. Núñez-Gil, I.J., Cerrato, B.M., Nombela-Franco, L., Terol, B., et al. CAAR investigators. Coronary artery aneurysms, insights from the international coronary artery aneurysm registry (CAAR). Int J Cardiol. 2020 Jan 15;299:49-55.
15. Morrad B, Yazici HU, Aydar Y, Ovali C, Nadir A. Role of gender in types and frequency of coronary artery aneurysm and ectasia. Medicine (Baltimore). 2016 Aug;95(31):e4395.
16. Hartnell GG, Parnell BM, Pridie RB. Coronary artery ectasia: Its prevalence and clinical significance in 4993 patients. Br Heart J. 1985;54:392-95.
17. Ernesto F, Marco A, Marianna I, et al. Coronary artery aneurysms detected by computed tomography coronary angiography. European Heart Journal - Cardiovascular Imaging 2017;18(11):1229-35.
18. Fang CT, Fang YP, Huang YB, Kuo CC, Chen CY. Epidemiology and risk factors of coronary artery aneurysm in Taiwan: a population based case control study. BMJ Open. 2017;7(6):e014424. Published 2017 Jun 30. doi:10.1136/bmjopen-2016-014424

19. Manginas A, Cokkinos DV. Coronary artery ectasias: imaging, functional assessment and clinical implications. European heart journal. 2006;27(9):1026-1031.
20. Antoniadis AP, Chatzizisis YS, Giannoglou GD. Pathogenetic mechanisms of coronary ectasia. International journal of cardiology. 2008;130(3):335-343.
21. Khubber S, Chana R, Meenakshisundaram C, et al. Coronary artery aneurysms: outcomes following medical, percutaneous interventional and surgical management. Open Heart. 2021;8(1):e001440.
22. Bell MR, Garratt KN, Bresnahan JF, Edwards WD, Holmes DR. Relation of deep arterial resection and coronary artery aneurysms after directional coronary atherectomy. Journal of the American College of Cardiology. 1992;20(7):1474-1481.
23. Holmes Jr DR, Vlietstra RE, Mock MB, et al. Angiographic changes produced by percutaneous transluminal coronary angioplasty. The American journal of cardiology. 1983;51(5):676-683.
24. Aoki J, Kirtane A, Leon MB, Dangas G. Coronary artery aneurysms after drug-eluting stent implantation. JACC: Cardiovascular interventions. 2008;1(1):14-21.
25. Yoshikai M, Hamada M, Takarabe K. Coronary artery aneurysm with systemic lupus erythematosus. The Japanese Journal of Thoracic and Cardiovascular Surgery. 2004;52(8):379-382.
26. Fang C-T, Fang Y-P, Huang Y-B, Kuo C-C, Chen C-Y. Epidemiology and risk factors of coronary artery aneurysm in Taiwan: a population based case control study. BMJ open. 2017;7(6):e014424.

27. Tandon V, Tandon AA, Kumar M, et al. Coronary artery aneurysms: analysis of comorbidities from the National inpatient sample. Cureus 2019;11: e4876. 10.7759/cureus.4876
28. Daoud AS, Pankin D, Tulgan H, Florentin RA. Aneurysms of the coronary artery: report of ten cases and review of literature. The American journal of cardiology. 1963;11(2):228-237.
29. Helgadottir A, Thorleifsson G, Magnusson KP, et al. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. Nature genetics. 2008;40(2):217.
30. Lakshmanadoss U. Novel Strategies in Ischemic Heart Disease. BoD–Books on Demand; 2012.
31. Syed M, Lesch M. Coronary artery aneurysm: a review. Progress in cardiovascular diseases. 1997;40(1):77-84.
32. Kawsara A, Núñez Gil IJ, Alqahtani F, Moreland J, Rihal CS, Alkhouli M. Management of coronary artery aneurysms. JACC: Cardiovascular interventions. 2018;11(13):1211-1223.
33. Sheikh A.S., Hailan A., Kinnaird T., Choudhury A., Smith D. Coronary Artery Aneurysm: evaluation, prognosis, and proposed treatment strategies. Heart Views. 2019; 20:101–108.
34. Díaz-Zamudio M, et al. Coronary artery aneurysms and ectasia: Role of coronary CT angiography. RadioGraphics. 2009;29:1939–54.
35. Aintablian A, Hamby RI, Hoffman I, Kramer RJ. Coronary ectasia: incidence and results of coronary bypass surgery. Am Heart J. 1978; 96: 309–315.
36. Sherif A, Ozden TO, Taskoylu O, et al. Coronary artery aneurysms: A review of the epidemiology, pathophysiology, diagnosis, and treatment. Front Cardiovasc Med. 2017;4:24.
37. El Guindy, M.S., El Guindy A.M. Aneurysmal coronary artery disease: An overview. Glob Cardiol Sci Pract. 2017;2017(3):e201726. Published 2017 Oct 31. doi:10.21542/gcsp.2017.26

38. Cohen P, O'Gara PT. Coronary artery aneurysms: a review of the natural history, pathophysiology, and management. Cardiol Rev 2008;16(6):301–304.

39. Hvelplund A, Galatius S, Madsen M, et al. Women with acute coronary syndrome are less invasively examined and subsequently less treated than men. Eur Heart J 2010; 31:684–690.

40. Keteepe-Arachi, T., Sharma, S. Cardiovascular Disease in Women: Understanding Symptoms and Risk Factors. Eur Cardiol. 2017;12(1):10-13.

41. Johnson BD, Shaw LJ, Pepine CJ, et al. Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: Results from the NIH-NHLBIsponsored Women's Ischaemia Syndrome Evaluation (WISE) study. Eur Heart J 2006;27:1408–15.

42. Canto JG, Rogers WJ, Goldberg RJ, et al. NRMI Investigators. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. JAMA 2012;307:813–22.

TABLES

Table 1. Baseline Characteristics of Hospitalized Patients With and Without a Coronary Artery Aneurysm, Overall and by Sex; the HCUP-NIS, United States, 2016-2018

Risk factors	Overall			Men			Women			
	CAA (*n* = 607) (%)	**No CAA** (*n* = 7,326,573) (%)	*P*[1]	**CAA** (*n* = 427) (%)	**No CAA** (*n* = 3,174,632) (%)	*P*[1]	**CAA** (*n* = 180) (n%)	**No CAA** (*n* = 4,151,941) (%)	*P*[1]	*P*[2]
Age (years)										
<20	15.2	16.4		14.1	18.7		17.8	14.5		
20-39	3.6	19.7		3.0	10.7		5.0	26.6		
40-59	21.8	20.7		23.0	24.0		18.9	18.2		
60-79	46.5	29.5		48.0	33.8		42.8	26.2		
>80	13.0	13.8	<0.0001	11.9	12.8	<0.0001	15.6	14.5	<0.0001	0.24
Race										
White	59.2	61.5		59.4	62.8		58.7	60.5		
Black	10.6	14.2		10.1	13.8		11.7	14.5		
Hispanic	11.4	11.6		12.0	11.0		10.1	12.1		
Asian or Pacific Islander	4.3	3.0		4.0	2.7		5.0	3.3		
Native American	1.3	0.9		1.6	0.9		0.6	0.9		
Other	13.2	8.8	0.0002	12.9	8.9	0.002	14.0	8.8	0.10	0.81
Income (percentiles)										
0-25	29.0	30.1		26.6	30.2		34.5	30.1		
26-50	21.7	25.3		22.4	25.4		20.1	25.3		
51-75	24.3	24.0		25.4	23.9		21.8	24.1		
76-100	25.0	20.5	0.03	25.6	20.6	0.04	23.6	20.5	0.24	0.29
Hospital division										
New England	6.9	7.2		6.8	7.4		7.2	7.0		
Mid Atlantic	13.2	13.5		12.9	13.8		13.9	13.3		
East North Central	13.7	14.9		11.9	14.9		17.8	14.9		
West North Central	8.4	6.7		8.9	6.7		7.2	6.8		
South Atlantic	18.3	20.1		19.2	20.1		16.1	20.0		
East South Central	6.4	6.7		6.1	6.5		7.2	6.8		
West South Central	11.5	11.5		11.0	11.1		12.8	11.8		
Mountain	8.1	6.1		9.4	6.1		5.0	6.1		
Pacific	13.5	13.4	0.40	13.8	13.4	0.08	12.8	13.4	0.93	0.43
Have hyperlipidemia	48.3	23.8	<0.0001	52.0	27.7	<0.0001	39.4	20.9	<0.0001	0.005
Have diabetes mellitus	26.0	22.2	0.02	27.4	25.6	0.39	22.8	19.5	0.27	0.24
Have hypertension	66.6	46.2	<0.0001	69.1	51.9	<0.0001	60.6	41.8	<0.0001	0.04
Sex, male	70.4	43.3	<0.0001							

Abbreviations: CAA, coronary artery aneurysm; HCUP-NIS, Healthcare Cost and Utilization Project Nationwide Inpatient Sample

[1] CAA vs. no CAA; from chi square test

[2] CAA in men vs. CAA in women; from chi square test

Table 2. Association[1] of sex with coronary artery aneurysms among US hospitalized patients (*n* = 7,326,573); the HCUP-NIS, United States, 2016-2018

Sex	Crude OR (95% CI)	Adjusted OR[2] (95% CI)
Male	1.0 (ref.)	1.0 (ref.)
Female	0.32 (0.27, 0.38)	0.40 (0.33, 0.48)

Abbreviations: CI, confidence interval; HCUP-NIS, Healthcare Cost and Utilization Project Nationwide Inpatient Sample; OR, odds ratio; ref., reference

[1] From unconditional logistic regression model

[2] Adjusted for age, race, income, hospital division, hyperlipidemia, diabetes mellitus, hypertension

Table 3. Associations[1] of demographic and medical factors with coronary artery aneurysms among US hospitalized patients (*n* = 7,326,573), by sex; the HCUP-NIS, United States, 2016-2018

	Men			Women		
Risk factors	OR	(95% CI)	*P*	OR	(95% CI)	*P*
Age (years)						
<20	1.00	(Ref.)		1.00	(Ref.)	
20-39	0.33	(0.17, 0.63)		0.16	(0.08, 0.33)	
40-59	0.89	(0.60, 1.32)		0.66	(0.38, 1.15)	
60-79	1.05	(0.71, 1.56)		0.81	(0.46, 1.43)	
>80	0.65	(0.40, 1.03)	0.0002	0.52	(0.27, 1.00)	<0.0001
Race						
White	1.00	(Ref.)		1.00	(Ref.)	
Black	0.96	(0.69, 1.35)		0.84	(0.51, 1.39)	
Hispanic	1.38	(0.99, 1.93)		1.06	(0.62, 1.82)	
Asian or Pacific Islander	1.77	(1.07, 2.95)		2.15	(1.05, 4.37)	
Native American	0.90	(0.22, 3.63)		1.07	(0.15, 7.74)	
Other	1.61	(1.17 2.21)	0.01	1.91	(1.19, 3.06)	0.03
Income (percentiles)						
0-25	1.00	(Ref.)		1.00	(Ref.)	
26-50	0.96	(0.72, 1.28)		0.66	(0.43, 1.01)	
51-75	1.13	(0.86, 1.50)		0.74	(0.48, 1.12)	
76-100	1.32	(0.99, 1.75)	0.14	0.91	(0.60, 1.40)	0.20
Hospital Division						
North East	1.00	(Ref.)		1.00	(Ref.)	
Mid Atlantic	0.99	(0.63, 1.56)		1.01	(0.52, 1.98)	
East North Central	0.89	(0.56, 1.41)		1.13	(0.59, 2.18)	
West North Central	1.32	(0.80, 2.19)		0.90	(0.41, 2.01)	
South Atlantic	1.08	(0.70, 1.67)		0.80	(0.41, 1.55)	
East South Central	1.16	(0.67, 2.01)		0.98	(0.44, 2.19)	
West South Central	1.11	(0.69, 1.78)		1.01	(0.50, 2.05)	
Mountain	1.66	(1.01, 2.72)		0.83	(0.35, 1.96)	
Pacific	1.09	(0.69, 1.72)	0.27	0.90	(0.45, 1.80)	0.97
Hyperlipidemia						
No	1.00	(Ref.)		1.00	(Ref.)	
Yes	2.55	(2.02, 3.21)	<0.0001	1.91	(1.03, 2.47)	0.0004
Diabetes mellitus						
No	1.00	(Ref.)		1.00	(Ref.)	
Yes	0.66	(0.53, 0.84)	0.0006	0.67	(0.45, 0.99)	0.04
Hypertension						
No	1.00	(Ref.)		1.00	(Ref.)	
Yes	1.60	(1.20, 2.21)	0.001	1.59	(1.03, 2.47)	0.04

Abbreviations: CI, confidence interval; HCUP-NIS, Healthcare Cost and Utilization Project Nationwide Inpatient Sample; OR, odds ratio; Ref., reference

[1] From unconditional logistic regression models; models for each risk factor adjusted for each of the other risk factors

Table 4. Association[1] of sex with all-cause mortality among US hospitalized patients with coronary artery aneurysms (*n* = 24) in the HCUP-NIS, United States, 2016-2018

Sex	# Died	Crude OR (95% CI)	Adjusted OR[2] (95% CI)
Male	14	1.00 (ref.)	1.00 (ref.)
Female	10	1.74 (0.76, 3.98)	1.38 (0.50, 3.77)

Abbreviations: CI, confidence interval; HCUP-NIS, Healthcare Cost and Utilization Project Nationwide Inpatient Sample; OR, odds ratio; ref., reference

[1] From unconditional logistic regression models

[2] Adjusted for age, race, income, hospital division, hyperlipidemia, diabetes mellitus, hypertension

Table 5 (Appendix). Associations[1] of demographic and medical factors with all-cause mortality among US hospitalized patients with coronary artery aneurysms (*n* = 24), by sex; the HCUP-NIS, United States, 2016-2018

	Men			Women		
Risk factors	OR	(95% CI)	*P*[1]	OR	(95% CI)	*P*[1]
Age (years)						
<20	1.00	(Ref.)		1.00	(Ref.)	
20-39	3.78	NE		6.08	NE	
40-59	NE	NE		NE	NE	
60-79	NE	NE		NE	NE	
>80	NE	NE	0.71	NE	NE	0.51
Race						
White	1.00	(Ref.)		1.00	(Ref.)	
Black	0.69	(0.07, 6.96)		NE	NE	
Hispanic	5.00	(0.76, 32.75)		NE	NE	
Asian or Pacific Islander	NE	NE		NE	NE	
Native American	NE	NE		1.28	NE	
Othe	NE	NE	0.66	4.88	(0.28, 84.64)	0.94
Income (percentile)						
0-25	1.00	(Ref.)		1.00	(Ref.)	
26-50	0.49	(0.07, 3.35)		NE	NE	
51-75	0.83	(0.16, 4.38)		0.87	(0.08, 10.15)	
76-100	0.83	(0.14, 4.75)	0.79	0.27	(0.02, 3.39)	0.76
Hospital Division						
North East	1.00	(Ref.)		1.00	(Ref.)	
Mid Atlantic	NE	NE		NE	NE	
East North Central	NE	NE		NE	NE	
West North Central	1.30	NE		0.73	NE	
South Atlantic	NE	NE		0.63	NE	
East South Central	0.66	NE		0.68	NE	
West South Central	NE	NE		1.41	NE	
Mountain	NE	NE		0.34	NE	
Pacific	NE	NE	0.91	NE	NE	1.00
Hyperlipidemia						
No	1.00	(ref.)		1.00	(ref.)	
Yes	0.57	(0.15, 2.19)	0.41	2.74	(0.24, 31.41)	0.42
Diabetes mellitus						
No	1.00	(ref.)		1.00	(ref.)	
Yes	2.21	(0.55, 8.86)	0.27	0.20	(0.01, 2.9)	0.24
Hypertension						
No	1.00	(ref.)		1.00	(ref.)	
Yes	0.57	(0.12, 2.76)	0.48	3.20	(0.25, 40.95)	0.37

Abbreviations: NE, not estimated due to insufficient sample size; CI, confidence interval; HCUP-NIS, Healthcare Cost and Utilization Project Nationwide Inpatient Sample; OR, odds ratio; Ref., reference

[1] From unconditional logistic regression models; models for each risk factor adjusted for each of the other risk factors