

Curriculum Vitae

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Education

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Doctor of Dental Surgery (DDS), University of Jordan, Amman, Jordan	2016

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Professional Experience

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Teacher Assistant – Predoctoral fixed and removable laboratory	2019-2020
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ADEX dental examination Endodontics , 2020
Prosthodontics, Periodontics Restorative : PASS

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Dental license, Amman Jordan 2017-present

Basic life support (BLS) Certified – American Heart
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National Board Dental Examinations Part II : PASS 2016

National Board Dental Examinations Part I : PASS 2015

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Member, American Academy of Fixed Prosthodontics
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Member, American Academy of Maxillofacial
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American College of Prosthodontics Meeting- Virtual	2020
Implant Symposium- Virtual	2020
Fixed Prosthodontics Meeting, Chicago, IL, USA	2019
American College of Prosthodontics Meeting, Miami, FL, USA	2019
Implant Symposium – New York City, NY, USA	2019
Fixed Prosthodontics Meeting – Chicago, IL, USA	2019
American College of Prosthodontics Meeting, Baltimore, MD, USA	2018
Implant symposium – Boston, MA, USA	2018
Current Trends in Modern Dentistry: Aesthetic Dentistry, Digital Workflow, Art of Photography, Amman, Jordan	2018
1st International & 11th Annual Dental Conference, The University of Jordan, Amman, Jordan	2018
The Ultimate Digital Workflow for Everyday Restorative Dentistry – eon digital esthetics, Amman, Jordan	2017
2nd Scientific Evening – Jordanian Commission of Cosmetic Dentistry, Amman, Jordan	2017
Comprehensive Training – Conelog Dental Implant System Surgical & Prosthetic Procedures –	2017
Interactive Treatment Planning Session	2017
Aesthetic Indirect Restorations from Veneer to Onlays, Amman, Jordan The University of Jordan Amman, Jordan	2017
Clinical Crown Lengthening Basis , Techniques , Contemporary Procedures In Smile Make Over- University of Jordan, Amman, Jordan	2016
Suturing Techniques in Dentistry – The University of Jordan, Amman, Jordan	2014

Service

- | | |
|--|------|
| Oral Health Awareness Day – Oral Health Education Committee, University of Jordan, Amman, Jordan | 2017 |
| Diabetes and hypertension awareness campaign and screening – University of Jordan, Amman, Jordan | 2014 |

Publications

Peer reviewed published manuscripts:

Priyamvara A, Dey AK, Bandyopadhyay D, Katikineni V, Zaghlol R, Basyal B, Barssoum K, Amarin R, Bhatt DL, Lavie CJ. Periodontal Inflammation and the Risk of Cardiovascular Disease. *Curr Atheroscler Rep.* 2020 Jun 8;22(7):28. PMID: 32514778.

Abu-Awwad M, Amarin R, Khouli F, Shaban S, AlTarawneh S. Dentists' Attitudes in Jordan towards the Shortened Dental Arch Concept: A Cross-Sectional Study. *Int J Dent.* 2019 Dec 4;2019:4163851. PMID: 31885586.

Ongoing research- Submission process

Amarin R, Alshalawi H, Romberg R, Zaghlol R, Driscoll C, Price, J, Masri R. Incidental Findings in Cone Beam Computed Tomography Images during Prosthodontic Evaluation: Characteristics of Head and Neck Atheromas. *Virtual ACP Meeting 2020, USA*

Poster Presentations

Amarin R, Alshalawi H, Romberg R, Zaghlol R, Driscoll C, Price, J, Masri R. Incidental Findings in Cone Beam Computed Tomography Images during Prosthodontic Evaluation: Characteristics of Head and Neck Atheromas. Presented at *Virtual ACP Meeting 2020, USA*

Amarin R, Nguyen J, Masri, R. Prosthodontic Management of Pediatric and Special Needs Patients. Presented at *ACP meeting 2019, Miami, FL, USA.*

Abstract

Objectives

Atheromas can be incidentally detected in routine CBCT images. This study aims to assess prevalence, and risk factors associated with these vascular lesions.

Materials and Methods

Full-volume CBCT images of 458 patients were evaluated and divided into 4 groups: Subjects with no atheroma, subjects with intracranial atheroma (ICA), subjects with extracranial atheroma (ECA), and subjects exhibiting combined lesions. Age, sex, medical conditions, family history, and size were documented.

Results

Of the 458 subject scans, 29.9% presented with incidental atheromas. Atheroma's incidence was significantly higher in older patients and in males compared to females. Patients with atheroma were significantly more likely to have a history of hyperlipidemia, hypertension, and myocardial infarction. Patients exhibiting combined lesions were more likely to have cardiovascular risk factors.

Conclusion

Incidentally detected atheromas are common and subjects with combined lesions are at higher risk for CVD, and this warrants early referral to medical specialists.

Incidental Findings in Cone Beam Computed Tomography Images During Prosthodontic
Evaluation: Characteristics of Head and Neck Atheromas

by
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Thesis submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the Requirements for the Degree
Master of Science
2021.

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List of Abbreviations

CCAA	Calcified carotid artery atheroma (CCAA)
CVA	cerebral vascular accidents
COPD	Chronic Obstructive Pulmonary Disease
PAD	Peripheral arterial disease
MI/CAD	Myocardial infarction/coronary artery disease
CBCT	Cone beam computed tomography
CBCT-A	Cone beam CT angiography
ICA	Intracranial atheroma
ECA	Extracranial atheroma
(IRB)	Institutional Review Board
IV	Independent variable
DV	Dependent variable
ANOVA	Analysis of Variance
LX ²	likelihood ratio test
X ²	Chi-square

Chapter 1: Introduction

Atherosclerosis was previously thought to be a disease of the elderly given its increased prevalence with age.¹ However, data is now suggestive of early development in healthy young adults. For instance, coronary atherosclerosis was evident in 1 of every 6 asymptomatic teenagers.² Moreover, a study showed that all autopsies of 2867 adults who died of non-cardiac causes had evidence of fatty streaks.³ Thus, worldwide interest in early detection and prevention of atherosclerotic disease is on the rise.⁴

Atheroma is a term given to describe the lesion of atherosclerosis. Atherosclerosis is a pathological process that results in narrowing and occlusions in different arteries such as the aorta, coronaries, cerebral and peripheral blood vessels. Atheromatous plaques are related to the development of myocardial infarctions and strokes which are among the leading cause of death worldwide.⁵ The pathogenesis of atherosclerosis is complex and involves fatty deposition in the walls of arteries⁶ resulting in a significant degree of vessel narrowing.^{5,7} Several complex pathways such as inflammation, foam cell deposition and smooth muscle proliferation have been attributed to the development of atheroma.⁵ Fatty streak formation was found to be among the earliest histological changes in atheroma formation.⁸ Subsequently this results in the disruption of the smooth lining of blood vessels and contact between blood cells and the now rough endothelium which accelerates the formation of atherosclerosis. The contact of erythrocyte membranes with exposed molecules along the blood vessel damaged lining accelerates the enlargement of the necrotic core and the deposition of cholesterol and macrophages.⁹ Macrophages engulf deposited cholesterol and results in the advancement of lipid rich cores and areas of calcification.¹ Calcification increases as the atheroma matures and is

subsequently radiographically visible.⁶ The formed plaque can then become unstable with continuous shear forces caused by blood circulation, eventually resulting in intraplaque hemorrhage with sudden plaque rupture and luminal occlusion, causing ischemic vascular events.

Head and neck atheroma were incidentally detected by panoramic radiographs beginning in 1981. Over time, their presence became more important to consider due to their association with increased risk of cerebral vascular accidents (CVAs).¹⁰

Calcified carotid artery atheroma (CCAA)

Calcified carotid artery atheromas are lesions in the common carotid artery or its branches and are often detected by head and neck imaging performed for various reasons by dentists.¹¹ Carotid atheroma was shown to be an important indicator of generalized atherosclerosis and thromboembolism as calcifications in the carotid and aortic arteries had been associated with coronary artery calcifications.^{12 13} Embolization from carotid atherosclerotic lesions was found to be the most common source of strokes.¹⁴ Carotid artery lesions and stenosis have been extensively studied because they are an independent predictor of cerebrovascular events.¹⁵ It was shown that severe asymptomatic carotid artery stenosis (exceeding 50%-60% luminal stenosis) was responsible for 12-21% of anterior ischemic strokes.¹⁶ The prevalence of asymptomatic carotid artery stenosis is 0.5% in individuals less than 50 years old and increases to 5.0-10% over 65 years of age.¹⁵ A systematic review assessing the relationship between incidental CCAA on panoramic images with the development of cerebrovascular accidents in 54 articles found the data to be incomplete and inconclusive.¹¹ Another study found anterior circulation (cerebral arteries forming the anterior part of the circle of Willis, a circulatory

anastomosis supplying blood to the brain) CVAs to be 1.5 times higher in patients with CCAA and that severe plaques were associated with a ten times increased chance of lacunar infarctions (infarcts affecting deep brain structures by occlusions of penetrating arteries).¹³

Surgical and medical interventions such as stenting or carotid artery endarterectomy have been shown to be effective interventions in carotid artery stenosis.¹⁷ In fact, early intervention with carotid endarterectomy reduces the risk of strokes by approximately 30% over three years.¹⁸

The incidental prevalence of CCAA on panoramic radiographs was reported between 0.43-5.0% and varied by gender, age and ethnicity.¹¹ It was found to be significantly higher in populations of increased risk factors such as diabetes mellitus,¹⁹ cardiomyopathies,²⁰ renal disease,²¹ obstructive sleep apnea,²² history of radiation and osteoradionecrosis^{19, 23, 24} and in postmenopausal women.²⁵

The intracranial carotid artery has been highlighted in several studies. Intracranial atheroma has been highly detected in patients with ischemic strokes²⁶ and by itself contributes to 75% of all strokes.²⁷ Moreover, there is a strong association between intracranial calcifications and chronic kidney disease.²⁶ Prior studies found intracranial atheroma to be more prevalent among certain ethnicities such as the white population.²⁷ Therefore, its' detection and differentiation among different races might be of great importance.

In a recent case report about Mönckeberg medial calcinosis, a type of atherosclerosis that only affects the tunica media of arteries, the authors highlighted the importance of its' early detection by cone beam computed tomography (CBCT) in patients with underlying

systemic disease (i.e., chronic kidney disease and diabetes mellitus).²⁸ These calcifications may be found incidentally on panoramic radiographs and are commonly found in CBCT imaging.²⁸ This type of calcification is found in the lower extremities and is higher in prevalence in middle-aged men.²⁹ Although Mönckeberg calcification does not occlude the vessel lumen, it does reduce the elasticity of the wall, compromising perfusion and eventually leading to arterial diseases.³⁰

Risk factors associated with Mönckeberg medial calcinosis also include chronic inflammation, age, systemic lupus erythematosus, and hypervitaminosis D.³¹ It was first described in the facial arteries in association with patients with serious comorbidities.³²

A recent case report described how extensive advanced calcifications were detected by dental radiographs in a diabetic patient with end stage renal disease.³³ In another case study on a patient with chronic kidney failure, it was suggested that the bilateral calcification of facial arteries was due to metastatic calcification of secondary hyperparathyroidism.³⁴

In one reported incident, a 64-year-old male diabetic patient with chronic kidney disease, hypercalcemia and hyperphosphatemia was sent for a scan for a brown tumor that had developed due to secondary hyperparathyroidism. Upon review of his radiographs, there were findings of Mönckeberg calcifications in the external carotid artery and its branches, the suprahyoid of the lingual artery, the facial artery, transverse facial artery, internal maxillary artery, superficial temporal arteries and common plaques in the internal and common arteries.³⁵

Some findings in the literature suggest that thyroid disease can be related to vascular calcifications. In an in vivo study conducted on animals, elevation of thyroid hormones

was thought to play a role in vascular calcifications.³⁶ Reports of studies on female patients with papillary carcinoma, cystic adenomatous nodules, and chronic lymphocytic thyroiditis showed positive finding of calcinosis of the thyroid gland vessels. These patients were all further examined because of the high risk of cardiovascular events.³⁷

Radiographs have been used extensively in the medical field to detect and recognize several diseases including but not limited to diabetes, chronic kidney disease, hyperthyroidism and coronary artery diseases.³⁸⁻⁴¹

Despite their wide use in dentistry, panoramic radiographs have limited ability to detect atheromas as they are dependent on patient positioning and focal trough width. Also they offer only 2-dimensional spatial resolution limiting their abilities to detect lesions.⁴²

On the other hand, CBCT offers a higher resolution, and a three-dimensional image with greater reliability in detecting incidental atheroma²². The role of CBCT for detecting atheroma was also highlighted in 2014 and 2017 by Safain et al and Soares et al respectively.^{43,44} In prior studies, the incidence of atheromas on CBCT was estimated to be around 18%,^{44,45} and was significantly higher in men than in women with no significant difference on laterality.⁴⁴ However, data regarding CBCT utility for important lesions other than CCAA such as vertebral, ophthalmic and intracranial arteries is lacking. Moreover, there is a lack of data on the impact of patient characteristics such as age, gender, ethnicity, and risk factors on the prevalence of head and neck atheroma.

Hypotheses

The aim of this study was to investigate the prevalence of various types of incidental head and neck atheroma detected on CBCT radiographs and study their relationship with patients' characteristics such as age gender, ethnicities, and systemic diseases.

Null hypotheses

- There is no significant difference between patients with and without head and neck atheroma regarding the following characteristics:
 - (A) Age
 - (B) Sex
 - (C) Ethnicity
 - (D) Medical conditions (endocrine related diseases, cardiovascular diseases, chronic kidney disease, respiratory disease, malignancy, and depression)
 - (E) Medications
 - (F) Family history of systemic disease (diabetes and cardiovascular disease)
- There is no significant difference in number of lesions in patients with cardiovascular diseases and/or history of malignancies.

Research hypotheses

- There is a significant difference between patients with and without head and neck atheroma for the following groups:
 - (A) Older patients would have more atheroma than younger patients.
 - (B) Males would have more atheroma than females.
 - (C) There is a difference in incidence of atheroma between different ethnicities.
 - (D) The incidence of atheroma is higher in diabetic patients, patients with thyroid disease, high cholesterol level, high blood pressure, history of myocardial infarctions or chronic arterial disease MI/CAD, peripheral arterial disease (PAD), cerebrovascular accidents (CVA), chronic kidney disease, chronic obstructive pulmonary disease, asthma, sleep apnea, malignancy and depression.
 - (E) The incidence of atheroma is higher in patients taking anti-platelet agents, anticoagulants, antihypertensives, oral hypoglycemic agents, insulin, and statin.
 - (F) The incidence of atheroma is higher in patients with a family history of diabetes or family history of atherosclerotic arterial disease.
- There is a significant difference in number of lesions in patients with cardiovascular diseases and/or history of malignancies.

Chapter 2: Materials and Methods

This is a cross-sectional study that investigated consecutive patients that underwent CBCT at the University of Maryland School of Dentistry, from January 1st, 2016 to August 31st, 2019. Inclusion criteria were: Patients older than 18 years of age who underwent maxillofacial CBCT for dental reasons unrelated to the purpose of this study. The University of Maryland Baltimore Institutional Review Board (IRB) approved the study (HP-00084560). Between the years 2016 and 2019, 817 patients were initially included. A total of 359 files were excluded for the following reasons: Duplicates for patients who had multiple full-volume CBCTs (156), no radiographic reports or available radiographs (142), limited view CBCTs (18), incomplete medical charts (34), trial file (1), and patients under the age of 18 (8).

The following data were collected from the patients' charts: age, sex, ethnicity, alcohol use, smoking, endocrine diseases, cardiovascular diseases, chronic kidney diseases, respiratory diseases, malignancy, depression, and medications. Family history of diabetes and cardiovascular disease were also recorded. The medication list was closely examined for indications of any of the above diseases since patients may not have mentioned their particular disease or the providers might not have indicated this in the medical chart and clinical notes.

The primary investigator (RA) was responsible for reviewing the scan results and performing chart reviews.

The following methods of blinding were implemented to prevent potential bias:

1. CBCT images were provided to the primary investigator (RA) by the interpreting radiologist (JP) by without access to the patients' medical chart, thus preventing any bias in interpreting or studying the CBCT images.

2. Interpretations were labelled by serial numbers then the primary investigator was provided the dental record numbers for the scans and chart review was conducted by the primary investigator to obtain patient information.

The studied scans included only full head and neck scans. Each subject's full-volume CBCT was analyzed, and a report was written by the radiologist for the presence of intracranial (ICA) and extra-cranial (ECA) atheroma. The primary investigator was trained and calibrated to read the scans by the radiologist (JP).

Collected images were limited to two Carestream 9300 devices. For ECA, lesions in both the extracranial carotid artery and lesions in the vertebral artery were recorded. For ICA, data were recorded for intracranial carotid atheroma, anterior, middle, and posterior cerebellar arteries.

For each of these sites, the following characteristics were recorded by the primary investigator (RA):

- A. Presence or absence of atheroma
- B. Side of atheroma (right and left)
- C. Number of atheroma lesions in each site
- D. Bilateral incidence (Yes, No)

In each view (sagittal, axial, or coronal), the largest measurement was collected for each separate lesion.

In situations where there are multiple lesions, the total size (mm) was also indicated separately for the axial, the coronal, and the sagittal views.

Detected atheroma were measured by the primary investigator (RA) using a digital ruler on In-Vivo version 6 by Anatomage dental computer software. To prevent duplicate recordings of measurements, each lesion was examined in the three different views. This prevented the primary investigator from counting the same lesion twice.

Lesions of atheroma were distinguished by the evident radio-opacity when compared to the surrounding structure in the specified anatomical location they are commonly detected in and recognized in considerations of important landmarks. For example:

- i. Location of calcified carotid atheroma is commonly found at the level of the C3 and C4 vertebrae
- ii. Using an axial view, precerebral calcified carotid artery atheroma is found lateral and posterior to the airway.
- iii. Cerebral intracranial atheroma is found in the cavernous sinus superior and lateral to the sphenoid sinus.
- iv. Vertebral artery atheroma is found at the level of the C2 and C3 vertebrae in the lateral foramina of cervical vertebra. The vertebral artery continues its' pathway to the foramen magnum and merges to form the basilar artery (Circle of Willis).
- v. Structures near the area of interest; for example, near the external carotid artery that might be confused with calcified atheroma (such as the calcified greater horn of the thyroid cartilage) were not recorded as calcified atheroma.

Data was then combined in a separate Excel file and divided into 4 groups based on atheroma characteristics: Subjects with no atheroma (controls), subjects with ICA, subjects with ECA, and subjects with both ICA and ECA in the same scan. Following this, data from both sets were combined and housed for statistical analysis by the primary investigator.

Statistical analysis

The independent variables (IV) in this study were divided into measured and categorical variables. Age was a measured variable. Categorical data were sex, ethnicity, medical conditions, medications, family history of diabetes and family history of atherosclerotic arterial disease. The dependent variables (DV) in this study were the presence and absence of intracranial atheroma, extracranial atheroma and both extracranial and intracranial atheroma combined.

Between-group comparisons for measured data were conducted using Analysis of Variance (ANOVA) and Tukey's highly significance difference test. A Shapiro-Wilk test was used to assess normality. Age was reported as mean and standard deviation. A p value of ≤ 0.05 was considered statistically significant.

Categorical variables (e.g presence or absence of atheroma, presence or absence of hypertension, presence or absence of high cholesterol level, presence or absence of diabetes, smoker and non-smoker, male and female, ethnicity, location of atheroma) were reported as frequencies and percentages. Categorical variables were compared using chi-square. When a significant difference was found, partitioning⁴⁶ was used to determine the specific differences. This post hoc test, partitioning, is used to divide the Chi-square

table into multiple 2x2 orthogonal sub-tables that are statistically independent of each other. These sub-tables were analyzed by the likelihood ratio test (LX^2). Analyzed subgroups are represented in boxes with thick lines.

Four rules have been established for the partitioning.⁴⁷ The degrees of freedom determine the number of sub-tables that can be analyzed.

1. The number of sub-tables must equal the degrees of freedom.
2. Each cell count taken from the full chi-square contingency table must appear in only one sub-table.
3. Marginal totals in the sub-tables must reflect only one total of the full Chi-square table.
4. The sum of the likelihood ratio tests of the sub-tables must equal the likelihood ratio of the full Chi-square table or the tables are not independent. (The chi-square values of the sub-tables do not necessarily add up to the chi-square of the full chi-square table).

A p value of ≤ 0.05 was considered statistically significant.

Chapter 3: Results

A. Statistical analysis

Collected data are summarized in tables 1-15 (A-D). Of the four hundred and fifty-eight subjects, 137 (29.9%) had an incidentally detected atheroma on CBCT. Forty-seven had ICAs, 59 had ECAs and 31 had both.

Incidence of IA, EA, both IA+EA and no atheroma is compared to all patient characteristics using analysis of variance and Tukey honestly significant difference test. Data are presented as means (\bar{x}) and standard deviation (SD).

B. Patient characteristics

Of the 458 subjects included 230(50.2%) were males and 228 (49.8%) were females. The age of patients ranged between 21 and 90 years. Of the ethnicities collected, 240 (52.4%) were unrecorded, 112 (24.5%) were Caucasians, 11 (2.4%) were Hispanics, 72 (15.7%) were African Americans, 21 (4.6%) were Asians, 1 (0.2%) was Native Americans, and 1 (0.2%) was a Pacific Islander (Table 1A). There were an insufficient number of recordings in some of the listed ethnicities in the patients' files to conduct a statistical analysis on the differences between all the various ethnicities.

Table 2 shows that patients with atheroma were significantly older as compared to those without atheroma (Both IC and EC \bar{x} = 69.2 (SD 7.6), IC \bar{x} = 65.3(SD 9.3), EC \bar{x} = 64.7(SD 10.1), vs no atheroma \bar{x} = 55.8(SD 13.4), p=0.004).

Atheroma and Ethnicity

There was an insufficient number of subjects for statistical analysis in the groups labeled Hispanic, Asian, Native American, and Pacific Islander (Table 1.A) .

Table 1.A: Incidence of intracranial, extracranial, both intracranial and extracranial and no atheroma for all ethnicities

Ethnicity	Intracranial Atheroma (n)	Extracranial Atheroma (n)	Intracranial and Extracranial atheroma (n)	No Atheroma (n)	Total n (%)
Unknown	24	31	17	168	240(52.4%)
Caucasian	15	16	10	71	112(24.5%)
Hispanic	1	1	0	9	11(2.4%)
African American	5	9	3	55	72(15.7%)
Asian	2	2	1	16	21(4.6%)
Native American	0	0	0	1	1(0.2%)
Pacific Islander	0	0	0	1	1(0.2%)
Total n (%)	47 (10.3%)	59 12.9%)	31 (6.8%)	321 (70%)	458 (100%)

Caucasians comprised a total of 112 subjects (24.5%) and African Americans a total of 72(15.7%) subjects. (Table 1.B).

Table 1.B: Incidence of intracranial, extracranial, both intracranial and extracranial and no atheroma for Caucasians and African Americans.

Ethnicity	Intracranial Atheroma (n)	Extracranial Atheroma (n)	Intracranial and Extracranial atheroma (n)	No Atheroma (n)	Total n(%)
Caucasian	15	16	10	71	112(24.5%)
African American	5	9	3	55	72(15.7%)

See Table 1C-F for statistical analysis between Caucasians and African Americans.

Results shows that there was no significant difference between Caucasians and African Americans in the incidence of any type of atheroma (Table1.C), $p = 0.22$.

Table 1.C: Incidence of intracranial, extracranial, both intracranial and extracranial and no atheroma for Caucasians as compared to African Americans.

Type of atheroma	Ethnicity		
	Caucasians n (%)	African American n (%)	Total
Intracranial and Extracranial atheroma	10(76.9%) ^a	3(23.1%)	13(%)
Intracranial Atheroma	15(75%) ^a	5(25%)	20(%)
Extracranial Atheroma	16(75%) ^a	9(36%)	25(%)
No Atheroma	71(56.3%) ^a	55(43.7%)	126(%)
Total	112(61%)	72(39%)	184(100%)
$X^2=4.3, p = 0.23$	$LX^2=4.5, p = 0.22$		

*groups with the same letter are not significantly different.

There was no significant difference between Caucasians and African Americans as compared to patients with intracranial and extracranial atheroma and patients with extracranial atheroma alone (Table 1.D), $p=0.41$.

Table 1.D: Incidence, between Caucasians and African Americans as compared to patients with the combination of intracranial and extracranial atheroma as compared to extracranial atheroma alone.

Type of atheroma	Ethnicity		
	Caucasians n (%)	African American n (%)	Total
Intracranial and Extracranial atheroma	10(76.9%)	3(23.1%)	13(34%)
Extracranial Atheroma	16(64%)	9(36%)	25(66%)
Total	26(68%)	12(32%)	38(100%)
$X^2=0.7, p= 0.42$	$LX^2=0.7, p =0.41$		

There was no significant difference between Caucasians and African Americans in the incidence of intracranial and extracranial atheroma, extracranial atheroma alone and intracranial atheroma alone (Table 1.E), $p=0.60$.

Table 1.E: Incidence between Caucasians and African Americans in the occurrence of the combination of intracranial and extracranial atheroma and extracranial atheroma alone as compared to the incidence of intracranial atheroma alone.

Type of atheroma	Ethnicity		
	Caucasians n (%)	African American n (%)	Total
Intracranial and Extracranial atheroma Extracranial Atheroma	26(28.9%)	12(13.3%)	90 (66%)
Intracranial Atheroma	15(75%)	5(25%)	47(34%)
Total	41(71%)	17(29%)	137(100%)
$X^2=0.274, p = 0.601$		$LX^2=0.278, p = 0.598$	

Table 1.F shows that the result of the chi-square approaches significance. This indicates that Caucasians were possibly more likely to have one of the types of atheroma when compared to African Americans (Table 1.F), $p=0.061$.

Table 1.F: Incidence between Caucasians and African Americans in the occurrence of either intracranial, extracranial, or both intracranial and extracranial atheroma as compared to no atheroma.

Type of atheroma	Ethnicity		
	Caucasians n (%)	African American n (%)	Total
Intracranial and Extracranial atheroma	41(70.7%)	17(29.3%)	58(32%)
Extracranial Atheroma			
Intracranial Atheroma			
No Atheroma	71(56.3%)	55(43.7%)	126(68%)
Total	112(61%)	72(39%)	184(100%)
$X^2=3.4, p = 0.064$		$LX^2=3.5, p=0.061$	

Atheroma and Age

Patients with the three different types of atheroma were significantly older when compared to patients with no atheroma (Table 2) , $p \leq 0.004$.

Table 2: Incidence of intracranial, extracranial, both intracranial and extracranial and no atheroma by age.

Parameter	Intracranial Atheroma (n=47) mean (SD)	Extracranial Atheroma (n=59) mean (SD)	Intracranial and Extracranial atheroma (n=31) mean (SD)	No Atheroma (n=321) mean (SD)	ANOVA F	p-value
Age (years), mean (SD)*	65.3(9.3) ^{a*}	64.7(10.1) ^a	69.2(7.6) ^a	55.8(13.4) ^b	1.59	0.004

*Groups with the same letter are not significantly different.

Atheroma: Males vs Females

Males were more likely to have the combination of intracranial and extracranial atheroma while females were more likely to have intracranial atheroma alone (Table 3). According to the partitioning rules, (described on page 12), no further subgroup analysis was allowed as the fourth rule was not met. The combination of likelihood ratios does not allow the tables to be compared independently.

Table 3: Incidence of intracranial, extracranial, both intracranial and extracranial and no atheroma for males and females.

Type of atheroma	Gender		
	Males n (%)	Females n (%)	Total
Intracranial and Extracranial atheroma	21(67.7%) ^{a*}	10(32.3%)	31 (7%)
Extracranial Atheroma	36(61%) ^{ab}	23(39%)	59 (13%)
No Atheroma	152(47.4%) ^{ab}	169(52.6%)	321 (70%)
Intracranial Atheroma	21(44.7%) ^b	26(55.3%)	47 (10%)
Total	230 (50%)	228 (50%)	458(100%)
X ² =8.19, p ≤ 0.042		LX ² =8.303, p ≤ 0.040	

*Groups with the same letter are not significantly different.

Atheroma vs Hyperlipidemia

Patients with the combination of intracranial and extracranial atheroma were more likely to have hyperlipidemia as compared to patients with no atheroma (Table 4.A), $p \leq 0.001$.

Table 4.A: Incidence of intracranial, extracranial, both intracranial and extracranial and no atheroma for patients with and with no recorded history of hyperlipidemia.

Type of atheroma	Disease State		
	Hyperlipidemia n (%)	No hyperlipidemia, n (%)	Total
Intracranial and Extracranial atheroma	18(58.1%) ^{a*}	13(41.9%)	31(7%)
Extracranial Atheroma	29(49.2) ^{ab}	30(50.8%)	59(13%)
Intracranial Atheroma	17(36.2%) ^{ab}	30(63.8%)	47(10%)
No Atheroma	79(24.6%) ^b	242(75.4%) ^b	321(70%)
Total	143(31%)	315(69%)	458(100%)
$X^2=26.3, p < 0.001$		$LX^2=25.0, p < 0.001$	

*Groups with different letters are significantly different.

There was no significant difference in the hyperlipidemia disease state between patients with intracranial and extracranial atheroma as compared to patients with extracranial atheroma alone, (Table 4.B), $p = 0.42$.

Table 4.B: Incidence of patients with and without hyperlipidemia as compared to patients with the combination of intracranial and extracranial atheroma versus extracranial atheroma alone.

Type of atheroma	Disease State		
	Hyperlipidemia n (%)	No hyperlipidemia, n (%)	Total
Intracranial and Extracranial atheroma	18(58.1%)	13(41.9%)	31(44%)
Extracranial Atheroma	29(49.2)	30(50.8%)	59(66%)
Total	47(52%)	43(48%)	90(100%)
$X^2=0.647, p = 0.421$		$LX^2=0.649, p = 0.42$	

Table 4.C show that the result of the chi-square approached significance ($p=.07$). This indicates that patients with Intracranial and extracranial atheroma and extracranial atheroma were probably more likely to have a history of hyperlipidemia while patients with intracranial atheroma alone are more likely to have no history of hyperlipidemia.

Table 4.C: Incidence between the two disease states of hyperlipidemia versus the combination of intracranial and extracranial atheroma and extracranial atheroma alone.

Type of atheroma	Disease State		
	Hyperlipidemia n (%)	No hyperlipidemia, n (%)	Total
Intracranial and Extracranial atheroma	47(52.2%)	43(47.8%)	90 (66%)
Extracranial Atheroma			
Intracranial Atheroma	17(36.2%)	30(63.8%)	47(34%)
Total	64(47%)	73(53%)	137(100%)
$X^2=3.196, p=0.074$		$LX^2=3.229, p=0.072$	

Patients with all types of atheroma were significantly more likely to have hyperlipidemia when compared to patients with no atheroma,(Table 4.D), $p \leq 0.001$.

Table 4.D: Incidence between patients with and without a history of hyperlipidemia as compared to patients with either intracranial, extracranial, or both intracranial and extracranial atheroma and those patients without atheroma.

Type of atheroma	Disease State		
	Hyperlipidemia n (%)	No hyperlipidemia n (%)	Total
Intracranial and Extracranial atheroma	64(46.7%)	73(53.2%)	137 (30%)
Extracranial Atheroma			
Intracranial Atheroma			
No Atheroma	79(24.6%)	242(75.4%)	321(70%)
Total	143(31%)	315(69%)	458(100%)
$X^2=21.8, p <0.001$		$LX^2=21.1, p <0.001$	

Atheroma vs Hypertension

Patients with the combination of intracranial and extracranial atheroma were more likely to have hypertension as compared to patients with no atheroma (Table 5.A), $p < 0.001$.

Table 5.A: Incidence of intracranial, extracranial, both intracranial and extracranial and no atheroma for patients with and with no recorded history of hypertension.

Type of atheroma	Disease State		
	Hypertension n (%)	No hypertension n (%)	Total
Intracranial and Extracranial atheroma	23(74.2%) ^{a*}	8(25.8%)	31(7%)
Extracranial Atheroma	29(49.2%) ^{ab}	30(50.8%)	59(13%)
Intracranial Atheroma	22(46.8%) ^{ab}	25(53.2%)	47(10%)
No Atheroma	103(32.1%) ^b	218(67.9%) ^b	321 (70%)
Total	177(39%)	281 (61%)	458(100%)
$X^2=26.3, p < 0.001$		$LX^2=25.0, p < 0.001$	

*Groups with different letters are significantly different.

Patients with the combination of intracranial and extracranial atheroma were more likely to have hypertension as compared to patients with extracranial atheroma alone (Table 5.B), $p=0.02$.

Table 5.B: Incidence between patients with hypertension and without hypertension, as compared to patients with the combination of intracranial and extracranial atheroma vs extracranial atheroma alone.

Type of atheroma	Disease State		
	Hypertension n (%)	No hypertension n (%)	Total
Intracranial and Extracranial atheroma	23(74.2%)	8(25.8%)	31(44%)
Extracranial Atheroma	29(49.2%)	30(50.8%)	59(66%)
Total	52(58%)	38(42%)	90(100%)
$X^2=5.22, p= 0.022$		$LX^2=5.402, p = 0.020$	

There was no significant difference in the occurrence of hypertension between patients with the combination of intracranial and extracranial atheroma and extracranial atheroma when compared to intracranial atheroma alone (Table 5.C), $p \leq 0.222$.

Table 5.C: Incidence between patients with hypertension and without hypertension as compared to the combination of intracranial and extracranial atheroma vs (delete as to compared) extracranial atheroma alone.

Type of atheroma	Disease State		
	Hypertension, n (%)	No Hypertension, n (%)	Total
Intracranial and Extracranial atheroma	52(57.8%)	38 (42.2%)	90 (66%)
Extracranial Atheroma			
Intracranial Atheroma	22(46.8%)	25(53.2%)	47(34%)
Total	74(54%)	63(46%)	137(100%)
$X^2=1.496, p=0.221$	$LX^2=1.494, p=0.222$		

Patients with all types of atheroma were significantly more likely to have hypertension when compared to patients with no atheroma (Table 5.D), $p \leq 0.001$.

Table 5.D: Incidence between patients with and without a history of hypertension and patients with either intracranial, extracranial, or both intracranial and extracranial atheroma as compared to patients without atheroma.

Type of atheroma	Disease State		
	Hypertension n (%)	No Hypertension n (%)	Total
Intracranial and Extracranial atheroma	74(54%)	63(46%)	137 (30%)
Extracranial Atheroma			
Intracranial Atheroma			
No Atheroma	103(32.1%)	218(67.9%)	321(70%)
Total	177(39%)	281(61%)	458(100%)
$X^2=19.5, p \leq 0.001$	$LX^2=19.2, p \leq 0.001$		

Atheroma vs MI/CAD

Patients with the combination of intracranial and extracranial atheroma were more likely to have a history of MI/CAD as compared to patients with no atheroma (Table 6.A), $p \leq 0.001$.

Table 6.A: Incidence of myocardial infarction/coronary artery disease (MI/CAD) for patients with intracranial, extracranial, both intracranial and extracranial and no atheroma.

Type of atheroma	Disease State		
	MI/CAD n (%)	No MI/CAD n (%)	Total
Intracranial and Extracranial atheroma	6(19.4%) ^{a*}	25(80.6%)	31(7%)
Extracranial Atheroma	5(8.5%) ^{ab}	54(91.5%)	59(13%)
Intracranial Atheroma	5(10.6%) ^{ab}	42(89.4%)	47(10%)
No Atheroma	5(1.6%) ^b	316(98.4%)	321(70%)
Total	21(5%)	437(95%)	458(100%)
$X^2=28.2, p \leq 0.001$		$LX^2=22.4, p \leq 0.001$	

*Groups with different letters are significantly different.

There was no significant difference in MI/CAD disease between patients with intracranial and extracranial atheroma as compared to patients with extracranial atheroma alone, (Table 6.B), $p \leq 0.14$.

Table 6.B: Incidence between patients with and without a history of myocardial infarction/coronary artery disease (MI/CAD) with respect to having a combination of intracranial and extracranial atheroma as compared to extracranial atheroma alone.

Type of atheroma	Disease State		
	MI/CAD n (%)	MI/CAD n (%)	Total
Intracranial and Extracranial atheroma	6(19.4%)	25(80.6%)	31(34%)
Extracranial Atheroma	5(8.5%)	54(91.5%)	59(66%)
Total	11(12%)	79(88%)	90(100%)
$X^2=2.242, p \leq 0.134$		$LX^2=2.13, p \leq 0.14$	

There was no significant difference in MI/CAD disease between patients with the combination of intracranial and extracranial atheroma and extracranial atheroma alone vs patients with intracranial atheroma alone, (Table 6.C), $p \leq 0.79$.

Table 6.C: Incidence between having and not having MI/CAD vs intracranial and extracranial atheroma and extracranial atheroma alone as compared to intracranial atheroma alone.

Type of atheroma	Disease State		
	MI/CAD n (%)	No MI/CAD n (%)	Total
Intracranial and Extracranial atheroma	11(12%)	79(87%)	90 (66%)
Extracranial Atheroma			
Intracranial Atheroma	5(10.6%)	42(89.4%)	47(34%)
Total	16(12%)	121(88%)	137(100%)
$X^2=0.075, p \leq 0.784$		$LX^2=0.076, p \leq 0.783$	

Patients with all types of atheroma were significantly more likely to have a history of MI/CAD when compared to patients with no atheroma (Table 6.D), $p \leq 0.001$.

Table 6.D: Incidence between patients with and without MI/CAD) vs patients with intracranial, extracranial, or both intracranial and extracranial atheroma as compared to patients without atheroma.

Type of atheroma	Disease State		
	MI/CAD n (%)	No MI/CAD n (%)	Total
Intracranial and Extracranial atheroma			
Extracranial Atheroma	16(12%)	121(88%)	137 (30%)
Intracranial Atheroma			
No Atheroma	5(1.6%)	316(98.4%)	321(70%)
Total	21(5%)	437(95%)	458(100%)
$X^2=22.5, p < 0.001$		$LX^2=20.2, p < 0.001$	

Atheroma vs Anti-platelet agents

Patients with the combination of intracranial and extracranial atheroma were more likely to have a history of anti-platelet agents use as compared to patients with no atheroma,(Table 7.A), $p \leq 0.001$.

Table 7.A: Incidence of patients with the use of as opposed to no use of anti-platelet agent's vs intracranial, extracranial, both intracranial and extracranial and no atheroma.

Type of atheroma	Disease State		
	Use of anti-platelet agents n (%)	No Use of anti-platelet agents n (%)	Total
Intracranial and Extracranial atheroma	17(54.8%) ^{a*}	14(45.2%)	31(7%)
Extracranial Atheroma	15(25.4%) ^{ab}	44(74.6%)	59(13%)
Intracranial Atheroma	6(12.8%) ^{ab}	41(87.2%)	47(10%)
No Atheroma	39(12.2%) ^b	282(87.8%)	321(70%)
Total	77(17%)	381(83%)	458(100%)
$X^2=40.7, p \leq 0.001$	$LX^2=31.9, p \leq 0.001$		

*Groups with different letters are significantly different.

There was no significant difference between patients who use and don't use anti-platelet agents whether they have the combination of intracranial and extracranial atheroma or extracranial atheroma alone, (Table 4.B), $p = 0.14$.

Table 7.B: Incidence between patients with and without anti-platelet use vs patients with the combination of intracranial and extracranial atheroma as compared to extracranial atheroma alone.

Type of atheroma	Disease State		
	Use of anti-platelet agents n (%)	No Use of anti-platelet agents n (%)	Total
Intracranial and Extracranial atheroma	17(54.8%)	14(45.2%)	31(34%)
Extracranial Atheroma	15(25.4%)	44(74.6%)	59(66%)
Total	32(36%)	58 (64%)	90(100%)
X ² =7.7, p= 0.006		LX ² =7.6, p = 0.14	

Patients who use anti-platelet agents were more likely to have Intracranial and extracranial atheroma or extracranial atheroma alone while patients without use of anti-platelet agents are more likely to have intracranial atheroma alone, (Table 7.C), p=0.003.

Table 7.C: Incidence between use and no use of anti-platelet agent's vs the combination of intracranial and extracranial atheroma and extracranial atheroma alone as compared to the incidence of intracranial atheroma alone.

Type of atheroma	Disease State		
	Use of anti-platelet agents n (%)	No use of anti-platelet agents n (%)	Total
Intracranial and Extracranial atheroma	32(36%)	58(64%)	90 (66%)
Extracranial Atheroma			
Intracranial Atheroma	6(12.8%)	41(87.2%)	47(34%)
Total	38(28%)	99(72%)	137(100%)
X ² =8.00, p=0.005		LX ² =8.737, p =0.003	

Patients with all types of atheroma were significantly more likely to use anti-platelet agents when compared to patients with no atheroma, (Table 7.D), p=0.001.

Table 7.D: Incidence of patients with and without use of anti-platelet agents vs patients with either intracranial, extracranial, or both intracranial and extracranial atheroma as compared to patients without atheroma.

Type of atheroma	Disease State		
	Use of anti-platelet agents n (%)	Use of anti-platelet agents n (%)	Total
Intracranial and Extracranial atheroma			
Extracranial Atheroma	38(28%)	99(72%)	137 (30%)
Intracranial Atheroma			
No Atheroma	39(12.2%)	282(87.8%)	321(70%)
Total	77(17%)	381(83%)	458(100%)
$X^2=16.7, p <0.001$	$LX^2=15.6, p <0.001$		

Atheroma Vs Antihypertensives

Patients with the combination of intracranial and extracranial atheroma were more likely to have history of antihypertensive agent use as compared to patients with no atheroma, (Table 8.A), $p < 0.001$.

Table 8.A: Incidence of intracranial, extracranial, both intracranial and extracranial and no atheroma for patients with and with no recorded history of antihypertensive agent use.

Type of atheroma	Disease State		
	Antihypertensives n (%)	No Use Antihypertensives n (%)	Total
Intracranial and Extracranial atheroma	22(71%) ^{a*}	9(29%)	31(7%)
Extracranial Atheroma	29(49.2%) ^{ab}	30(50.8%)	59(13%)
Intracranial Atheroma	22(46.8%) ^{ab}	25(53.2%)	47(10%)
No Atheroma	98(30.5%) ^b	223(69.5%) ^b	321(70%)
Total	171(37%)	287(63%)	458(100%)
$X^2=26.7, p < 0.001$		$LX^2=26.1, p < 0.001$	

*Groups with different letters are significantly different.

Patients with the combination of intracranial and extracranial atheroma were more likely to have history of antihypertensive agent use as compared to patients with extracranial atheroma alone, (Table 8.B), $p=0.047$.

Table 8.B: Incidence, between patients with and without history of antihypertensive agent use, compared to patients with the combination of intracranial and extracranial atheroma as compared to extracranial atheroma alone.

Type of atheroma	Disease State		
	Use of antihypertensives n (%)	No Use of antihypertensives n (%)	Total
Intracranial and Extracranial atheroma	22(71%)	9(29%)	31(34%)
Extracranial Atheroma	29(49.2%)	30(50.8%)	59(66%)
Total	51(57%)	39(43%)	90(100%)
$X^2=3.94, p= 0.047$		$LX^2=4.04, p = 0.045$	

There was no significant difference in the use or lack of use of antihypertensive agents between patients with intracranial and extracranial atheroma and extracranial atheroma alone as compared to patients with only intracranial atheroma alone, (Table 8.C), $p \leq 0.28$.

Table 8.C: Incidence between use or no use of antihypertensive agents vs the combination of intracranial and extracranial atheroma and extracranial atheroma alone as compared to the incidence of intracranial atheroma alone.

Type of atheroma	Disease State		
	Use of antihypertensives n (%)	Use of antihypertensives n (%)	Total
Intracranial and Extracranial atheroma	55(61%)	39(39%)	90 (66%)
Extracranial Atheroma			
Intracranial Atheroma	22(46.8%)	25(53.2%)	47(34%)
Total	73(53%)	64(47%)	137(100%)
$X^2=1.205, p =0.272$		$LX^2=1.205, p =0.272$	

Patients with all types of atheroma were significantly more likely to use antihypertensive agents when compared to patients with no atheroma, (Table 8.D), $p=0.001$.

Table 8.D: Incidence of use and lack of use of antihypertensive agent's vs patients with intracranial, extracranial, or both intracranial and extracranial atheroma as compared to patients without atheroma.

Type of atheroma	Disease State		
	Use of antihypertensives n (%)	Use of antihypertensives n (%)	Total
Intracranial and Extracranial atheroma	73(53.3%)	64(46.7%)	137 (30%)
Extracranial Atheroma			
Intracranial Atheroma			
No Atheroma	98(30.5%)	223(69.5%)	321(70%)
Total	171(37%)	287(63%)	458(100%)
$X^2=21.3, p <0.001$		$LX^2=21.9, p <0.001$	

Atheroma vs Oral hypoglycemic agents

Patients with use of hypoglycemic agents were more likely to have intracranial and extracranial atheroma as compared to patients with intracranial atheroma alone, (Table 9.A), $p \leq 0.05$.

Table 9.A: Incidence of use or non-use of oral hypoglycemic agent's vs patients with intracranial, extracranial, both intracranial and extracranial and no atheroma.

Type of atheroma	Disease State		
	Oral hypoglycemic agents n (%)	No use of oral hypoglycemic agents n (%)	Total
Intracranial and Extracranial atheroma	8(25.8%) ^{a*}	23(74.2%)	31(7%)
Extracranial Atheroma	7(11.9%) ^{ab}	52(88.1%)	59(13%)
No Atheroma	28(8.7%) ^{ab}	293(91.3%)	321(70%)
Intracranial Atheroma	3(6.4%) ^b	44(93.6%)	47(10%)
Total	46(10%)	412(90%)	458(100%)
$X^2=10.1, p = 0.018$		$LX^2=7.9, p = 0.049$	

*Groups with different letters are significantly different.

There was no significant difference in the use of oral hypoglycemic agents between patients with intracranial and extracranial atheroma as compared to patients with extracranial atheroma alone, (Table 9.B), $p=0.10$.

Table 9.B: Incidence of patients with and without use of oral hypoglycemic agents vs patients with the combination of intracranial and extracranial atheroma as compared to extracranial atheroma alone.

Type of atheroma	Disease State		
	Use of Oral hypoglycemic agents n (%)	No use of Oral hypoglycemic agents n (%)	Total
Intracranial and Extracranial atheroma	8(25.8%)	23(74.2%)	31(34%)
Extracranial Atheroma	7(11.9%)	52(88.1%)	59(66%)
Total	15(17%)	75(83%)	90(100%)
$X^2=2.8, p= 0.09$		$LX^2=2.7, p = 0.099$	

There was no significant difference in the use and non-use of oral hypoglycemic agents between patients with intracranial and extracranial atheroma and extracranial atheroma alone as compared to patients with intracranial atheroma alone. This result is approaching significance and therefore might be significant with a larger pool of subjects, (Table 9.C), $p \leq 0.08$.

Table 9.C: Incidence between use and lack of use of oral hypoglycemic agent's vs the combination of intracranial and extracranial atheroma and extracranial atheroma alone as compared to the incidence of intracranial atheroma alone.

Type of atheroma	Disease State		
	Use of oral hypoglycemic agents n (%)	No use of oral hypoglycemic agents n (%)	Total
Intracranial and Extracranial atheroma	15(17%)	75(83%)	90 (66%)
Extracranial Atheroma			
Intracranial Atheroma	3(6.4%)	44(93.6%)	47(34%)
Total	18(13%)	119(87%)	137(100%)
$X^2=2.861, p = 0.091$		$LX^2=3.175, p =0.075$	

There was no significant difference in use or non-use of oral hypoglycemic agents vs patients who have all types of atheroma as compared to patients with no atheroma, (Table 9.D), $p=0.16$.

Table 9.D: Incidence of patients with and without use of oral hypoglycemic agent's vs patients with either intracranial, extracranial, or both intracranial and extracranial atheroma as compared to patients without atheroma.

Type of atheroma	Disease State		
	Use of oral hypoglycemic agents n (%)	No use of oral hypoglycemic agents n (%)	Total
Intracranial and Extracranial atheroma	18(13%)	119(87%)	137 (30%)
Extracranial Atheroma			
Intracranial Atheroma			
No Atheroma	28(8.7%)	293(91.3%)	321(70%)
Total	46(10%)	412(90%)	458(100%)
$X^2=2.1, p = 0.15$		$LX^2=2, p <0.16$	

Atheroma vs Statins

Patients with the combination of intracranial and extracranial atheroma were more likely to use statins as compared to patients with no atheroma, (Table 10.A), $p \leq 0.001$.

Table 10.A: Incidence of intracranial, extracranial, both intracranial and extracranial and no atheroma for patients with and without the use of statins.

Type of atheroma	Disease State		
	Statins n (%)	No use of statins n (%)	Total
Intracranial and Extracranial atheroma	15(48.4%) ^{a*}	16(51.6%)	31(7%)
Extracranial Atheroma	22(37.3%) ^{ab}	37(62.7%)	59(13%)
Intracranial Atheroma	13(27.7%) ^{ab}	34(72.3%)	47(10%)
No Atheroma	61(19%) ^b	260(81%)	321(70%)
Total	111(24%)	347(76%)	458(100%)
$X^2=20.4, p \leq 0.001$	$LX^2 18.8, p \leq 0.001$		

*Groups with different letters are significantly different.

There was no significant difference in the use of statins between patients with intracranial and extracranial atheroma as compared to patients with extracranial atheroma alone, (Table 10.B), $p=0.31$.

Table 10.B: Incidence of patients with and without the use of statins vs combination of intracranial and extracranial atheroma as compared to extracranial atheroma alone.

Type of atheroma	Disease State		
	Use of statins n (%)	No use of statins n (%)	Total
Intracranial and Extracranial atheroma	15(48.4%)	16(51.6%)	31(34%)
Extracranial Atheroma	22(37.3%)	37(62.7%)	59(66%)
Total	37(41%)	53(59%)	90(100%)
$X^2=1.034, p=0.31$	$LX^2=1.0, p=0.311$		

There was no significant difference in the use or non-use of statins between patients with intracranial and extracranial atheroma and extracranial atheroma alone as compared to patients with intracranial atheroma alone, (Table 10.C), $p=0.12$.

Table 10.C: Incidence of the use and non-use of statins vs the combination of intracranial and extracranial atheroma and extracranial atheroma alone as compared to intracranial atheroma alone.

Type of atheroma	Disease State		
	Use of statins n (%)	No use of statins n (%)	Total
Intracranial and Extracranial atheroma Extracranial Atheroma	37(41.1%)	53(58.9)	90 (66%)
Intracranial Atheroma	13(27.7%)	34(72.3%)	47(34%)
Total	50(36%)	87(64%)	137(100%)
$X^2=2.411, p = 0.121$		$LX^2=2.465, p =0.116$	

Patients with all types of atheroma were significantly more likely to use statins when compared to patients with no atheroma, (Table 10.D), $p \leq 0.001$.

Table 10.D: Incidence between patients with and without the use of statins vs patients with either intracranial, extracranial, or both intracranial and extracranial atheroma as compared to patients without atheroma.

Type of atheroma	Disease State		
	Use of statins n (%)	No use of statin n (%)	Total
Intracranial and Extracranial atheroma Extracranial Atheroma Intracranial Atheroma	50(36.5%)	87(63.5%)	137 (30%)
No Atheroma	61(19%)	260(81%)	321(70%)
Total	111(24%)	347(76%)	458(100%)
$X^2=16.0, p = <0.001$		$LX^2=15.3, p <0.001$	

Atheroma vs Family History of Diabetes

Patients with intracranial atheroma were more likely to have a family history of diabetes as compared to patients with extracranial atheroma, (Table 11.A), $p \leq 0.02$.

Table 11.A: Incidence of intracranial, extracranial, both intracranial and extracranial and no atheroma vs patients with and without a family history of diabetes.

Type of atheroma	Disease State		
	Family history of diabetes n (%)	No family history of diabetes n (%)	Total
Intracranial atheroma	12(25.5% ^{a*})	35(74.5%)	47(10%)
Intracranial and Extracranial Atheroma	7(22.6%) ^{ab}	25(77.4%)	31(7%)
No Atheroma	33(10.3%) ^{ab}	288(89.7%)	47(55.5%)
Extracranial Atheroma	6(10.2%) ^b	53(89.8%)	321(55.1%)
Total	58(13%)	400(87%)	458(100%)
$X^2=11.8, p=0.008$	$LX^2=10.1, p=0.018$		

*Groups with different letters are significantly different.

There was no significant difference in patients with and without a family history of diabetes in the occurrence of intracranial and extracranial atheroma as compared to patients with extracranial atheroma alone, (Table 11.B), $p=0.12$.

Table 11.B: Incidence between patients with and without a family history of diabetes vs patients with the combination of intracranial and extracranial atheroma as compared to extracranial atheroma alone.

Type of atheroma	Disease State		
	Family history of diabetes n (%)	No family history of diabetes n (%)	Total
Intracranial and Extracranial atheroma	7(22.6%)	24(77.4%)	31(34%)
Extracranial Atheroma	6(10.2%)	53(89.8%)	59(66%)
Total	13(14%)	77(86%)	90(100%)
$X^2=2.5, p=0.11$	$LX^2=2.4, p=0.12$		

There was no significant difference in family history of diabetes between patients with intracranial and extracranial atheroma and extracranial atheroma alone as compared to patients with intracranial atheroma alone, (Table 11.C), $p \leq 0.12$.

Table 11.C: Incidence of family history diabetes or lack of family history diabetes vs the combination of intracranial and extracranial atheroma and extracranial atheroma alone as compared to intracranial atheroma alone.

Type of atheroma	Disease State		
	Family history of diabetes n (%)	No family history of diabetes n (%)	Total
Intracranial and Extracranial atheroma	13(14.4%)	77(85.6%)	90 (66%)
Extracranial Atheroma			
Intracranial Atheroma	12(25.5%)	35(74.5%)	47(34%)
Total	25(18%)	112(82%)	137(100%)
$X^2=2.544, p = 0.111$		$LX^2=2.454, p = 0.117$	

Patients with all types of atheroma were significantly more likely to have a family history of diabetes when compared to patients with no atheroma, (Table 11.D), $p=0.03$.

Table 11.D: Incidence between patients with and without a family history of diabetes vs patients with either intracranial, extracranial, or both intracranial and extracranial atheroma as compared to patients without atheroma.

Type of atheroma	Disease State		
	Family history of diabetes n (%)	No family history of diabetes n (%)	Total
Intracranial and Extracranial atheroma	25(18.3%)	112(81.7%)	137 (30%)
Extracranial Atheroma			
Intracranial Atheroma			
No Atheroma	33(10.3%)	288(89.7%)	321(70%)
Total	58(13%)	400(87%)	458(100%)
$X^2=5.5, p = 0.019$		$LX^2=5.21, p = 0.022$	

Atheroma vs Family History of Atherosclerotic Arterial Disease

Patients with intracranial atheroma were more likely to have a family history of atherosclerotic arterial disease as compared to patients with no atheroma, (Table 12.A), $p \leq 0.03$.

Table 12.A: Incidence of intracranial, extracranial, both intracranial and extracranial and no atheroma for patients with and without a family history of atherosclerotic arterial disease.

Type of atheroma	Disease State		
	Family history of atherosclerotic arterial disease n (%)	No Family history of atherosclerotic arterial disease n (%)	Total
Intracranial atheroma	16(34% ^{a*})	31(66%)	47(10%)
Extracranial Atheroma	15(25.4%) ^{ab}	44(74.6%)	59(13%)
Intracranial and Extracranial Atheroma	7(22.6%) ^{ab}	24(77.4%)	31(7%)
No Atheroma	52(16.2%) ^b	269(83.8%)	321(70%)
Total	90(20%)	368(80%)	458(100%)
$X^2=10.0, p=0.019$	$LX^2=9.2, p \leq 0.027$		

*Groups with different letters are significantly different.

There was no significant difference in the occurrence of family history of atherosclerotic arterial disease between patients with intracranial and extracranial atheroma as compared to patients with extracranial atheroma alone, (Table 12.B), $p=0.80$.

Table 12.B: Incidence between patients with and without a family history of atherosclerotic arterial disease as compared to patients with the combination of intracranial and extracranial atheroma as compared to extracranial atheroma alone.

Type of atheroma	Disease State		
	Family history of atherosclerotic arterial disease n (%)	No family history of atherosclerotic arterial disease n (%)	Total
Intracranial and Extracranial atheroma	7(22.6%)	24(77.4%)	31(34%)
Extracranial Atheroma	15(25.4%)	44(74.6%)	59(66%)
Total	22(24%)	68(76%)	90(100%)
X ² =0.09, p= 0.8		LX ² =0.09, p =0.8	

There was no significant difference in the occurrence of family history of atherosclerotic arterial disease between patients with intracranial and extracranial atheroma and extracranial atheroma alone as compared to patients with intracranial atheroma alone, (Table 12.C), p=0.24.

Table 12.C: Incidence between patients with and without a family history of atherosclerotic arterial disease as compared to patients with the combination of intracranial and extracranial atheroma and extracranial atheroma alone as compared to the incidence of intracranial atheroma alone.

Type of atheroma	Disease State		
	Family history of atherosclerotic arterial disease n (%)	No family history of atherosclerotic arterial disease n (%)	Total
Intracranial and Extracranial atheroma	22(24.4%)	68(75.6%)	90 (66%)
Extracranial Atheroma			
Intracranial Atheroma	16(34%)	31(66%)	47(34%)
Total	38(28%)	99(72%)	137(100%)
X ² =1.419, p = 0.234		LX ² =1.394, p = 0.238	

Patients with all types of atheroma were significantly more likely to have a family history of atherosclerotic arterial disease when compared to patients with no atheroma, (Table 12.D), $p=0.005$.

Table 12.D: Incidence between patients with and without a family history of atherosclerotic arterial disease and patients with either intracranial, extracranial, or both intracranial and extracranial atheroma as compared to patients with no atheroma.

Type of atheroma	Disease State		
	Family history of atherosclerotic arterial disease n (%)	No family history of atherosclerotic arterial disease n (%)	Total
Intracranial and Extracranial atheroma	38(27.8%)	99(72.2%)	137 (30%)
Extracranial Atheroma			
Intracranial Atheroma			
No Atheroma	52(16.2%)	269(83.8%) b	321(70%)
Total	90(20%)	368(80%)	458(100%)
$X^2=8.1, p = 0.004$	$LX^2=7.7, p = 0.005$		

Incidence of Atheroma and CVD with Malignancy

Patients with malignancy and cardiovascular disease (CVD) and patients with CVD and no malignancy had a higher number of lesions in comparison to patients with malignancy and no CVD and no malignancy, (Table 14), $p \leq 0.001$.

Table 14: Comparison in the mean number of lesions between the four different disease situations, No CVD and no malignancy, malignancy and no CVD, CVD and no malignancy, and malignancy and CVD

Parameter	No CVD and no Malignancy	Malignancy and no CVD	CVD and no malignancy	Malignancy and CVD	F	P value
Number of lesions \bar{x} (SD)	0.56(1.99) ^{a*}	1.11(2.21) ^a	2.49(4.52) ^b	2.87(4.16) ^b	12.10	<0.001

*Groups with the same letter are not significantly different.

Table 15: Characteristics that showed no significant difference in the incidence of different types of atheroma.

Parameter	Intracranial Atheroma (n=47)	Extracranial Atheroma (n=59)	Intracranial and Extracranial atheroma (n=31)	No Atheroma (n=321)	Total (n=458)	p-value
Alcohol abuse No alcohol abuse	2 (4%) 45 (96%)	2 (3%) 57 (97%)	0 (0%) 31 (100%)	9 (3%) 312 (97%)	13 (3%) 445 (97%)	0.726
Smoking No smoking	11 (23%) 36 (77%)	12 (20%) 47 (80%)	9 (29%) 22 (71%)	58 (18%) 263(82%)	90 (20%) 368(80%)	0.445
Endocrine Diseases						
Diabetes No diabetes	3 (6%) 44 (94%)	8 (14%) 51 (86%)	8 (26%) 23 (74%)	39 (12%) 282 (88%)	58 (13%) 400 (87%)	0.084
Hypothyroidism No hypothyroidism	4 (9%) 43 (91%)	4 (7%) 55 (93%)	5 (16%) 26 (84%)	31 (10%) 290 (90%)	4 (1%) 454 (99%)	0.779
Hyperthyroidism No hyperthyroidism	0 (0%) 47 (100%)	1 (2%) 58 (98%)	0 (0%) 31 (100%)	3 (1%) 318 (99%)	44 (10%) 414 (90%)	
Cardiovascular Diseases						
PAD No PAD	1 (2%) 46 (98%)	1 (2%) 58 (98%)	0 (0%) 31 (100%)	0 (0%) 321 (100%)	2 (0.4) 456 (99.6%)	0.079
CVA No CVA	4 (9%) 43 (91%)	4 (7%) 55 (93%)	0 (0%) 31 (100%)	8 (3%) 313 (97%)	16 (4%) 442 (96%)	0.058
Chronic kidney disease No chronic kidney disease	1 (2%) 46 (98%)	2 (3%) 57 (97%)	1 (3%) 30 (97%)	3 (1%) 318 (99%)	7 (2%) 451 (98%)	0.421
Respiratory Diseases						
Chronic Obstructive Pulmonary Disease (COPD) No COPD	2 (4%) 45 (96%)	2 (3%) 57 (97%)	2 (7%) 29 (93%)	9 (3%) 312 (97%)	15 (3%) 443 (97%)	0.716
Asthma No asthma	5 (11%) 42 (89%)	6 (10%) 53 (90%)	4 (13%) 27 (87%)	33 (10%) 288 (90%)	48 (11%) 410 (89%)	0.975
Sleep apnea No sleep apnea	2 (4%) 45 (96%)	4 (7%) 55 (93%)	0 (0%) 31 (100%)	23 (7%) 298 (97%)	29 (6%) 429 (94%)	0.418
Malignancy No Malignancy	6 (13%) 41 (87%)	10 (17%) 49 (83%)	5 (16%) 26 (84%)	28 (9%) 293 (91%)	49 (11%) 409 (89%)	0.18
Depression No depression	8 (17%) 39 (83%)	9 (15%) 50 (85%)	5 (16%) 26 (84%)	45 (14%) 276 (86%)	67 (15%) 391 (85%)	0.943
Medications						
Anticoagulants No anticoagulants	4 (9%) 43 (91%)	2 (3%) 57 (97%)	3 (10%) 28 (90%)	8 (3%) 313 (97%)	17 (4%) 441 (96%)	0.058
Insulin use No insulin use	1 (2%) 46 (98%)	2 (3%) 57 (97%)	0 (0%) 31 (100%)	8 (3%) 313 (97%)	11 (2%) 447 (98%)	0.793

Chapter 4: Discussion

I. Overall findings

This study investigated 458 patients who underwent full-volume CBCT radiographs for various dental reasons. The findings of this study were novel in investigating four different categories (intracranial and extracranial lesions, extracranial lesions, intracranial lesions and no atheroma) and their association with various medical conditions.

There was a total of 137 (29.9%) patients with an incidentally detected head/neck atheroma. This was higher than other studies which found the incidence of atheroma on CBCT's to be 17.89%⁴⁴ and incidence on panoramic radiographs at 0.43-5.00%¹¹ Moreover, the current study found that of the 137 patients with atheroma, 34% had ICAs, 43% had ECAs and 23% had both. This was a new finding as the different types of atheroma were rarely recorded therefore not present in previous studies. Indeed, to the authors' knowledge, there were no previous studies that compared the incidence of IC, EC, and both IC and EC atheroma to medical history or medications in a similar way. Most studies have conducted a separate association of only one type of atheroma to medical conditions (e.g., intracranial or extracranial separately).^{48, 49}

A study conducted by Safain et al highlighted the importance that radiographic inspection has in patient treatment and associated systemic cardiovascular diseases. In their research, they examined the effectiveness of cone-beam CT angiography (CBCT-A) in studying the size and morphological shape of intracranial lesions. Eighteen consecutive patients who either presented with transient ischemic attack or stroke were examined.

Seventy-eight percent of these patients had hypertension, 22% had coronary artery disease, 89% had diabetes mellitus and 67 % had hyperlipidemia.^{43, 44}

II. Findings of the Current Study

In the following discussion, we will discuss all the findings in our current study.

Atheroma and Ethnicity

Previous studies have shown that the incidence of atheroma varies with ethnicity^{11 27}, in the current study, there was insufficient data to evaluate the difference in ethnicity aside from comparing Caucasians and African Americans, which showed that Caucasians are possibly more likely to have one of the types of atheroma when compared to African Americans. This aspect was a limitation of this Amarin study since ethnicity had only been collected in the Dental School since January 2018, causing a high percentage of unknown ethnicities (51.1%). The Baltimore population is primarily Caucasians and African Americans; therefore, the Dental School was not likely a good location to study the other ethnicities.

Atheroma and Age

In regards to age and the incidence of atheroma, a previous study had shown that the prevalence of asymptomatic carotid artery stenosis increases with patients over 65 years of age.¹⁵ This result was consistent with the current study which showed that patients with the three different types of atheroma were significantly older when compared to patients with no atheroma. These findings might be explained by the fact that older adults are more likely to present with the systemic diseases, comorbidities, and lifestyle habits which tend to increase their risk of atherosclerotic lesions. Previous studies have

explained that with age the vessel walls lose the elastic elements and medial muscular elements⁵⁰. Especially closer to the fifth and sixth decade in life, more vascular damage was noted, mostly contributing to an increase in intracranial atherosclerosis.⁵¹

Atheroma in Males and Females

A novel finding of the current study found that males are significantly more likely to have the combination of intracranial and extracranial atheroma while females are more likely to have intracranial atheroma alone. Partitioning rules allowed no further subgroup analysis of this question.⁴⁷

A number of previous studies were compared to the current study. A study by Soares et al examining the detection of atheroma in the carotid space by CBCT was published in 2017.⁴⁴ The study used 285 CBCT images where the C3 and C4 vertebrae were visible. This study was conducted in a private dental clinic and included men and women between the ages of 50 and 75. The Soares et al study showed that the incidence of atheroma was significantly higher in men than in women.⁴⁴

A previous study by López-Cancio et al, which attempted to isolate intracranial and extracranial atherosclerotic lesions and compare the associated risk factors, found that males are significantly more likely to have isolated extracranial atheroma in comparison to females.⁵² Previous studies have also indicated that the difference in risk of atherosclerosis in men and women might be attributed to hormones and differences in maintenance of vascular endothelial functions between men and women.⁵³ This could be an indication why males are more likely to have a combination of both intracranial and extracranial atheroma as indicated in the current study.

Atheroma and Cardiovascular Disease

The current study was consistent with previous studies that have shown that atheroma was found to be significantly higher in populations with cardiomyopathies.^{20,52} This study showed that patients with any type of atheroma were significantly more likely to have a history of hyperlipidemia, hypertension, and myocardial infarction/coronary artery disease as compared to those with no atheroma.

Subgroup analyses of the different locations of atheroma showed in this study that patients with the combination of intracranial and extracranial atheroma are more likely to have hyperlipidemia, hypertension, or MI/CAD as compared to patients with no atheroma.

Moreover, patients with the combination of intracranial and extracranial and extracranial atheroma alone were probably more likely to have hyperlipidemia when compared to patients with intracranial atheroma alone. In addition, patients with the combination of intracranial and extracranial atheroma are more likely to have hypertension as compared to patients with extracranial atheroma alone. These findings highlight the significance of identifying patients with both extracranial and intracranial lesions to enable further medical consultation and evaluation.

Previous study have shown that hypertension was a risk factor for only isolated extracranial atheroma whereas diabetes and other metabolic syndromes are more predictive risk factors of intracranial atheroma.⁵² Moreover, a previous study by Caplan et al have indicated that patients with hypertension, smoking and vascular disease in the periphery are more likely to have extracranial vascular problems while intracranial

vascular problems are more common in patients with hyperlipidemia and diabetes.⁵⁴

However, these findings were not consistent with other studies that showed that patients with diabetes are more likely to have extracranial atherosclerosis.⁵⁵ In the current study, these differences were not noted, and diabetes did not show any significant findings.

Overall, our findings show that patients with extracranial and intracranial lesions have a significantly higher risk for cardiovascular comorbidities than patients who no atheroma.

In the literature, both malignancy and atherosclerosis have been linked to an increase in inflammation and are a common pathway in disease development.⁵⁶ Therefore, the current study examined if there is an association of atheroma in relation between the combination of malignancy and cardiovascular disease. Cardiovascular disease was found to be a stronger contributing factor in increased number of lesions of atheroma where patients with malignancy and cardiovascular disease and patients with cardiovascular disease and no malignancy have a higher number of lesions in comparison to patients with malignancy and no cardiovascular disease and no malignancy.

Atheroma and Medications

This study showed that patients with the combination of intracranial and extracranial atheroma are more likely to have a history of anti-platelet agents use, antihypertensive agent use, or statin use as compared to patients with no atheroma. Also, patients with both intracranial and extracranial lesions are more likely to have a history of antihypertensive use as compared with patients with only extracranial atheroma.

Moreover, patients with only incidental intracranial atheroma are less likely to be using anti-platelet agents as compared to patients with both intracranial and extracranial lesions

and extracranial lesions. This could indicate that patients' with only intracranial atheroma were undetected and untreated.

Atheroma and Family History of Comorbidities

An interesting association between family history and associated atheroma was explored in this study. It was shown that patients with no atheroma are less likely to have a family history of diabetes, or family history of atherosclerotic arterial disease. Also, patients with intracranial atheroma are more likely to have a family history of diabetes as compared to patients with extracranial atheroma alone and patients with intracranial atheroma are more likely to have family history of atherosclerotic arterial disease when compared to patients with no atheroma. These findings indicate that patients with family history of diabetes or atherosclerotic disease are more likely to have atheroma especially intracranial atheroma.

III. Comparison of Non-significant Findings to Previous Studies

Previous studies have shown that atheroma is significantly higher in populations with diabetes mellitus¹⁹. The current study showed no association between the incidence of atheroma and reported diabetes. However, the incidence of atheroma was higher in patients on oral hypoglycemic drugs and patients with a family history of diabetes. This might indicate that some patients could be using oral hypoglycemic drugs for other reasons (e.g., weight loss). Also, these findings could indicate that patients were not screened for diabetes or were left undetected or unrecorded in the files by medical personnel.

In previous studies, the incidence of atheroma was found to be higher with patients who report obstructive sleep apnea (OSA),²² This was not found to have a significant effect in the present study. This might be attributed to either low medical screening for obstructive sleep apnea in the current population or that simply the Dental school population did not present with any incidence of OSA. Furthermore, previous studies have shown that the incidence of atheroma is higher in patients with renal disease²¹ and that the incidence of intracranial calcifications are linked to a higher risk of chronic kidney disease.²⁶ However, chronic kidney disease, chronic lung disease and thyroid disease were considered a limitation in this study, since they were only occasionally documented, rarely reported in charts or were undiagnosed. In a prospective situation, the sample might be screened for undiagnosed kidney and thyroid diseases.

IV. Limitations and Suggestions for Future Studies

The current study was retrospective; It looked at the association between patients' characteristics and the incidence of atheroma. A more comprehensive evaluation might be obtained if this study was prospective and planned so that patients might be followed for a number of years.

Also, through a prospective study, data could be collected using rank order or measured data for lesion size. In the current study, categorical data was utilized: with and without lesions and with or without cardiovascular diseases or malignancy. This type of data limited the analysis to the use of the weakest statistical analysis, the use of chi-square. More statistical power for the study Numerous patient charts had missing data. This led to many patient exclusions from specific items in the study, yielding a smaller

sample size for these items. For future studies, a larger item sample size might result through the collection of data for a longer period of time.

In terms of data documentation, it was found that a number of patients' files did not record patients' ethnicity, which led to excluding these files in the ethnic comparisons of the incidence of atheroma. A longer time period might result in a greater variety or number of ethnic groups, yielding additional results.

Additionally, since smoking status and use of alcohol were rarely recorded, the numbers of subjects in the study of smoking and alcohol use as related to atheroma were low. This may be the reason that the current study found no significant relationship between smoking and alcohol use whereas previous studies have shown this association.^{43, 44}

Chapter 5: Conclusion and Clinical Implications

Incidental findings of atheroma are common during routine prosthodontic procedures is common (29.9%). This study found that subjects exhibiting both ICA and ECA in the same scan are at higher risk for cardiovascular disease. The incidental detection of atheroma in dental care warrants referral to medical specialists to prevent grave sequelae for the patient.

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