

Association of Aortic Arch Calcification and Cerebrovascular Disease

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Abstract

Objective: This study was undertaken to determine whether there is a significant association between aortic arch calcification (AAC) on digital chest radiography (DCXR) and cerebrovascular disease (CVD) by computed tomography of the brain plain (BCT). It also aimed to determine if DCXR may be used to predict stroke.

Research Design: Retrospective Cross Sectional Chart Review Design

Methodology: All the 483 patients who underwent DCXR and BCTs at the Doctors Hospital, Inc. from January 2010 to December 2012 were included in the study. Demographic data and risk factors for atherosclerosis and CVD were obtained and analyzed. The DCXR were graded by three radiologists and its association with CVD on BCT using the Chi Square Test of Independence was done. Kruskal Wallis Test was employed. Cochran Inter rater validity between the three readers was tested. Odds ratio, sensitivity and specificity of DCXR to diagnose CVD on BCT were then determined.

Results: Of the 483 patients included in the study,

52.8% were females with an average age of 65.86 ± 14.46 years old. Patients of the older age group had a higher AAC grade (3) and had more infarcts on BCT. Although risk factors for AAC on DCXR and CVD on BCT were hypertension, dyslipidemia and renal disease, these were not statistically significant.

Cross sectional analysis of variables showed that patients with an AAC grade of 1 was highly associated with infarcts and an AAC grade of 2 was associated with hemorrhagic stroke ($p=0.0200$). A statistically significant inter rater agreement was noted among the three radiologists that read the DCXR.

Conclusion: The AAC grade (1) on DCXR is significantly associated with infarcts on BCT scan with a high specificity and strong positive predictive value. Larger studies may be necessary to determine the association of the other AAC grades (2 and 3) with the types of stroke.

Keywords: aortic arc calcification, cerebrovascular disease, stroke,

Introduction

Rationale of the study

Aortic arch calcification (AAC) on chest radiography (CXR) is associated with cerebrovascular disease (CVD). It is also associated with modifiable and non-modifiable risk factors for stroke.

Background of the study

Atherosclerosis is a systemic disease that affects various regions of the circulation. It occurs in the intima of arteries and have clinical manifestations

depending on the particular circulatory bed affected.^{3,4} In the arteries supplying the central nervous system, it provokes strokes and transient cerebral ischemia.³ As early as 1914, extra cranial arterial occlusion was noted to be associated with stroke.⁵ Through the years, subsequent studies have shown that the thickening and occlusion of internal carotid artery was correlated with risk factors for cardiovascular disease and stroke.⁴⁻¹⁵ In the 1990's, aortic arch atherosclerosis (AAA) was identified as another cause of cerebrovascular disease (CVD).^{16,17} The prevalence of severe aortic plaques in stroke patients are in the same order of magnitude as that of carotid artery disease and atrial fibrillation.¹⁸ The size of these atherosclerotic plaques on the aorta of symptomatic patients was associated with a higher risk of stroke and peripheral embolization.^{17,18-26} In the French Aortic Plaque in Stroke Study and the Stroke Prevention Assessment of Risk in a Community (SPARC) Study, the risk for stroke was higher in patients with aortic plaques greater than 4mm.^{23,24} More recent studies

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showed that plaques occurred and became mobile despite the use of warfarin and aspirin.²⁷⁻³⁰

The relationship of stroke with hypertension, hypercholesterolemia, diabetes mellitus and smoking have been identified in the Framingham Heart Study.³¹ Women had a higher risk for stroke and were noted to be significantly older on their first ever stroke.³²

Vascular calcifications are considered markers of vascular atherosclerosis.^{33,34} At present, modalities used to visualize vascular atherosclerosis are chest radiography, transthoracic (TTE) and transesophageal (TEE) echocardiographic examinations, computed tomography, magnetic resonance imaging and angiography.^{16-26,33-36} Most of these studies utilized TEE and CT to document the positive correlation of AAC with CVD.^{34,37-39}

Although plain chest radiography (CXR) is a non-invasive and less expensive way to assess AAC, only two studies used radiography in documenting AAC and correlated it with CVD. One study revealed that there was a significant correlation with a 1.46 fold risk for ischemic stroke in women only with no associations for ischemic and hemorrhagic strokes in men.⁴⁰ In another study, however, AAC on CXR was not correlated with stroke.⁴¹ Both of these studies did not use a grading system to classify AAC.⁴⁰

In a study of cardiovascular events in hemodialysis patients, a classification AAC on CXR was noted to be a reflection of the magnitude of calcification of the whole aorta.⁴² This grading was validated in a study by Hashimoto.⁴³

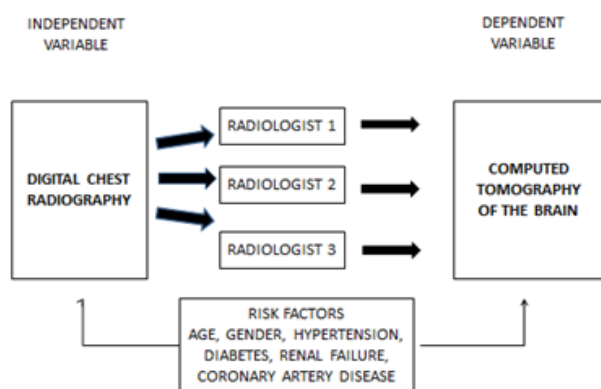


Figure 1: Conceptual framework of the study

Significance of the Study

AAC grading through DCXR may be useful in predicting the presence of CVD on computed tomography of the brain plain (BCT).

Research Question

Is there an association between AAC on DCXR and CVD on BCT? Could AAC on DCXR be used as a marker for CVD on BCT?

Objectives

Primary Objective:

To determine the association between AAC by DCXR and CVD by BCT

Specific Objective:

1. To determine the association between hypertension, diabetes, coronary artery disease, renal disease, smoking, alcohol drinking and age with CVD by BCT.
2. To determine the association between hypertension, diabetes, coronary artery disease, renal failure, smoking, alcohol drinking and age with AAC on DCXR.
3. To determine the sensitivity and specificity of DCXR as a diagnostic tool in CVD

Definition of Terms

1. Aortic Arch Calcification (AAC) - refers to the presence of calcium deposition in the intima and media of the arch of the aorta
2. Aortic Arch Calcification on Digital Chest Radiography (AAC on DCXR) - refers to the presence of calcium deposition in the arch or the aorta that is measured by digital chest radiography. This is read by three different radiologists and graded as (0) no visible calcification, (1) with small spots of calcification or a single thin area of calcification, (2) one or more areas of thick calcification and (3) as circular calcifications of the aorta.
3. Cerebrovascular Disease (CVD) - refers to the presence of a stroke and is classified as infarct, haemorrhage, both infarct and haemorrhage or none.
4. Cerebrovascular Disease on Computed Tomography of the brain plain (CVD on BCT) - refers to presence of an infarct or haemorrhage or both on computed tomography as read by a single reader and is classified as (0) no visible infarct, haemorrhage, atherosclerosis of cerebral arteries, (I) presence of atherosclerosis of one or more cerebral arteries, and (II) infarct, haemorrhage or both infarct and haemorrhage on computed tomography of the brain plain.

Scope and Limitation of the Study

This study was conducted in a tertiary hospital in

Bacolod City from January 2010 to December 2012 and focused on determining the presence of an association between AAC on DCXR and CVD on BCT. A retrospective cross sectional chart review design was utilized.

All patients who had a DCXR and BCT taken from January 1, 2010 to December 31 2012 were included in the study. For patients who had more than one DCXR and BCTs, only the first DCXR and BCT was utilized in the study. Demographic data and information regarding these patients' comorbidities were obtained through chart review.

Patients from January 2010 to December 2012 who did not undergo both procedures or whose DCXR and BCTs could not be obtained were excluded from the study. Subjects whose charts could not be retrieved from the medical records were still included in the study, however, these were not included in the analysis for the association of comorbidities with AAC on DCXR and CVD on BCT.

Methodology

Design

This study utilized a Retrospective Cross-Sectional Chart review Design

Setting

This study was conducted in a Tertiary Hospital in Bacolod City.

Subjects

This study involved 483 cases from The Doctors' Hospital from January 2010 to December 2012 with the following inclusion criteria

Inclusion Criteria

1. All patients who underwent DCXR from January 1, 2010 to December 31, 2012.
2. All patients who underwent BCT from January 1, 2010 to December 31, 2012.

Exclusion Criteria

1. Patients who were not admitted at the Doctors' Hospital from January 1, 2010 to December 31, 2012.
2. Subsequent BCT scans of patients previously included in the study
3. Subsequent DCXR of patient previously included in the study.

Sample Size Determination

A minimum sample size of 301 would achieve a 95% power to detect an effect size of 1.000 using a six degrees of Chi Square Test with a significance level (alpha) of 0.01000.

Data Collection Procedure

All radiographs of patients who had DCXR at a tertiary hospital in Bacolod were retrieved. These were then coded and sent to three different radiologists. Each were blinded to the clinical profile of the patients and the reading of the other radiologists. Radiographs were then classified according to AAC grades (Appendix 3). BCTs of patients from January 1, 2010 to December 31, 2012 was reviewed and were classified according to three grades and to the type of stroke (Appendix 4). Medical records of all these patients were then retrieved and analyzed.

Statistical treatment

This study utilized frequency and percentage distribution in expressing categorical data while mean, standard deviations, and ranges were used as indicators of continuous data. In comparing rates and associations among categorical variables, Chi Square Test for independence was used. Meanwhile, in comparing mean differences among continuous variables, Kruskal Wallis Test was employed due to the non-parametrical distribution of data.

Any associated p-values lesser than 0.05 alpha were considered significant. IBM SPSS version 20 was used as statistical software to assure accuracy of the computation.

Results

Table I: Distribution of retrieved cases from 2010-2012

Year	Total	Percent (%)
2010	137	28
2011	98	20
2012	248	51
Total	483	100

In total, the investigators were able to retrieve 483 DCXR and BCTs from 2010 to 2013. Two hundred forty eight (248) subjects or 51% were from 2012, 137 subjects or 28% were from 2010 and 98 subjects or 20% were from 2011 (Table I).

The demographic features and patients profiles are presented in Table II. The mean age was 65.86 $\pm$ 14.46 years old (range 13 to 96) and there were more women (52.8 %) than men (47.2%). Most of these patients had other medical problems with the top comorbidities as being hypertension (33%), dyslipidemia (16%), renal disease (14%), and diabetes mellitus (13%). Some data regarding subjects comorbidities were not included or were designated as missing since these were either not extracted during the actual history taking nor were they documented in the patient's records.

Table II: Patients' demographic characteristics and profile

Patients' Characteristics		Descriptive N=483(%)
Age		
Mean+/-sd	65.86	±14.46
Median	67	
Range (min-max)	13	96
Sex		
females	255	52.8
males	228	47.2
Co-morbidities		
HPN		
(+)	158	33
(-)	44	9
missing	281	58
Diabetes mellitus		
(+)	61	13
(-)	134	28
missing	288	60
History of alcohol intake		
(+)	25	5
(-)	82	17
missing	376	78
Smoking history		
(+)	29	6
(-)	78	16
missing	376	78
Increased calcium states		
(+)	12	2
(-)	144	30
missing	327	68
Arrythmia on ECG		
(+)	28	6
(-)	177	37
missing	278	58
CAD		
(+)	33	7
(-)	164	34
missing	286	59
Dyslipidemia		
(+)	79	16
(-)	90	19
missing	314	65
Renal disease		
(+)	70	14
(-)	116	24
missing	297	61

Table III: Patients' BCT scan, DCXR Grades and types of strokes as agreed by three readers

Diagnostic Test Results	Frequency	Percent (%)
CXR Grade		
0	106	21.9
1	213	44.1
2	151	31.3
3	13	2.7
CT SCN GRADE		
0	103	21.3
I	24	5.0
II	356	73.7
Type of Stroke		
infarct	287	59.4
hemorrhage	58	12.0
Both	11	2.3
No stroke	127	26.29

All DCXR retrieved were graded with 106 or 21.9% of the subjects were graded as 0, 213 or 44.1.0% of the subjects were graded as 1, 151 subjects were graded as 2 and 13 subjects were graded as 3. Most of the subjects were graded as having an AAC grade 1.

Of the 483 BCT scans retrieved, 103 or 21.3% were graded as 0, 24 or 5.0% were graded as 1 and 356 or 73.7% were graded as II. Of those graded as having a stroke (grade II), 287 or 59.4% were noted to have infarct alone, 58 or 12% had hemorrhages alone and 11 had both infarct and hemorrhages. Seventy three percent (73.7%) of the subjects had a stroke on CT scan with the most common type of stroke being infarct (59.4%).

On a cross-sectional analysis of AAC grade on DCXR with patients' profiles (Table IV), those with AAC grade 3 on DCXR were observed to be older than those with AAC grades 0,1, and 2 ($p=0.002$). Gender differences were not statistically significant for any of the three grades ($p =0.572$).

Hypertension was noted to be the most common comorbidity across all AAC grades (0, 1, 2, and 3). This was followed by dyslipidemia, renal disease and diabetes mellitus. In this study, the investigators noted that only renal disease was noted to be associated with AAC on DCXR with a p value of 0.048.

There were 103 patients classified as having no stroke on BCT scan (grade 0), 24 as having atherosclerotic plaques (grade I) and 356 as having overt stroke (grade II). The cross sectional analysis of the BCT scan grade with the patients' profiles (Table V) showed that those with BCT scan grade of I were older than those with grade 0 and grade II ($p=0.00001$). This was followed by a CT scan grade of

Table IV: Cross-section of AAC Grade on DCXR and patients' profiles

Patients' Characteristics		CXR Grade								p-value
		0 n=106(%)		1 n=213(%)		2 n=151(%)		3 n=13(%)		
Age										
mean		64.29		64.38		68.11		76.62		0.002*
std. deviations		14.94		15.11		12.57		13.83		
Sex										
females		53	50	120	56	75	50	7	54	0.572
males		53	50	93	44	76	50	6	46	
Co-morbidities										
Hypertension										
(+)		32	82	78	79	45	75	3	75	0.863
(-)		7	18	21	21	15	25	1	25	
missing		67	63	114	54	91	60	9	69	
Diabetes										
(+)		14	38	28	29	19	33	0	0	0.42
(-)		23	62	68	71	39	67	4	100	
missing		69	65	117	55	93	62	9	69	
History of alcohol intake										
(+)		6	29	10	21	9	24	0	0	0.786
(-)		15	71	37	79	28	76	2	100	
missing		85	80	166	78	114	75	11	85	
Smoking history										
(+)		6	29	10	21	13	35	0	0	0.426
(-)		15	71	37	79	24	65	2	100	
missing		85	80	166	78	114	75	11	85	
Increased calcium states										
(+)		3	10	3	4	6	12	0	0	0.346
(-)		27	90	70	96	43	88	4	100	
missing		76	72	140	66	102	68	9	69	
Arrythmia on ECG										
(+)		4	10	16	16	8	13	0	0	0.68
(-)		35	90	84	84	54	87	4	100	
missing		67	63	113	53	89	59	9	69	
cad										
(+)		5	13	15	15	11	19	2	50	0.279
(-)		33	87	82	85	47	81	2	50	
missing		68	64	116	54	93	62	9	69	
Dyslipidemia										
(+)		17	59	39	47	21	40	2	50	0.433
(-)		12	41	44	53	32	60	2	50	
missing		77	73	130	61	98	65	9	69	
Renal disease										
(+)		14	40	26	28	28	51	2	50	0.048*
(-)		21	60	66	72	27	49	2	50	
missing		71	67	121	57	96	64	9	69	

Table V: Cross-section of BCT SCAN grade and patients' profiles

Table 1: Cross section of CT scan grade and patients' profiles							
Patients' Characteristics		CT Scan Grade					p-value
		0 n=103(%)		I n=24(%)		II n=356(%)	
Age							
mean	58.91		70.21		67.57		0.00001
std.deviation	14.53		14.64		13.83		
Sex							
females	59	57	17	71	179	50	0.088
males	44	43	7	29	177	50	
Co-morbidities							
hypertension							
(+)	34	71	10	77	114	81	0.346
(-)	14	29	3	23	27	19	
missing	55	53	11	46	215	60	
Diabetes mellitus							
(+)	14	29	3	23	44	31	0.72
(-)	34	71	10	77	90	64	
missing	55	53	11	46	222	62	
History of alcohol drink-ing							
(+)	8	25	0	0	17	24	0.527
(-)	24	75	4	100	54	76	
missing	71	69	20	83	285	80	
Smoking history							
(+)	9	28	1	25	19	27	0.985
(-)	23	72	3	75	52	73	
missing	71	69	20	83	285	80	
Increased calcium states							
(+)	3	11	1	9	8	7	0.775
(-)	25	89	10	91	109	93	
missing	75	73	13	54	239	67	
Arrythmia on ECG							
(+)	6	12	2	15	20	14	0.938
(-)	43	88	11	85	123	86	
missing	54	52	11	46	213	60	
Coronary artery disease							
(+)	6	12	5	38	22	16	0.077
(-)	43	88	8	62	113	84	
missing	54	52	11	46	221	62	
Dyslipidemia							
(+)	22	54	2	20	55	47	0.16
(-)	19	46	8	80	63	53	
missing	62	60	14	58	238	67	
Renal disease							
(+)	14	31	5	38	51	40	0.581
(-)	31	69	8	62	77	60	
missing	58	56	11	46	228	64	

CT scan grade 0- no stroke nor atherosclerosis, grade I atherosclerosis of one or more arteries, grade II infarct or hemorrhage or both

Table VI: Cross-section of types of stroke and patients' profiles

Patients' Characteristics	Type of Stroke								p-value
	infarct n=287 (%)		Infarct and hemorrhage n=11(%)		hemorrhage n=58(%)		No stroke n=127(%)		
Age									0.00001
mean	68.38		67.36		63.53		61.03		
std.deviation	12.8		14.75		17.51		15.24		
Sex									0.076
female	150	52	7	64	23	40	75	60	
male	138	48	4	36	35	60	51	40	
Co-morbidities									0.323
HPN									
(+)	92	79	6	100	16	84	44	72	
(-)	24	21	0	0	3	16	17	28	
missing	171	60	5	45	39	67	66	52	
DM									0.359
(+)	40	36	1	25	3	17	17	28	
(-)	72	64	3	75	15	83	44	72	
missing	175	61	7	64	40	69	66	52	
History of alcohol intake									0.793
(+)	13	23	0	0	4	31	8	22	
(-)	43	77	2	100	9	69	28	78	
missing	231	80	9	82	45	78	91	72	
Smoking history									0.611
(+)	13	23	1	100	5	38	10	28	
(-)	43	77	1	100	8	62	26	72	
missing	231	80	9	82	45	78	91	72	
Inc calcium states									0.879
(+)	7	7	0	0	1	6	4	10	
(-)	90	93	2	100	17	94	35	90	
missing	190	66	9	82	40	69	88	69	
Arrhythmia on ECG									0.65
(+)	18	15	1	17	1	5	8	13	
(-)	99	85	5	83	19	95	54	87	
missing	170	59	5	45	38	66	65	51	
Coronary artery disease									0.646
(+)	18	16	2	33	2	11	11	18	
(-)	93	84	4	67	16	89	51	82	
missing	176	61	5	45	40	69	65	51	
dyslipidemia									0.79
(+)	44	46	2	33	9	56	24	47	
(-)	52	54	4	67	7	44	27	53	
missing	191	67	5	45	42	72	76	60	
Renal disease									0.714
(+)	40	38	3	50	8	44	19	33	
(-)	64	62	3	50	10	56	39	67	
missing	183	64	5	45	40	69	69	54	

II. Gender differences were not statistically significant for all of the three BCT grades ($p=0.088$).

Hypertension, renal disease and coronary disease were co-morbidities noted in patients with BCT scans graded as having atherosclerosis (grade I) while hypertension, dyslipidemia, and renal disease were noted to be associated with BCT scans graded as no stroke (grade 0) and those with a stroke (grade II). The presence of these comorbidities among all the BCT scan grades was not noted to be statistically significant.

In the cross-sectional analysis of patients with stroke and their profiles (Table VI), subjects with infarcts were older (68.38 ± 12.8 years old) than those with multiple hemorrhage, both infarcts and hemorrhage and those with no stroke ($p=0.00001$). Although subjects with infarcts were mostly females and those with hemorrhages were mostly males, this was not noted to be statistically significant.

Subjects with no stroke (NS), infarcts alone (A) and multiple hemorrhage alone (B) were observed to have hypertension, dyslipidemia, renal disease as comorbidities. Subjects with both infarcts and multiple hemorrhage (AB) were noted to have a history of smoking on top of hypertension and renal disease. Profiles of patients who developed stroke and did not develop stroke did not differ significantly.

Table VII: Cross-section of BCT scan grade and types of stroke

Type of Stroke	CT SCN GRADE			Total
	0	I	II	
infarct	0	0	287	287
Infarct and hemor-rhage	0	0	11	11
hemorrhage	0	0	58	58
Total	0	0	356	356

Chi-Square test of goodness fit=180, df=2, p-value =0.00001

Cross sectional analysis of BCT scan grade with type of stroke shows (Table VII) that a BCT Scan grade 0 was associated with no stroke while type of strokes such as infarcts, infarcts and hemorrhages, and hemorrhages alone were associated with BCT scan grade II ($p=0.00001$).

Table VIII: Cross-section of DCXR and BCT scan grades

CT SCN GRADE	CXr Grade (based on 3 read-ers)				Total
	0	1	2	3	
0	25	54	24	0	103
I	1	12	11	0	24
II	80	147	116	13	356
Total	106	213	151	13	483

Chi-Square=14.756, df=6, p-value=0.022

AAC on DCXR was associated with a stroke on BCT scan grading ($p=0.022$). Sub group analysis showed that out of the 106 subjects without AAC on DCXR (AAC grade 0) only 80 patients developed stroke. Twenty five (25) subjects with an AAC grade 0 did not have stroke (CT grade 0) while only one subject developed atherosclerosis (CT grade I). Of the 213 subjects with AAC grade 1, 147 developed stroke and of the 151 patients with AAC grade of 2, 116 developed stroke. Of the patients with AAC grade 1, only 54 subjects and 12 subjects had a BCT scan grade of 0 and I, respectively. While for those with AAC grade 2, 24 had a BCT grade of 0 and 11 had a grade of I. All patients with AAC grade of 3 had a stroke.(p value =0.022)

Table IX: Cross-section of DCXR grade and types of stroke

Type of Stroke	CXr Grade (based on 3 readers)				Total
	0	1	2	3	
Infarct alone	59	121	95	12	287
Both (Infarct and hemor-rhage)	3	6	2	0	11
Hemorrhage alone	18	18	21	1	58
Total	80	145	118	13	356

Chi-Square=6.59, df=6, p-value=0.0360

Cross sectional analysis of variables (Table IX) revealed that subjects with an AAC grading of 1 was highly associated with infarcts alone, both infarcts and hemorrhages. This was noted to be statistically significant with a p value of 0.0360. An AAC grading of 2 was associated with hemorrhagic stroke (p value =0.0360).

Table X: Inter-rater agreement of three readers on DCXR grades

Agreement Among Readers	Kappa	p-value
Reader 1 and Reader 2	0.184	0.00001
Reader 1 and Reader 3	0.186	0.00001
Reader 2 and Reader 3	0.069	0.0130

In Table X, readers 1, 2, and 3 have significant agreement on their CXr grading. Analysis of inter-reader validity showed that the agreement between all readers of AAC on DCXR was significant ($p=0.00001$) between reader 1 and reader 2, ($p=0.00001$) between reader 1 and reader 3($p=0.013$) as well as reader 2 and reader 3 ($p=0.0130$).

As noted on Table XI, patients with a BCT scan grade of I would have a 1.60 risk of having an infarct (CI at 95%), 0.21 risk of having both an infarct and a hemorrhage (CI 0.0040 to 10.7608), and 0.04 risk of having a hemorrhage alone (CI 0.0019 to 0.8965). On the other hand, patients with

Table XI: Association of ratio of BCT scan DCXR findings in predicting types of stroke

Test Done	Type of Stroke								
	infarct			Both (infarct and hemorrhage)			hemorrhage		
	OR	Lower - Upper Limits	p-value	OR	Lower - Upper Limits	p-value	OR	Lower - Upper Limits	p-value
CT SCN GRADE									
I	1.60	0.06 to 40.74	0.7744	0.21	0.0040 to 10.7608	0.4352	0.04	0.0019 to 0.8965	0.0424
II	14780.50	1326.14 to 164735.6	P < 0.0001	0.00	0.0000 to 0.0232	P < 0.0001	0.00	0.0000 to 0.0045	P < 0.0001
CXR Grade									
1	1.25	0.7195 to 2.1584	0.4322	1.29	0.2998 to 5.5372	0.7333	2.58	1.1638 to 5.7061	0.0196
2	0.79	0.4291 to 1.4479	0.4431	1.90	0.2959 to 12.2492	0.4978	1.09	0.4826 to 2.4522	0.839
3	0.09	0.0051 to 1.5739	0.099	0.50	0.0022 to 7.7759	0.3303	0.23	0.0090 to 6.0333	0.38

Table XII: Sensitivity and specificity of BCT scan and DCXR in predicting type of stroke

Type of Stroke	Sensitivity (%)	Specificity (%)	Predictive Value		Likelihood ratio		Overall accuracy (%)
			(+) %	(-) %	(+)	(-)	
Infarct							
CT Scan	99.70	98.40	99.30	99.20	62.78	0.00	99.3
CXR	37.20	73.80	76.40	33.90	1.42	0.85	48.3
Both (infarct and hemorrhage)							
CT Scan	100.00	98.40	84.60	100.0	63.00	0.00	98.5
CXR	18.20	73.80	5.70	91.20	0.69	1.11	69.3
Hemorrhage							
CT Scan	96.60	98.40	96.60	98.40	60.83	0.04	97.8
CXR	37.90	73.80	40.00	72.10	1.45	0.84	62.5

a BCT scan grade of 2 would have a 14780.50 of developing an infarct (CI 1326.14 to 164735.6), a 0.00 risk of developing both an infarct and a stroke (CI 0.0000 to 0.0232), and a 0.00 risk of developing a hemorrhage alone (CI=0.0000 to 0.0045).

Patients with an AAC of 1 on DCXR would have a 1.25 risk of having an infarct (CI 0.7195 to 2.1584), a 1.29 risk of having both an infarct and a stroke (CI 0.2998 to 5.5372), and a 2.58 risk of having a hemorrhage alone (CI 1.1638 to 5.7061). Patients with AAC 2 on DCXR would have a 0.79 risk of having an infarct (CI 0.4291 to 1.4479), 1.90 risk of having both an infarct and hemorrhage (CI 0.2959 to 12.2492), and 1.09 risk of having a hemorrhage alone (CI 0.4826 to 2.4522). An AAC grade of 3, would have a 0.09 risk of having an infarct (CI 0.0051 to 1.5739), 0.50 risk of having both an infarct and hemorrhage (CI 0.0022 to 7.7759), and a 0.23 risk of having a hemorrhage alone (CI 0.0090 to 6.0333).

It has been demonstrated that BCT scan is highly sensitive and specific for all kinds of stroke. For infarcts it is 99.70% sensitive and 98.40% specific with an overall accuracy of 99.3%. For both infarct and hemorrhages it is 100% specific and 98.4% sensitive with an overall accuracy of 98.5%.

For hemorrhages alone, BCT scan is 96.6% sensitive and 98.4% specific with an overall accuracy rate of 97.8%.

AAC on DCXR, on the other hand, has been noted to be specific but not sensitive to all kinds of stroke. For infarcts it has 37.2% sensitivity and a 73.8% specific with an overall accuracy rate of 48.3%, for both infarcts and hemorrhages it has 18.20% sensitivity and 73.8% specificity with an overall accuracy rate of 69.3%, while for hemorrhages alone it has 37.90% sensitivity and 73.80% specificity with an overall accuracy rate of 62.5%.

BCT scan has been noted to have a strong positive and negative predictive value for all types of strokes. For infarcts it has a predictive value of 99.30% and a negative predictive value of 99.20%, for both hemorrhages and infarcts it has an 84.60% positive predictive value and 100 % negative predictive value. For multiple hemorrhage alone, it has a 96.60 % positive and a 98.40% negative predictive value.

AAC on DCXR has been noted to have a positive predictive value for infarcts (76.40%), a strong negative predictive value for both infarcts and hemorrhages (91.2%) and a negative predictive value for hemorrhages alone (72.10%).

Discussion

Although atherosclerosis of the aortic arch was noted to be associated with cerebrovascular disease in several studies.^{18,21,22,35,37-38} The use of DCXR on determining AAC in various research works have been used sparingly.^{40,41} The primary purpose of this study is to determine if there is an association between AAC on DCXR with the occurrence of CVD on BCT.

In a study of 483 subjects, AAC on DCXR is associated with CVD on BCT ($p=0.022$). Subgroup analysis shows that of the 356 subjects who developed stroke, AAC grade of 1 was associated with infarcts alone as well as both infarcts and hemorrhages while an AAC grade of 2 was associated with hemorrhages alone ($p=0.036$). Inter-reader agreement among AAC DCXR grades were assessed and were noted to be significant (reader 1 and 2 $p=0.00001$, reader 1 and 3 $p=0.00001$ and reader 2 and 3 $p=0.013$).

The findings of the study were consistent with other studies that utilized transesophageal echocardiography and computed tomography.^{16-26,33,35-36} During the initial stages, early atherosclerotic lesions are marked by foam cell infiltration. As maturation ensues, plaques are formed. Plaques contain a large lipid core, smooth muscle and connective tissue.³ Due to a high cholesterol and lipid content, these plaques soften, through time, producing an atheroma that has a high tendency to rupture.³³ The atheromatous core is devoid of supporting collagen, is avascular and hypocellular. As the fibrous cap separates from the atheromatous core, it may disintegrate, tear or break exposing the thrombogenic gruel into the flowing blood.⁴⁷ We surmise that the plaques noted on DCXR were ulcerated and complex thus causing CVD on BCT. Another recent study by Shimuda et al showed similar results. Using a similar grading system to classify AAC, brain embolizations were noted to be associated with both mobile, ulcerated aortic plaques on transesophageal echocardiography and AAC on chest radiography.⁴⁸

The size of the atherosclerotic plaques have been associated cerebrovascular disease in studies that used transesophageal echocardiography.^{23,24} Unlike these studies, however, it was observed that as the size of the atherosclerotic plaques increased (AAC grade 2 and 3) on DCXR, less embolizations were noted. Transesophageal echocardiography can visualize not only size but also ulcerations and mobility of plaques.²⁷⁻³⁰ Only calcifications, on the other hand, are noted on DCXR. These calcifications do not increase fibrous cap stress, are less lipid laden, have lower risk of plaque rupture, thrombus

formation and embolization.³⁵ Calcifications may, therefore, increase plaque stability and bring about less embolizations.

A second mechanism of atherosclerosis had been proposed. The expansion of the internal elastic lamina which brings about plaque hemorrhages or the presence of a vulnerable plaque and that of shrinkage of the internal elastic lamina which brings about erosions and narrowing of lumen size.⁵¹ Expansion of the elastic lamina and subsequent hemorrhages occur in those arteries with large lipid cores, infiltrates of macrophages and calcific deposits.⁵¹ In a study that did a cardiovascular magnetic resonance imaging of carotid, thoracic and abdominal aorta, all of the three vessels produced an increase in rate of atherosclerosis as measured by mean total vessel area and mean total wall area. The abdominal aorta, however, showed an increase in the lumen size as atherosclerosis progressed, unlike that in the carotid arteries and the thoracic aorta.⁵² This indicates that different vascular beds exhibit varying progression or regression of atherosclerosis or remodelling.⁵² The AAC on this type of DCXR grading has been validated to be reflective of the calcification of the aorta as a whole not only of the thoracic nor abdominal aorta.⁴³ Remodelling and calcification in the aorta may differ from other vascular beds. This may explain why an increase in AAC on DCXR (grade 2 and 3) are not associated with ischemic strokes.

Although AAC score of 2 is noted to be associated with both infarcts and hemorrhages and AAC score of 3 is associated with hemorrhages, to make an overall conclusion, however, the sample size for these subgroups are insufficient since there were only 11 subjects that had both infarcts and hemorrhages and only 58 subjects that had hemorrhages alone. Furthermore, variation in the results was not adequate thus, a strong conclusion with regards to the occurrence of hemorrhages and both infarcts and hemorrhages could not be made.

In this study, the odds of having an infarct on computed tomography is 1.25 times higher if an AAC grade of 1 is noted. On the other hand, the odds of having a haemorrhage in subjects with arch calcification of 1 is 2.58 and that of having both haemorrhage and infarct is 1.9x higher in subjects with AAC grade of 2. Sample sizes of the subgroups with hemorrhages alone and both infarcts and hemorrhages were insufficient.

Computed Tomography scan is currently being used as a screening for cerebrovascular disease thus explaining its 99.7% sensitivity and 98.4% specificity for infarcts, 96.6% sensitivity and 98.4% specificity for hemorrhages and 98.4% sensitivity and 100%

specificity for both types of strokes. AAC grading on digital chest radiography, however, is not as specific and sensitive as computed tomography in detecting cerebrovascular disease. In this study it has been noted to be 73% specific but not highly sensitive to cerebrovascular disease. AAC on DCXR also has a high positive predictive value of 76.4% for infarcts on computed tomography and a strong negative predictive value for hemorrhages alone and both infarcts and hemorrhages. This indicates that although AAC grading cannot be used as a method to diagnose stroke since its specificity is less than 95%, it may indicate, however, that the occurrence of an infarct is likely and that work up to determine and medications to treat asymptomatic systemic atherosclerosis may be started.

AAC on DCXR, on the other hand, had a strong negative predictive value for multiple hemorrhage alone and both infarcts and hemorrhage. The number of subjects for both of these subgroups is again, small, hence an adequate conclusion could not be adequately made.

Several non-modifiable and modifiable factors have been identified as risk factors of atherosclerosis and stroke.^{53,54} Age, gender, race and ethnicity are non-modifiable risk factors with age being the most important risk factor of stroke. As age increases above 55, the stroke rate also doubles.^{55,56} In our study a mean age of 67.57 ± 13.83 is associated with stroke with $p=0.00001$. Although not statistically significant, subjects in the older age group 70 ± 14.64 did not develop stroke. Most of them, however, had atherosclerosis on their BCT.

Although women were noted to have more incidence of CVD on BCT, gender differences were not noted to be statistically significant for all three CT grades in this study. Studies have shown that the overall risk of infarction was seen on women. Similar results were noted in this study. A larger sample size, therefore, may produce a more statistically significant result.

Hypertension, cardiac disease and renal disease were noted to be present in patients with cerebrovascular disease. A similar profile was also noted in patients without cerebrovascular disease. Cross sectional analysis of the subjects' profiles with BCT grades showed that these were not statistically significant unlike the results of several studies which showed that modifiable factors like hypertension, cardiac disease, diabetes mellitus, dyslipidemia, cigarette smoking, alcohol intake, and illicit drug use are associated with stroke.⁵¹ This may be because the researchers were unable to retrieve all the data on the subjects' comorbidities. Most of the charts were either difficult to retrieve or some data was missing from the charts. Adequate retrieval of the

patients' records may, however, change the results and mimic data from previous studies.

The cross sectional analysis of the subjects' profiles with ACC on DCXR grading revealed that hypertension was the most common comorbidity in all grades from 0 to 3. This was followed by dyslipidemia, renal disease and diabetes mellitus. In this study, it is surprising to note that despite the limited amount of data retrieved, renal disease was noted to be associated with AAC on DCXR $p=0.04$. Calcification of the aortic arch on DCXR reflects the magnitude of calcification in the whole aorta.⁴³ Embolization and plaque rupture of these calcifications were considered possible explanations.^{57,58} Recent studies by Mi et al. and Okuno et al., however, have shown that mortality is higher in patients with AAC progression in patients with renal disease.^{55,59} Embolization and plaque rupture may, therefore, not be the only reasons for this association and is beyond the scope of this study.

Conclusion

An AAC grade of 1 on DCXR is associated with infarct on computed tomography. AAC grading on DCXR could not be used to diagnose stroke. It has, however, a strong specificity and strong positive predictive value for infarcts that may enable a clinician to start medical management on asymptomatic atherosclerosis so as to prevent CVD.

Recommendations

The principal limitation of this study is that the assessment of using AAC grades by DCXR is crude and is not a quantitative approach. Measuring the calcification using chest CT with DCXR grades may provide a more significant result.

Furthermore, an increase in the sample size or a prospective study wherein the number of subjects may be increased may be necessary in order to analyse the different sub groups and make an adequate conclusion.

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References

1. Libby, P: The Pathogenesis, Prevention and Treatment of Atherosclerosis, Harrisons' 18th Edition, 2011, p1983.
2. Pasternak RC, Criqui MH, Benjamin EJ, Fowkes GR, Eisselbacher EM, McCullough PA, Wolf PA, Zheng ZJ. Atherosclerotic Vascular Disease Conference Writing Group I: Epidemiology. AHA Conference Proceedings. Circulation 2004;109:2605-2612.
3. Hunt JR. The role of the Carotid Arteries in the Causation of Vascular Lesions of the Brain, with Remarks on Certain Special Features of the symptomatology. American Journal of Medical Sciences. May 1914;147(5): 704-712.
4. Estol CJ. Dr. C. Miller Fisher and the History of Carotid Artery Disease. Stroke. 1996;27:559-566.
5. Fisher MC. Occlusion of the Internal Carotid Artery. Arch Neurol Psych. 1951;65:346-377.
6. O'Leary DH, Polak JF, Kronmal RA, Savage PJ, Borhani NO, Kithner SJ, Tracy R, Gardin JM, Price TR, Furberg CD. Thickening of the Carotid Wall. A Marker for Atherosclerosis in the Elderly? Cardiovascular Health Study Collaborative Research Group. Stroke; 1996;27(2) 224-231.
7. Wang TJ, Nam BJ, Wilson PW, Wolf PA, Levy D, Polak JF, D'Agostino RB, O'Donnell CJ. The Association of C-Reactive protein with Carotid Atherosclerosis in Men and Women: the Framingham Heart Study. Arterioscler Thromb Vasc Biol 2002 Oct 1;22(10):1662-7.
8. Howard G, Manolio TA, Burke GL, Wolfson SK, O'Leary DH. Does the Association of Risk Factors and Atherosclerosis Change with Age? An analysis of the combined ARIC and CHS cohorts. The Atherosclerosis risk in communities (ARIC) and Cardiovascular Health Study (CHS) Investigators. Stroke; 1997 Sep;28(9):1693-701.
9. Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, Burke GL. Carotid Artery Intimal-Medial Thickness Distribution in General Populations as Evaluated by B mode Ultrasound. ARIC Investigators. Stroke. 1993 Sep;24(9):1297-304.
10. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid Artery Intima and Media Thickness as a Risk Factor for Myocardial Infarction and Stroke in Older Adults. Cardiovascular health Study Collaborative Research Group. N Engl J Med. 1999 Jan 7; 340(1): 14-22.
11. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu Cr, Liu CH, Azen SP. The Role of Carotid Arterial Intima-Media Thickness in Predicting Clinical Coronary Events. Ann Intern Med 1998 Feb 15; 128(4) :262-9.
12. Hodis HN, Mack WJ, LaBree RH, Liu CR, Liu CH, Alaupovic P, Kwong-Fu H, Azen SP. Reduction in the Carotid Arterial Wall Thickness using Lovastatin and Dietary Therapy: A randomized Controlled Clinical Trial. Ann Intern Med. 1996 Mar 15;124(6): 548-56.
13. North American Symptomatic Carotid Endarterectomy Collaborators. Beneficial Effect of Carotid Endarterectomy in Symptomatic Patients with High grade Carotid Stenosis. N Eng J Med. 1991 Aug 15;325 (7):445-53.
14. Tunick PA, Kronzon I. Protruding Atherosclerotic Plaque in the Aortic Arch of Patients with Systemic Embolization: A New Finding Seen by Transesophageal Echocardiography. Am Heart J. 1990 Sep;120(3):658-60.
15. Zavala JA, Amarrenco P, Davis SM, Jones EF, Young D, Macleod MR, Horky LL, Donnan GA. Aortic Arch Atheroma. Int J Stroke. 2006 May; 1(2): 74-80.
16. Amarenco P, Cohen A, Tzourio C, Vertrand B, Hommel M, Besson G, Chauvel C, Touboul PJ, Bousser MG. N Engl J Med 1994;331:1474-79.
17. Tunick PA, Kronzon I. Atheromas of the Thoracic Aorta: Clinical and Therapeutic Update. Journal of the American College of Cardiology. 2000 Mar 1;35(3): 545-54.
18. Kronzon I, Tunick PA. Atheromatous Disease of the Thoracic aorta: Pathological and Clinical Implications. Ann Intern Med. 1997 Apr 15; 126 (8): 629-37.
19. Tunick PA, Perez JL, Kronzon I. Protruding Atheromas in the Thoracic Aorta and Systemic Embolization. Ann Intern Med. 1991 Sep 15; 115(6): 423-7.
20. Yoshimura S, Toyoda K, Kuwashiro T, Koga M, Otsubo R, Konaka K, Naganum M, Matwuoka H, Naritomi H, Minematsu K. Ulcerated Plaques in the aortic arch contribute to Wymptomatic Multiple Brain Infarction. J Neurol Neurosurg Psychiatry. 2010 Dec ;81(12):1306-11.
21. Tunick PA, Krinsky GA, Lee VS, Kronzon I. Diagnostic Imaging of the Thoracic Aortic Atherosclerosis. American Journal of Roentology. 2000 Apr;174(4):1119-25.
22. Matsumura Y, Osaki Y, Fukui T, Yabe T, Yamasaki M, Hamashige, Doi Y. Protruding Atherosclerotic Aortic Plaques and Dyslipidemia: Correlation to Subtypes of Ischemic Stroke. Eur J Echocardiography. 2002;3:8-12.
23. The French Study of Aortic Plaques in Stroke Group. Atherosclerotic Disease of the Aortic Arch as a Risk Factor for Recurrent Ischemic Stroke. N Engl J Med 1996;334:1216-21.
24. Meissner I, Whisnant JP, Khandheria BK, Spittell PC, O'Fallon WM, Pascoe RD, Enriquez-Sarano M, Sewart JB, Covalt JL, Sicks JD, Wiebers DO. Prevalence of Potential Risk Factors for Stroke Assessed by Transesophageal Echocardiography and Carotid Ultrasonography: the SPARC Study. Stroke Prevention:

- Assessment of Risk in a Community. *Mayo Clinic Proc.* 1999 Sep; 74(9):862-9.
25. Deif R, El-Sayed M, Allah FA, Baligh E, El Fayomy NM, Ezzat L, Gamal H. Atherosclerotic Aortic Arch Plaques in Acute Ischemic Stroke. *J Vasc Interv Neurol.* 2011 Jan;4(1):5-9.
 26. Di Tullio MR, Russo C, Homma S. Aortic Arch Plaques and Risk of Recurrent Death. *Circulation.* 2009 May 5; 119 (17):2376-2382.
 27. Capmany RP, Ibanez MO, Pesquer XJ. Complex Atheromatosis of the Aortic Arch in Cerebral Infarction. *Curr Cardiol Rev.* 2010 Aug;6(3):184-193.
 28. Sen S. Aortic Arch Plaque in Stroke. *Jan 2009.11(1):28-35.*
 29. O'Donnell, Elosua R. Cardiovascular risk Factors. Insights from Framingham Heart Study. *Rev Esp Cardiol.* 2008;61(3):299-10.
 30. Petrea RE, Beiser AS, Kelly-Hayes M, Kase CS, Wolf PA. Gender Differences in Stroke Incidence and Poststroke Disability in the Framingham Heart Study. *Stroke.* 2009 Apr;40(4):1032-7.
 31. Litovchik I, Krakover R, Blatt A and Vered Z. Coronary and Aortic Calcification: Is the Relationship Important?. *Isr Med Assoc J.* 2007 Apr; 9(4):328-30.
 32. London GM, Marchais SJ, Guerin AP, Metivier F. Arteriosclerosis, Vascular Calcifications and Cardiovascular Disease in Uremia. *Curr Opin nephrol Hypertens* 2005;14:525-31.
 33. Kronzon I, Tunick PA. Contemporary Reviews in Cardiovascular Medicine: Aortic Atherosclerosis and Stroke. *Circulation* 2006;114:63-75.
 34. Fazzio GP, Redberg RF, Winslow T, Schiller NB. Transesophageal Echocardiographically Detected Atherosclerotic Aortic Plaque is a Marker for Coronary Artery Disease. *J Am Coll Cardiol.* 1993 Jan; 21(1):144-50.
 35. Briley DP, Lababidi Z, Bowdler AJ, Krishnamurthy M, Cansino SP, Touchon RC. Aortic Atherosclerosis and Stroke. *J Stroke Cerebrovasc Dis.* 1997 Jan;6(3):125-9.
 36. Eisen A, Tenenbaum A, Koren-Morag N, Tanne D, Shemsesh J, Imazio M, Fisman EZ, Motro M, Schwammenthal E, Adler Y. Calcification of the Thoracic Aorta as Detected by Spiral Computed Tomography Among Stable Angina Pectoris Patients: Association With Cardiovascular Events and Death. *Circulation.* 2008;118:1328-34.
 37. Itane Y, Watanabe S, Matsuda Y. Relationship Between aortic Calcification and Stroke in a Mass Screening Program Using a Mobile Helical computed Tomography Unit. *Circ J.* 2006 Jun;70(6):733-6.
 38. Iribarren C, Sidney S, Stemfeld B, Browner WS. Calcification of the Aortic Arch: Risk Factors and Association with Coronary Heart Disease, Stroke, and Peripheral Vascular Disease. *JAMA.* 2000 Jun 7;283(21):2810-5.
 39. Xu L, Jiang CQ, Lam TH, Thomas GN, Zhang WS, Cheng KK. Aortic Arch Calcification and Vascular Disease: The Guangzhou Biobank Cohort Study. *Cardiology.* 2010;117:260-64.
 40. Inoue T, Ogawa T, Ishida H, Ando Y, Nitta K. Aortic Arch Calcification Evaluated on Chest X-ray is a Strong Independent Predictor of Cardiovascular Events in Chronic Hemodialysis Patients. *Hear Vessels.* 2012 Mar;27(2):135-42.
 41. Hashimoto H, Iijima K, Hashimoto M, Son BK, Ota H, Ogawa S, Eto M, Akishita M, Ouchi Y. Validity and Usefulness of Aortic Arch Calcification in Chest X-ray. *Journal of Atherosclerosis and Thrombosis* 16(3):226-64.
 42. Spagnoli LG, Bonanno E, Sangiorgi G, Mauriello A. Role of Inflammation in Atherosclerosis. *J Nuc Med.* 2007;48(11):1800-15.
 43. Davies MJ, Richardson PD, Woolf N, Katz DR, Mann J. Risk of Thrombosis in Human Atherosclerotic Plaques: Role of Extracellular Lipid, Macrophage and Smooth Muscle Content. *Br Heart J.* 1993 May; 69(5):377-81.
 44. Lundberg B. Chemical Composition and Physical State of Lipid Deposits in Atherosclerosis. *Atherosclerosis* 1985; Jul;56(1):93-110.
 45. Falk E, Shah PK, Fuster V. Coronary Plaque Disruption. *Circulation.* 1995;92:657-71.
 46. Shimada Y, Ueno Y, Tanaka Y, Okuzumi A, Miyamoto N, Yamashiro K, Tanaka R, Hattori N, Urabi T. Aging, Aortic Arch Calcification and Multiple Brain Infarcts are Associated with Aortogenic Brain Embolism. *Cerebrovasc Dis.* 2013;35(3):282-90.
 47. Fitzpatrick LA, Severson A, Edwards WD, Ingram RT. Diffuse Calcification in Human Coronary Arteries. Association of Osteopontin with Atherosclerosis. *J Clin Invest.* 1994 Oct;94(4):1597-604.
 48. Huang H. The Impact of Calcification on Biochemical Stability of Atherosclerotic Plaques. *Circulation.* 2001;103:1051-56.
 49. Burke AP, Kolodgie FD, Farb A, Wever D, Virmani R. Clinical Investigation and Reports Morphological Predictors of Remodeling in Coronary Atherosclerosis. *Circulation.* 2002;105: 927-303.
 50. Hayashi K, Mani V, Nemade A, Aguilar S, Postley J, Fuster V, Fayad Z. Variations in Atherosclerosis and Remodeling Patterns in Aorta and Carotids. *Journal of Cardiovascular Magnetic Resonance.* 2010;12:10.
 51. Anand S, Vallantyne CM, Chasman D, Cook NR, A'Agostino R, Kannel W, Levy D, Munroe P, O'Donnell CJ, Ridker PM, Eckardstein AV, Wald N, Wilson P. Risk Factors for Atherosclerosis. XV International Symposium on Atherosclerosis. 2009 June. 1-32.
 52. Sacco R, Benjamin E, Broderick J, Dyken M, Easton D, Feingerg W, Goldstein L, Gorelick P, Howard G, Kittner S, Manolio T, Whisnant J, Wolr P. Risk Factors. *Stroke.* 1997;28:1507-17.
 53. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wievers DO. Stroke Incidence, Prevalence, and Survival: Secular Trends in Rochester, Minnesota, through 1989. *Stroke.* 1996 Mar;27(3):73-80.
 54. Wolf PA, D'Agostino RB, O'Neal MA, Sytkowski P, Kase CS, Belanger AJ, Kannel WB. Secular Trends in Stroke Incidence and Mortality. The Framingham Study. *Stroke.* 1992. Nov;23(11):1551-5.
 55. Coy CM, Maurer G, Goodman D, Siegel RJ. Transesophageal Echocardiographic Detection of Aortic Atheromatosis May Provide Clues to Occult Renal Dysfunction in the Elderly. *American Heart Journal.* 1992;123:1684-86.
 56. Lee MJ, Shin HD, Kim SJ, Oh HJ, Yoo DE, Ko KI, Koo HM, Kim CH, Doh FM, Park JT, Han SH. Progression of Aortic Arch Calcification Over 1 Year is an Independent Predictor of Mortality in Incident Peritoneal Dialysis Patients. *PLoS One* 2012 Nov. DOI:10.1371/journal.pone.0048793.
 57. Okuno S, Ishimura E, Kitatani K, Fujino Y, Kohno K, Maeno Y, Maekawa KY, Yamakawa T, Imanishi Y, Inaba M, Nishizawa Y. The Presence of Abdominal Aortic Calcification is Significantly Associated with All Cause and Cardiovascular Mortality in Maintenance Hemodialysis Patients. *Am J Kidney Dis.* 2007 Mar; 49(3):417-25.

APPENDICES

APPENDIX 1

Copy of Letter to conduct the study

THE DOCTORS' HOSPITAL, INC.
B.S. Aquino Drive, Bacolod City

February 24, 2014

Dr. Vivienne Matriano-Akut
Dr. Rodan Andrew E. Nonato
Principal Investigators

Protocol Code	2013-002
Date of Protocol Submission	January 11, 2013
Date of Protocol Initial Review	January 28, 2013
Date of Protocol Approval	February 24, 2014
Protocol Title	Association of Aortic Calcification on Digital Chest Radiography and Cerebrovascular Disease on Computed Tomography among Selected Patients at The Doctor's Hospital: a Retrospective Three Year Study
Principal Investigator	Dr. Vivienne Matriano-Akut Dr. Rodan Andrew E. Nonato
Type of Review	Full
Primary Reviewers	1. Dr. Evelyn Lacson Chair 2. Dr. Luz Vicenta Guanzon Guest Reviewer 3. Editha Bayoneta Nurse 4. Emily Yulo Lay 5. Ma. Jennifer Torred Social Worker
Conflict of Interest	None
Sponsor	None Declared
Documents Received	Study Protocol with modification
Action	Approved

Dr. Evelyn Reinoso Lacson
Chair
TDHI REC

Ms. Ma. Jennifer Torred
Secretary
TDHI REC

APPENDIX 2

SAMPLE SIZE POWER ANALYSIS

REFERENCE:

During a routine chest radiography in a single check up of 139,849 subscribers of a health care program in North Carolina, AAC was correlated to occurrence of Coronary Heart Disease (CHD) and stroke. In this study, there was a 1.7 fold increase risk for CHD in men and 1.27 fold increased risk for CHD in women, there is a 1.46 fold increased risk of ischemic stroke in women, only, with no associations noted for ischemic and hemorrhagic stroke in men from 1964 to 1973. It was independently associated with older age, no college education, current smoking, and hypertension in both sexes. It was inversely related to body mass index and family cholesterol level. Among women it was independently associated with a 1.4 fold increase in ischemic stroke.(39)

Classification of aortic arch calcification on chest radiography had been validated and noted to be a reflection of the magnitude of calcification of the whole aorta. This grading was even associated with cardiovascular events in hemodialysis patients.(41)

ASSUMPTION:

There is an association between aortic arch calcification by digital chest radiography and cerebrovascular disease by computed tomography of the brain plain.

Chi-Square Test Power Analysis

Numeric Results for Chi-Square Test

Power	N	W	Chi-Square	DF	Alpha	Beta
0.95044	301	0.3000	27.0900	6	0.01000	0.04956

Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one.

N is the size of the sample drawn from the population. To conserve resources, it should be small.

W is the effect size--a measure of the magnitude of the Chi-Square that is to be detected.

DF is the degrees of freedom of the Chi-Square distribution.

Alpha is the probability of rejecting a true null hypothesis.

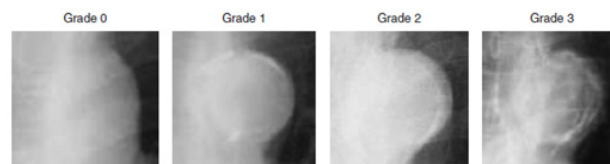
Beta is the probability of accepting a false null hypothesis.

Summary Statements

A minimum sample size of 301 achieves 95% power to detect an effect size (W) of 0.1000 using a 6 degrees of freedom Chi-Square Test with a significance level (alpha) of 0.01000. This would imply that a minimum of 301 samples are sufficient in detecting moderate level of association between between aortic arch calcification by digital chest radiography and cerebrovascular disease by computed tomography of the brain plain with 95% power and tested at 0.05alpha and 0.01alpha.

APPENDIX 3

Representative Chest X rays of Each Grade



Grade 0 – No Visible Calcification

Grade 1-Small Spots of Calcification or a single Thin area of calcification of the aortic knob

Grade 2- One or more areas of thick calcification

Grade 3- Circular calcification of the aortic knob

APPENDIX 4

Classification of Computed Tomography Scans

GRADE	CLASSIFICATION
0	Absence of infarct, haemorrhage and absence of atherosclerosis

I	Presence of atherosclerotic artery/arteries
II	Presence of stroke (infarct, hemorrhages or both)

Type of Stroke

Type of Stroke	Classification
A	Infarct
B	Haemorrhage
AB	Both Infarct and Haemorrhage
No stroke	Grade 0 and 1