

Vascular ultrasound of the radial artery

The right and left radial artery IMT was measured about 1-2cm proximal to the skinfold separating the palma manus from the regio antebrachia anterior.^[14] The mean RIMT was calculated and analyzed. A radial IMT >0.3mm was considered abnormal.^[15]

Ethical Clearance

Ethical clearance was obtained from the Health Sciences Research and Ethics Committee (HSREC) of the University of the Free State (**UFS-HSD2020/2018/2601**). Standard informed consent was obtained in all subjects.

Statistical analysis

All recorded data were captured in a datasheet using Microsoft® Excel® 2019. Data were quality controlled by an independent investigator for accuracy and transcription errors. The statistical analyses were performed using the R program. Continuous data were summarised using descriptive statistics, including but not limited to mean, standard deviation (SD), median, minimum, maximum and interquartile range (IQR). Descriptive analyses were carried out per subgroup depending on the number of patients. Linear regression was used to test for the effect of the covariates on the response variables, and logistic regression was used to determine the relative risk. Categorical data were summarized utilizing frequency tables. The cell counts were compared using a Chi² test or Fisher's exact test. The latter was used if one or more of the cell counts were less than 5. A p-value of < 0,05 was considered as statistically significant. Correlations were obtained using the Pearson correlation coefficient test.

Results

Two hundred and fifty patients met the inclusion criteria. As expected, most patients came from the Free State (97.2%) and only 2.8% from other provinces. Most of these patients resided in the Mangaung Metropolitan district (85.6%). The mean age of patients was 60.2 ± 16.5 years, with a female predominance (63.6% vs 36.4%), and most patients were Caucasian (76%).

In the total study group, 42% (n=104) of patients presented with three or more modifiable risk factors, 39% (n=98) with two risk factors, and 19% (n=48) with only one modifiable risk factor. Hypertension was the most common modifiable risk factor (89%), followed by obesity (66%). DM was present in 30% of patients, of which 55% presented with DM type 1 and 45% with DM type 2.

Carotid-intima media thickness

The mean CIMT of the total study group was 0.8 ± 0.2 mm, and the maximum CIMT was 1.9 mm (right carotid artery) and 1.7 mm (left carotid artery). The mean CIMT in men was 0.9 ± 0.2 mm and in women 0.8 ± 0.3 mm. A transient ischemic attack (TIA) or stroke was recorded in 24% (n=61) of the study population, and 51% (n=55) of patients diagnosed with a stroke or TIA had an abnormal CIMT (≥ 0.9 mm).

An abnormally thickened CIMT (≥ 0.9 mm) was observed in 107 (43%) patients with a mean CIMT of 1.1 ± 0.15 mm. The demographic, anthropometric, and modifiable risk factors of patients with normal and abnormal CIMT are summarized in Table 1.

Non-modifiable risk factors

The mean age of patients with an abnormal CIMT was similar to patients with a normal CIMT (62.4 ± 16.4 years vs 60.1 ± 16.5 years, respectively, $p=0.23$). Significantly more men presented with an abnormal CIMT compared to the normal CIMT group ($p<0.05$). The number of Caucasians in both groups was similar. A positive family history of cardiovascular disease was recorded in 89% of patients with an abnormal CIMT (Table 1).

Modifiable risk factors

Almost two-thirds of patients (63%, n=67) with abnormal CIMT measurements had three or more modifiable risk factors, 31% (n=33) with two risk factors, and only 6% (n=7) presented with one modifiable risk factor.

An abnormal CIMT was recorded in 50% (n=112) of hypertensive patients. Hypertension was the leading modifiable risk factor and was present in almost all patients with an abnormal CIMT (95%). Hypertension was followed by obesity (66%), hypercholesterolemia (51%), DM (44%), and smoking in 28% of patients. The BMI did not significantly differ between the abnormal and normal CIMT groups (28.9 ± 6.9 kg/m² vs 27.9 ± 6.8 kg/m²; $p=0.99$) (Table 1).

Table 1. Demographic, anthropometric and modifiable risk factors of patients with an abnormal CIMT

Variable (unit)	Hypertension n	DM	Hyper- cholesterolemia	Obesity	Smoking
Normal CIMT (n=143)	121	26	37	89	29
Age (y; mean±SD)	60.4±16.3	60.8±16	60.3±16.3	60.3±16.3	60.1±16.5
Sex:					
<i>Male</i>	35(28.9%)	7(27%)	8(21.6%)	28(31.5%)	12(41.3%)
<i>Female</i>	86(71.1%)	19(73%)	29(78.4%)	61(68.5%)	17(58.7%)
Ethnicity (n;%):					
<i>Caucasian</i>	85(70%)	15(57.7%)	25(67.6%)	62(70%)	27(93.1%)
<i>Mixed Race</i>	4(3%)	0	1(2.7%)	2(2.2%)	1(3.4%)
<i>Black African</i>	32(27%)	10(38.5%)	11(29.7%)	24(27%)	1(3.4%)
<i>Asian</i>	0	1(3.8%)	0	1(2.2%)	0
<i>Indian</i>	0	0	0	0	0
BMI (kg/m²; mean±SD):	29.0±6.9	29±6.9	29±7.0	29 ± 7.0	28.9±6.9
<i>Normal</i>	44(36.4%)	6(23%)	8(21.6%)		13(44.8%)
<i>Overweight</i>	77(63.6%)	20(77%)	29(78.4%)		16(55.2%)
Abnormal CIMT (n=107)	102	48	55	71	30
Age (y; mean±SD)	60.4 ± 16.4	61 ± 6.0	60.4 ± 16.4	60.4 ± 16.4	61.9 ± 16.4
Sex:					
<i>Male</i>	46(45%)	27(56.2%)	29(52.7%)	34(47.9%)	20(66.7%)
<i>Female</i>	56(55%)	21(43.8%)	26(47.3%)	37(52.1%)	10(33.3%)
Ethnicity (n;%):					
<i>Caucasian</i>	82(80.1%)	36(75%)	47(85.5%)	57(80.3%)	25(83.3%)
<i>Mixed Race</i>	4(3.9%)	2(4.2%)	3(5.5%)	4(5.6%)	1(3.3%)
<i>Black African</i>	15(14.7%)	10(20.8%)	4(7.3%)	10 (14.1%)	3(10%)
<i>Asian</i>	1(0.9%)	0	0	0	0
<i>Indian</i>	0	0	1(1.8%)	0	1(3.3%)
BMI (kg/m²; mean±SD):	28.9 ± 6.9	29 ± 6.7	28.9 ± 6.9	28.9 ± 6.9	29.0 ± 6.9
<i>Normal</i>	33(32.4%)	16(33.3%)	23(41.8%)		12(40%)
<i>Overweight</i>	69(67.6%)	32(66.7%)	32(58.2%)		18(60%)

[CIMT, carotid intima media thickness; y, years; SD, standard deviation; BMI, body mass index; kg, kilogram; DM, diabetes mellitus]

The non-modifiable risk factors analysis showed that more men with hypertension, DM and hypercholesterolemia had abnormal CIMT measurements. In contrast, females dominated the normal group (Fig. 1).

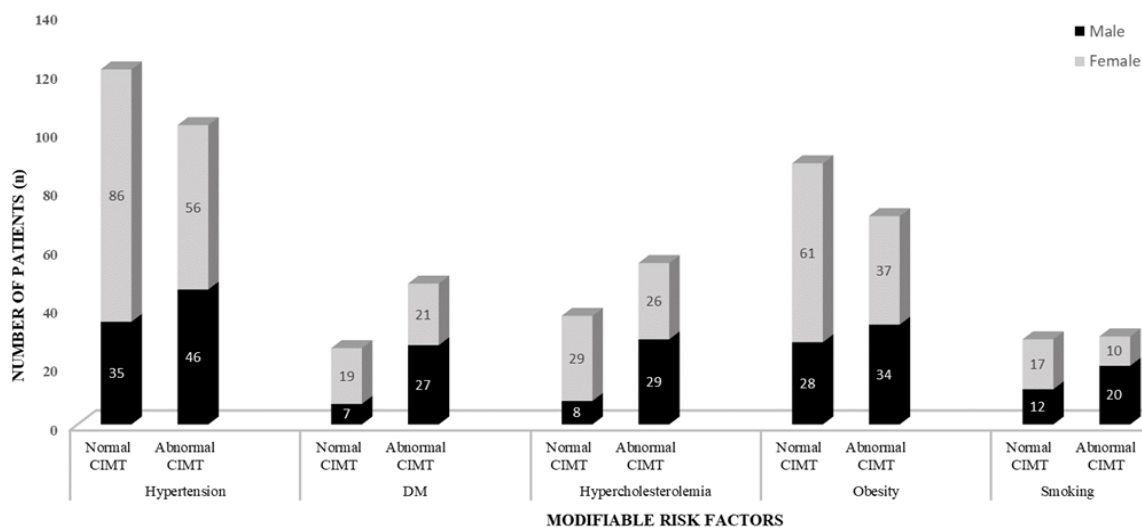


Fig. 1. Distribution of gender for normal and abnormal CIMT in modifiable risk factor groups.

Effect of risk factors on CIMT

The mean CIMT in patients with DM, hypertension, hypercholesterolemia, and smoking was significantly increased compared to those without. (Table 2). Male gender was associated with a significant increase in mean CIMT ($p < 0,05$). Age had some effect, and analyses projected that each year of ageing added 11% to the risk of having a thickened mean CIMT. This is supported by the fact that only 4 people under 50 years presented with an abnormal CIMT. The other non-modifiable risk factors did not contribute to a mean increase in CIMT. The odds ratios of modifiable risk factors associated with an increase in mean CIMT are represented in Table 2.

Table 2. The effects of individual modifiable risk factors on CIMT and risk associated with increased CIMT

Modifiable risk factor	Mean CIMT (mm)	95% CI	OR	95% CI
Hypertension	0.76*	0.05, 0.21	3.99	1.50, 12.7
Diabetes Mellitus	0.74*	0.06, 0.17	2.82	1.53, 5.24
Hypercholesterolemia	0.73*	0.05, 0.15	2.47	1.39, 4.40
Smoker	0.72*	0.03, 0.14	2.09	1.07, 4.17
Obesity	0.64	-0.04, 0.06	1.06	0.60, 1.88

* Indicate statistical significance = . [CIMT, carotid intima-media thickness; mm, millimetre; CI, confidence interval; OR, odds ratio;]

Several modifiable risk factor combinations were evaluated to assess whether an association with a thicker mean CIMT was present. The only risk factor combinations that statistically contributed to a thicker CIMT mean were DM and hypertension; DM and hypercholesterolemia; hypertension and smoking; hypercholesterolemia and obesity (Table 3).

Unexpectedly, the combination of hypercholesterolemia and DM and hypercholesterolemia and obesity appeared to reduce the risk of an increased mean CIMT and might have a protective effect. More than 50% of patients diagnosed with hypercholesterolemia were on anti-hypercholesterol treatment (Table 3).

Table 3. The effects of modifiable risk factor combinations on CIMT mean

Modifiable risk factor combinations	linear regression		logistic regression	
	p-value	95% CI	OR	95% CI
Diabetes mellitus + hypertension*	0.018	0.07, 0.75	6.92	2.32, 20.7
Hypertension + smoker*	0.033	0.02, 0.52	3.67	1.43, 9.41
Diabetes mellitus + hypercholesterolemia*	0.019	-0.24, -0.02	0.15	0.03, 0.70
Hypercholesterolemia + obesity*	0.003	-0.27, -0.06	0.12	0.03, 0.51

*Only the results of statistical significance are reported in the table above. [CIMT, carotid intima-media thickness; mm, millimetre; CI, confidence interval; OR, odds ratio]

Radial intima-media thickness

A minority of the study population (22%, n=55/250) had an abnormal thickened RIMT. As expected, the mean internal radial diameter of the abnormal RIMT group (2.6 ± 0.5 mm) was significantly thicker than the normal RIMT group (2.3 ± 0.5 mm $p < 0.05$). Only 38% of patients with abnormal CIMT also had an abnormal RIMT.

The mean age of the abnormal and normal RIMT patient groups was similar (61 ± 16.1 vs 60 ± 16.5 years, respectively). In contrast to CIMT, more female patients presented with an abnormal RIMT than men (57% vs 43%), and most patients were Caucasian (82%). Most patients in the abnormal RIMT group had a positive family history of ischemic heart disease (82%).

Similar to patients with abnormal CIMTs, hypertension was the most common modifiable risk factor in the abnormal RIMT group (91%), followed by obesity (73%) and hypercholesterolemia (56%). DM was present in 36% of patients with an abnormal RIMT. Hypercholesterolemia was the only individual risk factor that significantly contributed to a thicker mean radial IMT ($p < 0.05$). The only risk factor combinations that significantly contributed to a thicker mean RIMT were hypertension and obesity, DM and obesity and hypertension and hypercholesterolemia (Table 4).

Table 4. The effects of modifiable risk factors and combinations on RIMT mean

Modifiable risk factor combinations	linear regression		Logistic regression	
	p-value	95% CI	OR	95% CI
Hypertension*	0.5	0.00, 0.09		0.00, 0.09
Hypercholesterolemia*	<0.001	0.02, 0.08		0.02, 0.08
Hypertension + obesity*		0.05, 0.15	0.13	0.03, 0.61
Hypertension + hypercholesterolemia*	0.004	0.03, 0.14	2.87	1.41, 5.84
Diabetes mellitus + obesity*	0.009	-0.04, 0.06	3.64	0.69, 19.2

*Only the results of statistical significance are reported in the table above. [RIMT, radial intima-media thickness; mm, millimetre; CI, confidence interval; OR, odds ratio]

Correlations

A strong correlation was observed between carotid IMT left and right and radial IMT left and right. However, there was a poor correlation between CIMT and RIMT (Table 5). The latter is not unexpected, as only 38% of patients with abnormal CIMT had an abnormal RIMT.

Table 5. Correlation between CIMT and RIMT left and right

	Carotid IMT left*	Radial IMT right*	Radial IMT left*
Carotid IMT right	0.93	0.47	0.48
Carotid IMT left	-	0.42	0.43
Radial IMT right	-	-	0.98

* correlation co-efficient(r) for respective IMT's

Interestingly, 40 patients in the study presented with rheumatoid arthritis. In this subgroup, 70% of patients had an abnormal CIMT. The numbers were too small to analyze further, and the study was not designed to assess co-morbidity risks.

Discussion

The prognostic and predictive value of CIMT measurements and cardiovascular disease is a topic that is hotly debated in current literature.^[17] It is, however, clear that an increase in IMT thickness is an independent predictor for the risk of stroke apart from the traditional well-described risk factors^[15]. Only patients with individual risk factors for future cardiovascular system (CVS) events, such as stroke and CAD, were included in this study. This is the first study describing CIMT and RIMT ultrasound measurements in patients with modifiable risk factors in central SA.

The study group primarily consisted of older, affluent patients presenting at a general physician private practice which explains the demographic composition. The CIMT diameters of the total study group, men and women, were similar to the findings of a study conducted by Mostaza *et*

al. (2018).^[16] Despite the presence of several risk factors, 80% of patients had two or more risk factors. Only 40% of patients with risk factors had pathological thickening of the carotid intima. However, most patients with a CIMT of ≥ 0.9 mm had two or more risk factors. It is perturbing that hypertension was present in more than 90% of patients, and hypertension was the single most common risk factor observed in the study population. Two-thirds were obese, followed by hypercholesterolemia, diabetes and smoking. Male sex was the only non-modifiable risk factor associated with abnormal CIMT measurements. As a matter of fact, where females tended to be dominant in the normal CIMT group, an almost 50/50 distribution of gender was observed for those with an abnormal CIMT. More than 50% of patients diagnosed with stroke or transient ischemic attack (TIA) had an abnormal CIMT. This finding concurs with Roquer *et al.* (2011), who demonstrated that an increase in IMT thickness is an independent marker of major cardiovascular events. For each increment of 0.1 mm in IMT, the probability of experiencing a recurrent stroke is increased by 18%.^[17]

Our results show that individual risk factors played a role in a thickened CIMT. However, the high prevalence of hypertension in central South Africa is cause for concern. Hypertension was markedly higher in this study (90%) than that reported by Ren *et al.* and Dias *et al.* (67% and 72%, respectively) ^[3,18]. Forty-six percent of the hypertension group presented with an abnormal CIMT. Interestingly, only 20% of the hypertension group in the study of Ren *et al.* (2015) presented with carotid atherosclerosis.^[3] In our study, hypertension contributed to a thicker CIMT mean with an OR of 3.99. This result corresponds to the findings of Ferreira *et al.* (2016), demonstrating that individuals with a CIMT ≥ 0.9 mm had a significant association with a hypertension history, with an OR of 2.11.^[19] Shear forces produced by chronically high blood pressure damage the endothelial layer in cerebral arteries, coronary arteries and the aorta.^[20] According to Shrestha *et al.* (2009), an increase in systolic blood pressure correlates with atherosclerotic changes in the carotid arteries. An association with low and high-grade lesions correlates with increased systolic blood pressure.^[21] Patients with cognitive dysfunction that are hypertensive have changes in the vascular morphology supported by an increased carotid IMT, enhanced atherosclerotic lipid profile and impaired hemodynamic function. This is manifested by elevated central systolic blood pressure. Increased systolic blood pressure causes morphological changes characterized by an increased carotid IMT.^[22]

Diabetes was a prominent risk factor and was recorded in 30% of the study population. The prevalence of diabetes in our study is lower than the findings of Poznyak *et al.* (2013), who

investigated 3001 patients in South Africa and reported a 49.5% prevalence of DM.^[22] In 60% of our patients with DM, an abnormal CIMT was recorded. The mean CIMT in the diabetic patients was 0.9 ± 0.2 mm concurring with Yafei *et al.* (2019).^[23] They reported that CIMT were significantly thicker in diabetic patients compared to controls (0.79 ± 0.16 mm vs 0.58 ± 0.08 mm).^[24] In our study, DM significantly contributed to a thicker CIMT mean with an OR of 2.82. This agrees with Ren *et al.* (2015), who showed that diabetes is one of the significant risk factors associated with carotid atherosclerosis.^[3] All types of diabetes have been shown to be independent risk factors for accelerated atherosclerosis development.^[24] The pathogenesis of DM and atherosclerosis are closely linked, and among the known pathological mechanisms linking atherosclerosis and DM are hyperglycemia, inflammation, increased oxidative stress and dyslipidemia.^[24]

Hypercholesterolemia was present in more than half of the patients in the abnormal CIMT group. Interestingly, 86% of patients that presented with hypercholesterolemia and an abnormal CIMT were Caucasian, and only 7% were black Africans. Hypercholesterolemia contributed to a thickened CIMT with an OR of 2.47; this finding has also been reported in several other studies.^{[3] [24] [25]}

Our study showed that risk factor combinations like DM and hypertension, and hypertension and smoking significantly increase the risk of having thicker CIMT measurements. The odds ratios of the combinations were markedly higher than isolated risk factors, most likely indicating the summative effects when individual risk factors occur in combination. However, it appears that having hypercholesterolemia and DM or hypercholesterolemia and obesity reduces the risk of having a thickened CIMT. The authors speculate that many of these patients were on statin treatment which may have provided protection against an increased CIMT. According to Lind (2020), statin treatment is known to reduce cardiovascular events and age-related progression of IMT of the carotid artery in subjects with and without cardiovascular disease.^[24] A real-life observational study showed that statin treatment reduced the increase in IMT seen over 10 years compared to subjects not treated with statins. This is further supported by Kerola *et al.* (2021), who concluded that in hypercholesterolemic adults with subclinical atherosclerosis, one-year treatment with rosuvastatin significantly reduced the CIMTs bilaterally and improved the lipoprotein and lipid levels.^[25]

Age and male sex were the only non-modifiable risk factors contributing to the risk of an increase in mean CIMT: each year of age added 11% to the risk of having a thickened CIMT. This finding concurs with Ren *et al.* (2015); in this study, the authors demonstrated that middle-aged and older individuals with cardiac risk factors displayed an increased CIMT and higher severity grade than the younger age groups.^[3] Interestingly, Zyriax *et al.* (2021) found that each year of life translated to an additional 0.004 mm increase in CIMT. Apart from demonstrating a risk for thicker CIMTs, significantly more men had an abnormal CIMT compared to the normal CIMT group indicating male sex is a noteworthy risk factor.^[1] Similar findings were reported by Mostaza *et al.* (2018), where the male gender was associated with a thickened CIMT.^[16]

According to, Wahood *et al.* (2022), patients with hypertension and congestive heart failure usually have an increased radial artery diameter.^[26] Furthermore, Loh *et al.* (2007) concluded that hypertension, hyperlipidemia and male sex increased the radial artery diameter, whereas age, DM, race and smoking did not significantly influence the size of the radial artery. Vessel dilation is promoted by the release of endothelium-derived nitric oxide (NO) and defective synthesis.^[27]

Interestingly, more female patients presented with an abnormal RIMT than men (57% vs 43%). Similar to the CIMT group, hypertension was the most common modifiable risk factor, followed by obesity and hypercholesterolemia. Hypercholesterolemia was the only individual risk factor significantly contributing to a thicker radial IMT with an OR of 3.00. In contrast to CIMT, hypertension and obesity was the only combination contributing to a thicker RIMT. Eklund *et al.* (2013) concluded that RIMT assessed by ultrasound confers prognostic information in patients with suspected CAD. Similar findings were reported by Eklund *et al.* (2012), where RIMT may constitute a feasible imaging biomarker for systemic atherosclerotic burden.^[13] Our results demonstrate a poor correlation between RIMT and CIMT. The authors speculate that RIMT may be more valuable as a potential marker of coronary atherosclerotic disease while CIMT appears to be more valuable for neurovascular disease – this will provide some explanation for the difference in association with risk factors found in the study.

It is thought-provoking that in this study, forty patients with risk factors also had rheumatoid arthritis as a co-morbidity, and 70% had an abnormal thickened CIMT. According to Hannawi *et al.* (2007), CIMT in RA patients is increased compared to healthy individuals matched for

age, sex and cardiovascular risk.^[28] This statement is supported by Komici et al. (2021), showing that CIMT has previously been found to be increased in patients with longstanding RA.^[29] Patients with longstanding RA, >20 years, had a higher CIMT compared to patients of similar age but shorter disease duration, <7 years. An important factor related to cardiovascular risk in RA patients is an impairment of endothelial functions, which is a key element in the development of the atherosclerosis process. Endothelial impairment is related to RA being a chronic inflammatory process. Altered endothelial reactivity has been documented in RA patients prior to atherosclerotic plaque detection, even without cardiovascular risk factors.^[28]

Study limitations

This study was conducted during the Covid-19 pandemic resulting in relatively small numbers. Patients were recruited from private practice, thus consisting mainly of an affluent population. The lack of long-term follow-up of patients with abnormal CIMT was also regarded as a limitation. Based on the results obtained in this study, further studies are indicated.

Conclusion

Most patients had two or more risk factors, and hypertension was present in almost 90% of patients. Results showed that male sex, increasing age, hypertension, DM, hypercholesterolemia and smoking significantly contributed to a thickened CIMT. In contrast, only hypercholesterolemia was associated with a thickened RIMT. Hypertension had the biggest impact on increased mean CIMT compared to the other modifiable risk factors. Certain risk factor combinations were also associated with a thickened CIMT and RIMT, and combinations of risk factors appeared to add summative risk. A good correlation was observed between left and right CIMT and between left and right RIMT measurements. However, CIMT and RIMT did not correlate with each other.

Conflict of interest

The authors declare that there are no conflicts of interest relating to this study.

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Abbreviations

BMI	Body mass index
CAD	Coronary artery disease
CIMT	Carotid intimal media thickness
CI	Confidence interval
CM	Centimeter
CVS	Cardiovascular system
DM	Diabetes Mellitus
ETC	Et cetera
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein-cholesterol
HSREC	Health Sciences Research and Ethics Committee
HIV	Human immunodeficiency virus
IMT	Intima media thickness
Kg	Kilogram
Kg/m ²	Kilogram-Meter Squared
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein-cholesterol
MHz	Megahertz
mm	Millimeter
mmHg	Millimeter of mercury
mmol/L	Millimoles per litre
NO	Nitric Oxide
OR	Odds ratio
RA	Rheumatoid arthritis
RIMT	Radial intimal media thickness
SA	South Africa
SD	Standard deviation

References

1. Zyriax BC, Dransfeld K, Windler E. Carotid intima-media thickness and cardiovascular risk factors in healthy volunteers. *Ultrasound J* 2021;13(1):17. doi:10.1186/s13089-021-00218-6.
2. Banerjee C, Chimowitz MI. Stroke caused by Atherosclerosis of the major intracranial arteries. *Circ Res* 2017;120(3):502-513. doi:10.1161/circresaha.116.308441
3. Ren L, Cai J, Liang J, et al. Impact of cardiovascular risk factors on carotid intima-media thickness and degree of severity: A cross-sectional study. *PLoS One* 2015;10(12). doi:10.1371/journal.pone.0144182
4. Bentzon JF, Otsuka F, Virmani R, et al. Mechanisms of plaque formation and rupture. *Circ Res* 2014;114(12):1852-1866. doi:10.1161/circresaha.114.302721
5. Wajngarten M, Silva GS. Hypertension and stroke: Update on treatment. *European Cardiology* 2019;14(2):111-115. doi:10.15420/ecr.2019.11.1
6. Gorelick PB, Whelton PK, Sorond F, et al. Blood pressure management in stroke. *Hypertension* 2020;76(6):1688-1695. doi:10.1161/hypertensionaha.120.14653
7. Sacco RL, Roberts JK, Boden-Albala B, et al. Race-ethnicity and determinants of carotid atherosclerosis in a multiethnic population. The Northern Manhattan Stroke Study. *Stroke* 1997;28(5):929-935. doi:10.1161/01.str.28.5.929
8. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. *Circ Res* 2017;120(3):472-495. doi:10.1161/circresaha.116.308398
9. Iannuzzi A, Rubba P, Gentile M, et al. Carotid Atherosclerosis, ultrasound and lipoproteins. *Biomedicines* 2021;9(5):521. doi:10.3390/biomedicines9050521.
10. Shimoda S, Kitamura A, Imano H, et al. Associations of carotid intima-media thickness and plaque heterogeneity with the risks of stroke subtypes and coronary artery disease in the Japanese general population: The Circulatory Risk in Communities Study. *J Am Heart Assoc.* 2020;9(19): e017020. doi: 10.1161/JAHA.120.017020.

11. Tsvigoulis G, Vemmos K, Papamichael C, et al. Common carotid artery intima-media thickness and the risk of stroke recurrence. *Stroke*. 2006;37(7):1913-1916. doi: 10.1161/01.STR.0000226399.13528.0a.
12. Georgios T, Konstantinos V, Christos P, et al. Common carotid artery intima-media thickness and the risk of stroke recurrence. *Stroke* 2006;37(7):1913-1916. doi:10.1161/01.str.0000226399.13528.0a
13. Eklund C, Omerovic E, Haraldsson I, et al. Radial artery intima-media thickness predicts major cardiovascular events in patients with suspected coronary artery disease. *Eur Heart J Cardiovasc Imaging* 2014;15(7):769-775. doi:10.1093/ehjci/jet285.
14. Myredal A, Osika W, Li Ming Gan, et al. Increased intima thickness of the radial artery in patients with coronary heart disease. *Vasc Med* 2010;15(1):33-37. doi:10.1177/1358863X09106619
15. Della-Morte D, Dong C, Markert MS, et al. Carotid intima-media thickness is associated with white matter hyperintensities: The Northern Manhattan Study. *Stroke* 2018;49(2):304-311. doi:10.1161/strokeaha.117.018943
16. Mostaza JM, Lahoz C, Salinero-Fort MA, et al. Risk factors associated with the carotid intima-media thickness and plaques: Espredia study. Factores de riesgo asociados con el grosor íntima-media y la presencia de placas en arteria carótida: Estudio espredia. *Clin Investig Arterioscler* 2018;30(2):49-55. doi:10.1016/j.arteri.2017.07.005
17. Roquer J, Segura T, Serena J, et al. ARTICO Study. Value of carotid intima-media thickness and significant carotid stenosis as markers of stroke recurrence. *Stroke*. 2011;42(11):3099-3104. doi: 10.1161/STROKEAHA.110.612010.
18. Dias E, Giollo LT, Martinelli DD, et al. Carotid intima-media thickness is associated with cognitive deficiency in hypertensive patients with elevated central systolic blood pressure. *Cardiovascular Ultrasound* 2012;10(41). doi.org/10.1186/1476-7120-10-41

19. Ferreira JP, Girerd N, Bozec E, et al.. Intima-media thickness is linearly and continuously associated with systolic blood pressure in a population-based cohort (Stanislas cohort study). *J Am Heart Assoc* 2016;5(6):e003529.doi:10.1161/JAHA.116.003529
20. Lazenby RB. *Handbook of Pathophysiology*. 4th ed. Philadelphia: Wolters Kluwer Health; 2011:524–534.
21. Shrestha I, Takahashi T, Nomura E, et al. Association between central systolic blood pressure, white matter lesions in cerebral MRI and carotid atherosclerosis. *Hypertens Res* 2009; 32:869–874. doi.org/10.1038/hr.2009.121
22. Poznyak A, Grechko AV, Poggio P, et al. The Diabetes mellitus-atherosclerosis connection: The role of lipid and glucose metabolism and chronic inflammation. *International Journal of Molecular Sciences* 2019;21(5):1835. doi.org/10.3390/ijms21051835.
23. Yafei S, Elsewy F, Youssef E, et al. Echocardiographic association of epicardial fat with carotid intima-media thickness in patients with type 2 diabetes. *Diab Vasc Dis Res*. 2019;16(4):378-384. doi: 10.1177/1479164119827602.
24. Lind L. Effect of new statin treatment on carotid artery intima-media thickness: A real-life observational study over 10 years. *Atherosclerosis*. 2020;306:6-10. doi: 10.1016/j.atherosclerosis.2020.06.012.
25. Kerola AM, Rollefstad S, Semb AG. Atherosclerotic cardiovascular disease in rheumatoid arthritis: Impact of inflammation and antirheumatic treatment. *European Cardiology* 2021;16(18). doi.org/10.15420/ecr.2020.44.
26. Wahood W, Ghozy S, Al-Abdulghani A, et al. Radial artery diameter: a comprehensive systematic review of anatomy. *J Neurointerv Surg*. 2022;14(12):1274-1278. doi: 10.1136/neurintsurg-2021-018534.

27. Loh YJ, Nakao M, Tan WD, et al. Factors influencing radial artery size. *Asian Cardiovascular & Thoracic Annals* 2020;15(4):324–326. doi.org/10.1177/021849230701500412.
28. Hannawi S, Haluska B, Marwick TH, et al. Atherosclerotic disease is increased in recent-onset rheumatoid arthritis: a critical role for inflammation. *Arthritis Research & Therapy* 2007;9(6):116. doi.org/10.1186/ar2323.
29. Komici K, Perna A, Rocca A, et al. Endothelial progenitor cells and rheumatoid arthritis: Response to endothelial dysfunction and clinical evidence. *International Journal of Molecular Sciences* 2021;22(24):13675. doi: [10.3390/ijms222413675](https://doi.org/10.3390/ijms222413675)

Chapter 4 – General Conclusion



In this study, we aimed to investigate the possible relationship between CIMT and RIMT and modifiable and non-modifiable cardiac risk factors. Only patients with risk factors for future CVS events, such as CAD and stroke, were included in the study. To our knowledge, this is the first study describing CIMT and RIMT ultrasound measurements in patients with modifiable risk factors in central SA. To date, there is a lot of debate in the literature regarding the predictive and prognostic value of CIMT measurements. However, it is clear that apart from traditional cardiac risk factors, an increase in CIMT thickness is an independent predictor of stroke risk.

The study group primarily consisted of older, affluent patients who presented at a private practice with one or more modifiable cardiac risk factors. Male sex and increased age significantly contributed to a thickened CIMT. Only 40% of patients with risk factors had a thickened CIMT. The majority of patients in the abnormal CIMT group had two or more risk factors. Hypertension was the single most common risk factor in the study population, present in 89%; two-thirds were obese, followed by hypercholesterolemia, diabetes and smoking. Females tended to be dominant in the normal CIMT group, but almost a 50/50 distribution of gender was observed for the abnormal CIMT group. Nearly 60% of patients diagnosed with stroke or TIA had an abnormal CIMT.

Forty-six percent of the hypertension group had an abnormal CIMT (>0.8 mm), and hypertension contributed to a thicker CIMT mean (OR 3.99). Diabetes was an important risk factor in our study population, and 60% of our patients presenting with DM had an abnormal CIMT. The mean CIMT in the diabetic patients was 0.9 ± 0.2 mm. DM significantly contributed to a thicker CIMT mean (OR 2.82). Hypercholesterolemia was present in more than half of the patients in the abnormal CIMT group. Hypercholesterolemia contributed to a thickened CIMT (OR of 2.47).

Results of this study showed that risk factor combinations like DM and hypertension (OR 6.92) and hypertension and smoking (OR: 3.67) significantly increase the risk of having thicker

CIMT measurements – the odds ratios of the combinations were markedly higher than single risk factors, most likely indicating summative effects when individual risk factors occur in combination. However, it appears that having hypercholesterolemia and DM, hypercholesterolemia and obesity reduces the risk of having a thickened CIMT. The authors speculate that many of these patients were already on statin treatment which may have provided protection against an increased CIMT.

A good correlation was observed between left and right CIMT and between left and right RIMT measurements. However, CIMT and RIMT did not correlate with each other. Abnormal RIMT measurements were observed in only 22% of the study population, and only 38% of patients with abnormal CIMT also had an abnormal RIMT, indicating that these are not necessarily correlated. Interestingly, the mean internal radial diameter was significantly smaller in the normal RIMT group compared to the abnormal RIMT group (2.3 ± 0.5 mm vs 2.6 ± 0.5 mm, respectively). It is important to take cognizance of the radial artery diameters described in this study because radial artery catheterizations are increasingly being performed in these patients due to low complication rates and significantly reduced procedure times.

Interestingly, more female patients presented with an abnormal RIMT than men (57% vs 43%). Like the CIMT group, hypertension was the most common modifiable risk factor, followed by obesity and hypercholesterolemia. Hypercholesterolemia was the only individual risk factor contributing to a thicker radial IMT (OR 3.00), and, in contrast to CIMT, hypertension and obesity was the only combination that contributed to a thicker RIMT. Forty patients with risk factors also had Rheumatoid Arthritis as a co-morbidity, and 70% had an abnormal thickened CIMT. A high percentage of patients in the RA group presented with an abnormal CIMT, which warrants further investigations.

References



- Arbab-Zadeh A, Nakano M, Virmani R, Fuster V. (2012). Acute coronary events. *American Heart Association*, 125(9):1147-1156.
- Atkins PW, Perez HA, Spence JD, Muñoz SE, Armando LJ, García NH. (2019). Increased carotid plaque burden in patients with family medical history of premature cardiovascular events in the absence of classical risk factors. *Archives of Medical Science*, 15(6):1388–1396.
- Avan A, Digaleh H, Di Napoli M, Stranges S, Behrouz R, Shojaeianbabae, G, Amiri A, Tabrizi R, Mokhber N, Spence JD, Azarpazhooh MR. (2019). Socioeconomic status and stroke incidence, prevalence, mortality, and worldwide burden, an ecological analysis. *The Global Burden of Disease Study Medicine*, 17(1):191.
- Aziz M. (2016). Pathogenesis of atherosclerosis a review pathophysiology. *Medical and Clinical Reviews*, 2(3):1–6.
- Banerjee C, Chimowitz MI. (2017). Stroke caused by atherosclerosis of the major intracranial arteries. *Circulation Research*, 120(3):502–513.
- Bekwelem W, Jensen PN, Norby FL, Soliman EZ, Agarwal SK, Lip GY, Pan W, Folsom AR, Longstreth WT, Jr Alonso A, Heckbert SR, Chen LY. (2016). Carotid atherosclerosis and stroke in atrial fibrillation. The atherosclerosis risk in communities study. *American Heart Association*, 47(6):1643–1646.
- Bengtsson VW, Persson GR, Berglund J, Renvert S. (2019). Carotid calcifications in panoramic radiographs are associated with future stroke or ischemic heart diseases: a long-term follow-up study. *Clinical Oral Investigations*, 23(3):1171–1179.
- Bentzon JF, Otsuka F, Virmani R, Falk E. (2014). Mechanisms of plaque formation and rupture. *Circulation Research*, 114(12):1852–1866.
- Betriu-Bars Á, Fernández-Giráldez E. (2012). Carotid ultrasound for the early diagnosis of atherosclerosis in chronic kidney disease. *Nefrología: publicación oficial de la Sociedad Española Nefrología*, 32(1):7–11.
- Boehme AK, Esenwa C, Elkind MS. (2017). Stroke risk factors, genetics, and prevention. *Circulation Research*, 120(3):472–495.

- Bohlen A, Boll M, Schwarzer M, Groneberg DA. (2015). Body-Mass-Index. *Diabetologe Springer Verlag*, 11(4):331–345.
- Bruckert É, Gallo A. (2017). Familial hypercholesterolemia. *Bulletin de l'Academie Nationale de Medecine*. 201(7–9).
- Byrne J, Eksteen G, Crickmore C. (2016). Cardiovascular disease. Heart and stroke foundation South Africa cardiovascular disease statistics. *Heart and stroke foundation South Africa*. <https://www.heartfoundation.co.za/wp-content/uploads/2017/10/CVD-Stats-Reference-Document-2016-FOR-MEDIA-1.pdf> (Accessed January 2023).
- Carbonell M, Castelblanco E, Valldeperas X, Betriu À, Traveset A, Granado-Casas M, Hernández M, Vázquez F, Martín M, Rubinat E, Lecube A, Franch-Nadal J, Fernández E, Puig-Domingo M, Avogaro A, Alonso N, Mauricio D. (2018). Diabetic retinopathy is associated with the presence and burden of subclinical carotid atherosclerosis in type 1 diabetes. *Cardiovascular Diabetology*. 17(1):66.
- Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P, Brevetti G, Chiariello M. (2010). Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. *Journal of the American College of Cardiology*. 56(24):2006–2020.
- Dias EM, Giollo LT, Martinelli DD, Mazeti C, Júnior HM, Vilela-Martin JF, Yugar-Toledo JC. (2012). Carotid intima-media thickness is associated with cognitive deficiency in hypertensive patients with elevated central systolic blood pressure. *Cardiovascular ultrasound*. 18(10):41.
- Eklund C, Omerovic E, Haraldsson I, Friberg P, Gan LM. (2014). Radial artery intima-media thickness predicts major cardiovascular events in patients with suspected coronary artery disease. *European Heart Journal of Cardiovascular Imaging*. 15(7):769–775.
- Hamer M, von Känel R, Reimann M, Malan NT, Schutte AE, Huisman HW, Malan L. (2015). Progression of cardiovascular risk factors in black Africans: 3 year follow up of the SABPA cohort study. *Atherosclerosis*. 238(1):52–54.
- Harris S. (2012). The association of carotid intima-media thickness (cIMT) and stroke: A cross sectional study. *Perspectives in Medicine*. 1:164-166.
- Hennerici, M. and Neuerburg-Heusler, D. Hennerici MG, Gebel M, Driessen GK, Daffertshofer M. (2006) *Vascular Diagnosis with Ultrasound*. 2nd ed. Stuttgart: Thieme.
- Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. (2016). Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. *Circulation Research*. 118(4):535–546.

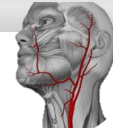
- Iannuzzi A, Rubba P, Gentile M, Mallardo V, Calcaterra I, Bresciani A, Covetti G, Cuomo G, Merone P, Di Lorenzo A, Alfieri R, Aliberti E, Giallauria F, Di Minno MND, Iannuzzo G. (2021). Carotid atherosclerosis. *Ultrasound and Lipoproteins Biomedicines*. 9(5):521.
- Judd SE, Gutiérrez OM, Newby PK, Howard G, Howard VJ, Locher JL, Kissela BM, Shikany JM. (2013). Dietary patterns are associated with incident stroke and contribute to excess risk of stroke in black Americans. *Stroke*. 44(12):3305–3311.
- Kajitani N, Uchida HA, Suminoe I, Kakio Y, Kitagawa M, Sato H, Wada J. (2018). Chronic kidney disease is associated with carotid atherosclerosis and symptomatic ischaemic stroke. *The Journal of International Medical Research* 46(9):3873–3883.
- Katakami N. (2018). Mechanism of development of atherosclerosis and cardiovascular disease in diabetes mellitus. *Journal of Atherosclerosis and Thrombosis*. 25(1):27–39.
- Kayashima Y, Maeda-Smithies N. (2020). Atherosclerosis in different vascular locations unbiasedly approached with mouse genetics. *Genes*. 11(12):1427.
- Kerola AM, Rollefstad S, Semb AG. (2021). Atherosclerotic cardiovascular disease in rheumatoid arthritis: Impact of inflammation and antirheumatic treatment. *European Cardiology*. 13(16):e18.
- Komici K, Perna A, Rocca A, Bencivenga L, Rengo G, Guerra G. (2021). Endothelial progenitor cells and rheumatoid arthritis: Response to endothelial dysfunction and clinical evidence. *International Journal of Molecular Sciences*. 22(24):13675.
- Kondo T, Nakano Y, Adachi S, Murohara T. (2019). Effects of tobacco smoking on cardiovascular disease. *Circulation Journal: Official Journal of the Japanese Circulation Society*. 83(10):1980–1985.
- Ku YM, Kim YO, Kim JI, Choi YJ, Yoon SA, Kim YS, Song SW, Yang CW, Kim YS, Chang YS, Bang BK. (2006). Ultrasonographic measurement of intima-media thickness of radial artery in pre-dialysis uraemic patients: comparison with histological examination. *Nephrology, dialysis, transplantation. European Dialysis and Transplant Association - European Renal Association*. 21(3):715–720.
- Lazenby, R. B. (2011) *Handbook of Pathophysiology*. 4th ed. Philadelphia: Wolters Kluwer Health.
- Lechner K, von Schacky C, McKenzie AL, Worm N, Nixdorff U, Lechner B, Kränkel N, Halle M, Krauss RM, Scherr J. (2020). Lifestyle factors and high-risk atherosclerosis: Pathways and mechanisms beyond traditional risk factors. *European Journal of Preventive Cardiology*. 27(4): 394–406.

- Loizou CP, Nicolaides A, Kyriacou E, Georghiou N, Griffin M, Pattichis CS. (2015). A comparison of ultrasound intima-media thickness measurements of the left and right common carotid artery. *IEEE Journal of Translational Engineering in Health and Medicine*. 3:1900410.
- Lovren F, Teoh H, Verma S. (2015). Obesity and atherosclerosis: mechanistic insights. *The Canadian Journal of Cardiology*. 31(2):177–183.
- Marieb, E. and Hoehn, K. (2014) *Human Anatomy & Physiology*. Pearson Ne. Essex: Pearson.
- Mathur P, Ostadal B, Romeo F, Mehta JL. (2015). Gender-related differences in atherosclerosis. *Cardiovascular Drugs and Therapy*. 29(4):319–327.
- Merriam-Webster's Collegiate Dictionary (10th ed.). (2023). Merriam-Webster Incorporated
- Mills KT, Stefanescu A, He J. (2020). The global epidemiology of hypertension. *Nature Reviews Nephrology*. 16(4):223–237.
- Mitchell C, Korcarz CE, Gepner AD, Kaufman JD, Post W, Tracy R, Gassett AJ, Ma N, McClelland RL, Stein JH. (2018). Ultrasound carotid plaque features, cardiovascular disease risk factors and events: The Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 276:195–202.
- Muller CJ, Alonso A, Forster J, Vock DM, Zhang Y, Gottesman RF, Rosamond W, Longstreth WT, MacLehose RF. (2019). Stroke incidence and survival in American Indians, Blacks, and Whites: The strong heart study and atherosclerosis risk in communities study. *Journal of the American Heart Association*. 8(12):e010229.
- Myredal A, Osika W, Li Ming G, Friberg P, Johansson M. (2010). Increased intima thickness of the radial artery in patients with coronary heart disease. *Vascular Medicine*. 15(1):33–37.
- Nezu T, Hosomi N, Aoki S, Matsumoto M. (2016). Carotid intima-media thickness for atherosclerosis. *Journal of Atherosclerosis and Thrombosis*. 23(1):18–31.
- Nuraini B. (2015). Risk factors of hypertension. *Medical Journal of Lampung University*. 4(5):10-19.
- O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson S K. (1999). Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular health study collaborative research group. *The New England Journal of Medicine*. 340(1):14–22.

- Pan B, Jin X, Jun L, Qiu S, Zheng Q, Pan M. (2019). The relationship between smoking and stroke: A meta-analysis. *Medicine*. 98(12).
- Petrák O, Češka R. (2019). Vaskulární věk, *Vnitr Lek*. 65(12):770-774.
- Petty GW, Brown RD, Whisnant JP, Sicks JD, Fallon WM, Wiebers DO. (1999). Ischemic stroke subtypes: a population-based study of incidence and risk factors. *Stroke*. 30(12):2513–2516.
- Ragino YI, Stakhneva EM, Polonskaya YV, Kashtanova EV. (2020). The role of secretory activity molecules of visceral adipocytes in abdominal obesity in the development of cardiovascular disease: A review. *Biomolecules*. 10(3):374.
- Ramrakha, P. and Hill, J. (2012). Oxford Handbook of Cardiology. 2nd ed. New York: Oxford University Press.
- Ren L, Cai J, Liang J, Li W, Sun Z. (2015). Impact of cardiovascular risk factors on carotid intima-media thickness and degree of severity: A cross-sectional study. *PLoS One*. 10(12):e0144182.
- Rockman CB, Hoang H, Guo Y, Maldonado TS, Jacobowitz GR, Talishinskiy T, Riles TS, Berger JS. (2013). The prevalence of carotid artery stenosis varies significantly by race. *Journal of Vascular Surgery*. 57(2):327–337.
- Sakakura K, Nakano M, Otsuka F, Ladich E, Kolodgie FD, Virmani R. (2013). Pathophysiology of atherosclerosis plaque progression. *Heart & Lung Circulation*. 22(6):399–411.
- Scarno A, Perrotta FM, Cardini F, Carboni A, Annibali G, Lubrano E, Spadaro A. (2014). Beyond the joint: Subclinical atherosclerosis in rheumatoid arthritis. *World Journal of orthopedics*. 5(3):328–335.
- Shea S, Ottman R, Gabrieli C, Stein Z, Nichols, A. (1984). Family history as an independent risk factor for coronary artery disease. *Journal of the American College of Cardiology*. 4(4):793–801.
- Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandebroek K, Benito-Vicente A, Martín C. (2022). Pathophysiology of atherosclerosis. *International Journal of Molecular Sciences*. 25(4):231-242.
- Shrestha I, Takahashi T, Nomura E, Ohtsuki T, Ohshita T, Ueno H, Kohriyama T, Matsumoto M. (2009). Association between central systolic blood pressure, white matter lesions in cerebral MRI and carotid atherosclerosis. Hypertension research: *Official Journal of the Japanese Society of Hypertension*. 32(10):869–874.

- Song P, Fang Z, Wang H, Cai Y, Rahimi K, Zhu Y, Fowkes FGR, Fowkes FJI, Rudan I. (2020). Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. *The Lancet. Global Health*. 8(5):721–729.
- Syed MB, Fletcher AJ, Forsythe RO, Kaczynski J, Newby DE, Dweck MR, van Beek EJ. (2019). Emerging techniques in atherosclerosis imaging. *The British Journal of Radiology*. 92(1103).
- Toth PP. (2008). Subclinical atherosclerosis: what it is, what it means and what we can do about it. *International Journal of Clinical Practice*. 62(8):1246–1254.
- Villablanca AC, Jayachandran M, Banka C. (2010). Atherosclerosis and sex hormones: current concepts. *Clinical Science* (London, England). 119(12):493–513.
- World Health Organization. (2011). Body mass index classification. Pharmacotherapy. Table 1: 4–9.
- Zyriax BC, Dransfeld K, Windler E. (2021). Carotid intima-media thickness and cardiovascular risk factors in healthy volunteers. *The Ultrasound Journal*. 13(1):17.

Appendices



Appendix A



Health Sciences Research Ethics Committee

19-Jan-2021

Dear Mr Fritz Van Schalkwyk

Ethics Clearance: **Carotid and radial intima-media thickness measurements in private patients presenting with modifiable cardiac risk factors in Central South Africa**

Principal Investigator: **Mr Fritz Van Schalkwyk**

Department: **Clinical Technology - CUT**

[Submission Page](#)

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is: **UFS-HSD2020/2018/2601**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act, No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Prof. A. Sheriff
Chair : Health Sciences Research Ethics Committee

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