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Ankle Brachial Index (ABI) predicts 2-year mortality risk among older adults in the Republic of Congo: The EPIDEMCA-FU study

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HIGHLIGHTS

- Peripheral artery disease (PAD) association with mortality in native older Africans is poorly documented.
- Low ABI (≤0.90) was associated with increased mortality risk in adults > =65 in Congo.
- ABI may be a reliable tool to identify older people at high risk of death in Sub-Saharan Africa.

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ABSTRACT

Background and aims: Peripheral artery disease (PAD) is known to be associated with mortality in high income countries but no data regarding Sub-Saharan Africa (SSA) populations are documented. This study aimed at assessing the prognostic value of the Ankle Brachial Index (ABI) among older adults in the Republic of Congo.
Methods: Congolese subjects ≥65 years were included in a longitudinal population-based survey (EPIDEMCA-FU). Demographic, biological, and clinical data were collected at baseline. PAD was defined by an ABI ≤ 0.90. Information on mortality was collected from key informants in participants' households. Cox proportional hazard models, adjusted for traditional and cardiovascular risk factors, were fitted to evaluate the association between an ABI ≤ 0.90 and death.
Results: 1029 participants were recruited at baseline. ABI measurement was obtained from 927 participants, of whom 17.4% presented an ABI ≤ 0.90. During a 2-year follow-up, a total of 83 (9.1%) deaths were recorded. Mortality was higher in the low-ABI group with 23 deaths (14.7%) *vs.* 57 (7.8%) and 3 (12.0%), respectively among those with 0.90 < ABI < 1.4 and ABI ≥ 1.40 (p = 0.039). After adjustment, an ABI ≤ 0.90 was associated with an increased risk of mortality (HR = 1.86; 95%CI 1.04–3.87). Mortality was also independently associated with increasing age (HR = 1.05; 95%CI 1.02–1.09), dementia (HR = 2.73; 95% CI 1.15–8.05), alcohol use (HR = 0.51; 95%CI 0.29–0.88) and female sex (HR = 0.37; 95%CI 0.19–0.72).
Conclusions: In this study, a low ABI predicted an increased mortality risk among older people. ABI may represent a simple and inexpensive tool to identify older people at high risk of death in SSA.

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1. Introduction

With population ageing, the burden of non-communicable diseases, such as cardiovascular diseases (CVDs), is increasing in sub-Saharan Africa (SSA) [1,2]. Among people living in high-income countries, those with lower-extremities peripheral artery disease (PAD) are at increased risk of subsequent cardiovascular events [3,4] and death [5–7]. Older adults are the most exposed and affected group [8,9]. Due to the lack of symptoms, PAD is frequently misdiagnosed [5,10]. Therefore, screening of asymptomatic patients with PAD might be an efficient method to identify those at an increased risk of death [10]. PAD can easily and reliably be detected at low cost by the measurement of the Ankle-Brachial Index (ABI) [4,11]. In high-income countries, PAD defined by an ABI ≤ 0.90 is associated with an increased risk of cardiovascular events and mortality [6,12–15].

In SSA, the prevalence of PAD is equal to or higher than what is observed in high income countries, exceeding 50% in some high-risk populations [16]. Despite the growing burden of PAD in this region [17], knowledge about ABI and its prognostic value remains scarce [7,16,18]. Information regarding the prognostic value of ABI in elderly people living in SSA may help identify high-risk individuals, in order to focus restrained healthcare resources on them. To our knowledge, there are no previous population-based studies investigating the prognostic value of ABI among older adults in SSA.

Therefore, the aim of this study is to assess the prognostic value of the ABI measurement as a screening tool for PAD, to predict mortality risk among Congolese older adults. Using ABI as a screening tool (ABI $\leq$ .90) [17], we previously estimated the prevalence of PAD in this population at 17.4%. We hypothesised that, despite the specific socio-economic context in this low-income country, a low ABI measurement would remain a significant predictor of mortality.

2. Patients and methods

2.1. Study design and participants

The EPIDEMCA-FU (Epidemiology of Dementia in Central Africa - Follow-Up) is a longitudinal population-based study carried out in the Republic of Congo [19]. It is part of a research programme studying the Epidemiology of Dementia in Central Africa (EPIDEMCA), which started in 2011 [20].

Adults aged 65 and over were included at baseline and then followed-up over a 2-year period (2012–2014). Baseline data collection has been described elsewhere [20]. Essentially, sampling methods differed between urban and rural areas. Due to logistical and financial constraints, door-to-door knocking was carried out in each district constituting the rural catchment area (Gamboma's main districts). In case of an inhabitant's absence during the day of screening, houses were revisited at least twice. A random sampling, proportional to the size of each main subdivision of the city, took place in the urban site. This was to ensure the representation of Brazzaville's diverse population. For each main subdivision, a district was randomly chosen. The procedure in each district remained consistent: a door to-door survey was conducted in a random direction, starting from the district chief's house, until the number of participants allocated to each subdivision was reached. If the number of participants was not reached in the first district, the procedure was applied in another random district belonging to the same subdivision. In both sites, the only exclusion criteria were refusal or the presence of severe diseases with a short-term high risk of death. A sample size was projected in order to estimate the prevalence of dementia. The minimum number of subjects needed to detect a prevalence of 5%, with a precision of 2%, was 456 subjects (EpiInfo 6.04, Epiconcept). The study population consisted of 1,029 participants living in Congo: 529 participants (51.4%) in Gamboma (rural area) and 500 (48.6%) in Brazzaville (urban area).

Data about ABI and other variables (age, sex, living area, cardiovascular risk factors, and life habits) used for analysis were collected during the EPIDEMCA baseline survey [20].

Throughout each stage of the programme (baseline and follow-up), written consent (or oral in case of illiteracy) was obtained from the participants and/or their relatives. The study was approved by the Congolese ethical committee CERSSA (Comité d'Ethique de la Recherche en Sciences de Santé) and by a French ethics review board (Comité de Protection des Personnes Sud-Ouest Outre Mer).

2.2. Baseline data

2.2.1. PAD: measurement, definition and diagnosis

Measurement protocol and ABI calculation were following the American Heart Association (AHA) guidelines [11]. Measurements of upper- and lower-extremity blood pressures were performed after at least 30 min of rest. Systolic blood pressures (SBP) were measured in both arms and legs, with the subject in the supine position. Hand-held Doppler ultrasound devices (Dopplex 900, Huntleigh Healthcare Ltd, Cardiff, UK) were used to measure SBP of posterior tibial and dorsal pedis arteries bilaterally. ABI measurement was not performed on participants with leg ulcers, fractures, sores, edema, hemiplegia, or other reasons preventing ABI measures. In agreement with recommendations, ABI in each leg was calculated by dividing the highest pressure between posterior tibial and dorsalis pedis arteries by the highest arm pressure. The ABI of the individual was the lowest ABI amongst the two legs. An ABI ≤ 0.90 was used to define PAD while an ABI ≥ 1.40 defined poorly compressible ankle arteries, a condition mostly associated with medial calcinosis and also associated with increased mortality [11]. If an ABI was ≤ 0.90 while the other was $>$ 1.40, the subject was categorised with an ABI $\leq$ 0.90. Thus, we defined three groups of participants according to their ABI: normal group ($0.90 <$ ABI < 1.40), PAD group (ABI ≤ 0.90) and poorly compressible ankle arteries group (ABI ≥ 1.40).

2.2.2. Questionnaire and measures (variables)

At baseline, a questionnaire was administrated to all participants prior to physical examination. The structured interview was conducted by trained investigators in local languages (Lingala, Kituba and Lari) or in French. The questionnaire collected information about participants' sociodemographic status (age, sex, residence area, marital status, education level and occupational activities), lifestyle (tobacco and alcohol use) and cardiovascular risk factors. History of hypertension, diabetes, and myocardial infarction were investigated by self-report.

Physical examination included body weight, height, blood pressure, and waist circumference measurements. In case of an elevated blood glucose level, according to WHO recommendations (above 126 mg/dL if the fasting period $>$ 2 h or above 200 mg/dL in non-fasting participants) [23] and/or self-reported treatment, participants were categorised as having diabetes. Hypertension was defined by self-reported treatment or in case of high blood pressure, as defined by the WHO [24] (i.e. brachial SBP at rest ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg). Body Mass Index (BMI) was calculated by dividing weight (in kg) by the square of height (in meters). BMI categories were defined according to WHO's classification: underweight (BMI $<$ 18.5); normal ($18.5 \leq$ BMI ≤ 24.9); overweight ($25.0 \leq$ BMI ≤ 29.9); obese (BMI $\geq$ 30) [25]. Abdominal obesity was defined according to the recommended waist circumference thresholds for abdominal obesity in SSA (94 cm for men and 80 cm for women) [26]. Total cholesterol and C-Reactive Protein (CRP) dosages were performed on plasma aliquots using standard procedures (Biochemistry department, Limoges

University Hospital on Cobas automaton). Hypercholesterolemia was defined by total cholesterol > 5.3 mmol/L. Tobacco and alcohol use were categorised as dichotomic variables (respectively current and former users *vs.* never, and sometimes and regularly *vs.* none).

Dementia was diagnosed using a two-stage design [20] and defined according to DSM-IV criteria [21]. Petersen's criteria was used for Mild Cognitive Impairment diagnosis (MCI) [22].

2.3. Follow-up data

The outcome collected was all-cause mortality within 2 years of the follow-up. In case of death or recurrent absence, information about the older person's vital status was obtained from relatives. If participants moved away between baseline and follow-up visits, they were traced and contacted at their new addresses. All participants whose vital statuses could not be filled accurately and reliably were considered as lost to follow-up. When it was possible, the date of death was recorded. If only the month of death was known, an arbitrary date set at the 15th of the month was considered. History of illness before death and probable cause of death were recorded using the WHO disease definition. Vital status was defined as a dichotomic variable: death/alive.

2.4. Statistical analyses

Categorical and continuous variables were respectively presented by numbers (percentages) and means (standard deviations). For descriptive analyses, Chi^2 or Fisher's exact tests were used when appropriate to compare categorical variables while the Student's t-test was used for continuous variables after checking the normality.

Cox proportional hazard models, with estimations of hazard ratios (HR) and their 95% confidence intervals (CI), were performed to assess the association between ABI categories and 2-year mortality. After a univariate analysis, the multivariate model included age, sex, residence area, cognitive status, and lifestyle and cardiovascular covariates: tobacco and alcohol use, diabetes, hypertension, BMI, hypercholesterolemia, and abdominal obesity. Covariates were then selected through a backward step-by-step regression, removing progressively variables which were not reaching statistical significance. This model was fitted using 2-year vital status (death/alive) as the dependent variable and baseline ABI groups as the main independent variable. Interaction between an ABI and sex was also tested in this model (introducing a multiplicative term ABI * sex). Statistical significance level was fixed at 0.05.

Data management and statistical analyses were performed using Stata (version 10.1, Stata-Corp, College Station, Texas, United States).

3. Results

The baseline study population consisted of 1,029 older adults (mean age 73.8 ± 6.8 years): 403 (39.2%) males and 626 (60.8%) females. Due to missing ABI measurement, 102 (9.9%) participants were excluded. Excluded participants were older and more likely to live in the urban area. They were less likely to have hypertension, but more likely to have dementia (Supplementary Table 1). For this study, analyses were therefore based on 927 participants: 161 (17.4%) with ABI ≤ 0.90, 740 (79.8%) with 0.90 < ABI < 1.4 and 26 (2.8%) with ABI ≥ 1.40 (Fig. 1).

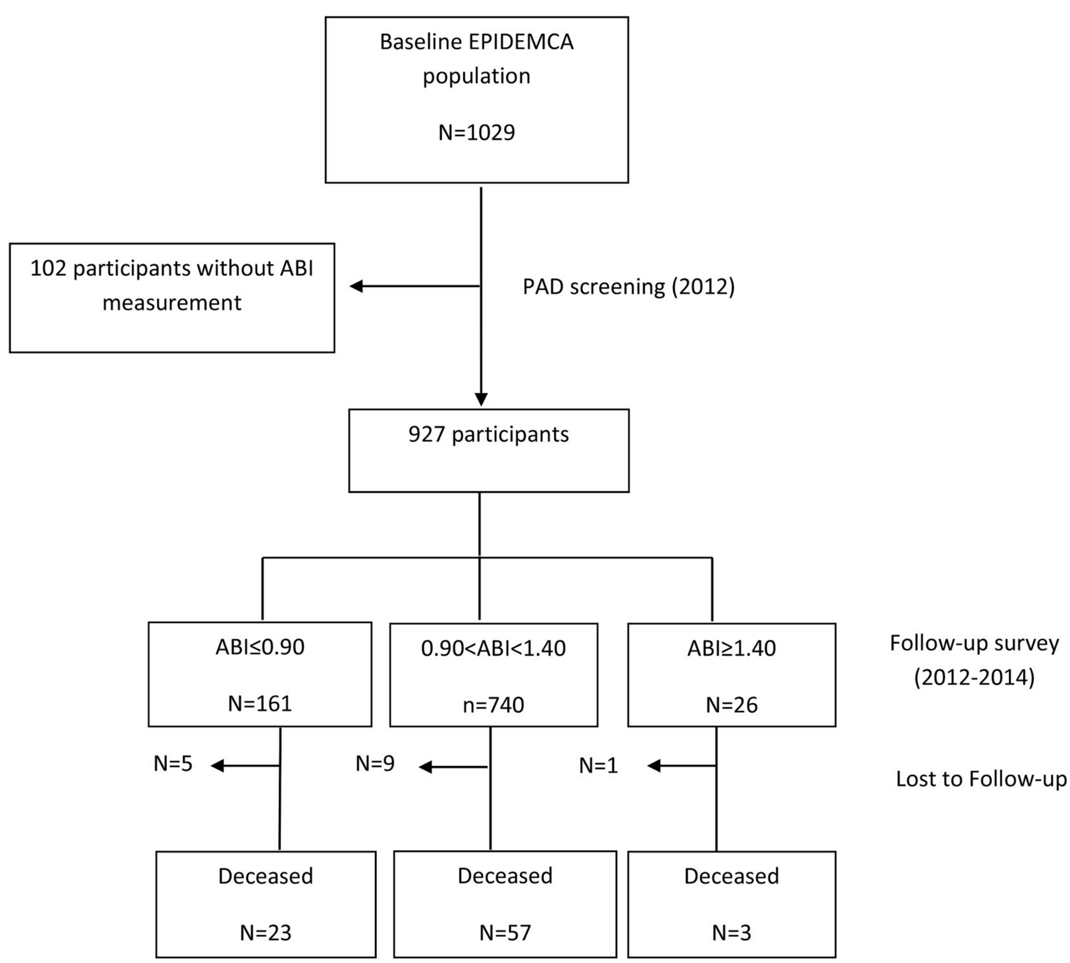

Fig. 1. Flow chart of participant selection, EPIDEMCA-FU, Congo, 2012–2014.

Table 1
Description of baseline characteristics of 927 participants according to ABI group, EPIDEMCA-FU, Congo, 2012–2014.

	0.90 < ABI < 1.40		ABI ≤ 0.90		ABI ≥ 1.40		Total		*p* -value
	n = 740	79.83%	n = 161	17.37%	n = 26	2.80%	N = 927	100%	
Sociodemographic characteristics									
Age (year) (mv = 0)									
[65–70]	271	36.62	39	24.22	7	26.92	317	34.20	0.009
[70–75]	194	26.22	45	27.95	6	23.08	245	26.43	
[75–80]	148	20.00	31	19.25	5	19.23	184	19.85	
[80–85]	80	10.81	31	19.25	7	26.92	118	12.73	
≥85	47	06.35	15	09.32	1	03.85	63	06.80	
Female sex (mv = 0)	444	60.00	112	69.57	13	50.00	569	61.38	0.038
Primary education (mv = 1)	121	16.37	14	08.70	5	19.28	140	15.12	0.040
Urban residence (mv = 0)	336	45.41	91	56.52	12	46.15	439	47.36	0.037
Clinical characteristics									
Cognitive status (mv = 100)									
Normal	595	89.61	117	84.78	22	88.00	734	88.75	0.463
MCI	40	06.02	11	07.97	1	04.00	52	06.29	
Dementia	29	04.37	10	07.25	2	08.00	41	04.96	
Hypercholesterolemia (mv = 162)	65	10.57	23	17.97	2	09.09	90	11.76	0.057
Hypertension[a] (mv = 0)	494	66.70	129	80.12	12	46.15	635	68.05	< 0.001
Diabetes (mv = 5)	78	10.58	18	11.32	5	19.23	101	10.95	0.377
BMI (kg/m^2) (mv = 24)									
BMI < 18.5	213	29.38	48	31.58	11	42.31	272	30.12	0.057
18.5 ≤ BMI ≤ 24.9	388	53.52	65	42.76	10	38.46	463	51.27	
25.0 ≤ BMI ≤ 29.9	87	12.00	24	15.79	3	11.54	114	12.62	
≥30	37	05.10	15	09.87	2	07.69	54	05.98	
History of myocardial infarction[a] (mv = 5)	46	06.25	20	12.50	1	03.85	67	07.27	0.026
Abdominal obesity[a] (mv = 45)	487	68.79	77	52.03	20	76.92	584	66.21	< 0.001
Lifestyle									
Alcohol use[a] (mv = 8)	132	17.84	24	14.92	6	23.08	162	17.48	0.484
Smoking[a] (mv = 5)	133	18.05	37	23.27	6	23.08	179	19.06	0.274

ABI: Ankle Brachial Index; BMI: Body Mass Index; MCI: mild cognitive impairment; mv: missing value.
[a] Omitted category for dichotomic variables.

Participant's characteristics, according to baseline ABI measurements, are displayed in Table 1. Participants with ABI ≤ 0.90 at baseline were more likely to be older ($p = 0.009$), female ($p = 0.038$), overweight ($p = 0.057$), to have hypertension ($p < 0.001$) and hypercholesterolemia ($p = 0.057$). Often, they lived in an urban area ($p = 0.037$) and were less likely to have formal education ($p = 0.040$). Notably, we found no significant differences regarding rates of diabetes, smoking and alcohol use (Table 1).

After 2 years of follow-up, vital status was obtained for all except 15 participants (1.6%) (Fig. 1). Hence, these participants were excluded from survival analysis. These participants were not different from the other participants regarding baseline data (data not shown).

During the 2-year period of follow-up, we recorded 83 (9.1%) deaths: 23 (14.7%) among those with ABI ≤ 0.90, 57 (7.8%) among those with 0.90 < ABI < 1.40 and 3 (12.0%) among those with ABI ≥ 1.40. Cause of the death remained unknown in 53% of the cases, whilst cardiovascular diseases were reported as a cause of death in 36%. The proportion of death was more important in the low-ABI group compared to the normal group ($p = 0.039$).

In univariate analysis, a low ABI was associated with an increased 2-year mortality risk. After adjustment, ABI ≤ 0.90 was still associated with increased mortality risk. People with ABI ≤ 0.90 had about a two-fold higher risk of death (HR = 1.86; 95%CI 1.04–3.87, $p = 0.044$) compared to those with a normal ABI. Mortality was also independently associated with increasing age (HR = 1.05; 95%CI 1.02–1.09; $p = 0.002$) and the presence of dementia (HR = 2.73; 95% CI 1.15–8.05; $p = 0.007$). A lower risk of mortality was associated with alcohol use (HR = 0.51; 95%CI 0.29–0.88; $p = 0.017$) and female sex (HR = 0.37; 95%CI 0.19–0.72; $p^{<}0.003$) (Table 2). No significant interaction was found between ABI and sex when mortality was considered as dependent variable ($p = 0.106$), ruling out a different effect of a low ABI on mortality according to sex.

4. Discussion

Our study confirms our hypothesis that PAD, defined as ABI ≤ 0.90, is associated with an increased risk of death in this older Congolese population. This association remained significant after adjustments and was not different according to sex.

Our findings are consistent with those reported in other studies conducted in high-income countries [5,6,27]. In the Edinburgh cohort study, 1592 men and women aged from 55 to 74 years were randomly selected from the registers of general practices and followed-up for over 12 years. The relative risks of all-cause mortality associated with ABI ≤ 0.90 varied after adjustment on sex, age and major cardiovascular risk factors from 1.42 (95%CI 1.15–1.74) to 1.14 (95%CI, 0.91–1.43), respectively [28]. In the Cardiovascular Health Study (CHS), the relative risk for 6-year total mortality was 1.62 (95% CI 1.24–2.12) for CVD-free participants aged ≥65 years [29]. In a primary care population, Diehm et al. described a 2-fold increased risk of death associated with a low ABI [6]. When Heald et al. reviewed available surveys on PAD and mortality risk, the pooled estimates for relative risk associated with low-ABI were 2.35 (95% CI 1.66–3.32) after adjustment on age and sex, and 1.60 (95% CI 1.32–1.95) when the adjustment was extended to cardiovascular risk factors, respectively [5]. Nevertheless, in the 5 studies included in the analysis, duration of follow-up ranged

Table 2
Association between PAD (ABI ≤ 0.90) and all-cause mortality after a 2-year follow-up, EPIDEMCA-FU, Congo, 2012–2014.

	Initial model			Final multivariate model		
	HR	95% CI	*p* -value	HR	95% CI	*p*- value
Age						
[65–70]	1	Reference	< 0.001	1	Reference	
[70–75]	1.14	0.61–2.17		0.84	0.29–2.37	0.746
[75–80]	0.87	0.41–1.86		0.78	0.26–2.34	0.660
[80–85]	2.91	1.60–5.33		**1.64**	**0.57–4.68**	**0.034**
> 85	3.41	1.66–6.97		**2.14**	**1.26–6.14**	**0.066**
Sex						
Men	1	Reference	0.010	1	Reference	
Women	0.56	0.36–0.86		**0.37**	**0.19–0.72**	**0.003**
Cognitive status						
Normal	1	Reference	0.003	1	Reference	
MCI	1.13	0.45–2.82		1.56	0.53–4.55	0.367
Dementia	3.59	1.88–6.85		**2.73**	**1.15–8.03**	**0.007**
Residence area						
Rural residence	1	Reference				
Urban residence	1.31	0.84–2.02	0.223			
ABI						
0.91 < ABI < 1.40	1	Reference	0.042	1	Reference	
ABI ≤ 0.90	1.91	1.17–3.10		**1.86**	**1.04–3.87**	**0.044**
ABI ≥ 1.40	1.49	0.46–4.77		0.77	0.26–2.47	0.240
BMI (kg/m^2)						
BMI < 18.5	1	Reference				
18.5 ≤ BMI ≤ 24.9	0.70	0.42–1.17	0.372			
25.0 ≤ BMI ≤ 29.9	1.15	0.59–2.23				
BMI ≥ 30	0.71	0.25–2.04				
Smoking (ref: no)						
Yes	0.70	0.37–1.33	0.284			
Alcohol use (ref: no)						
Yes	0.41	0.18–0.90	0.027	**0.51**	**0.29–0.88**	**0.017**
Hypertension (ref: no)						
Yes	1.42	0.86–2.35	0.160			
Hypercholesterolemia (ref: no)						
Yes	1.65	0.98–2.47	0.065			
Diabetes (ref: no)						
Yes	1.59	0.88–2.88	0.142			
Abdominal obesity (ref:no)						
Yes	0.93	0.55–1.56	0.796			

ABI: Ankle Brachial Index; BMI: Body Mass Index; CI: confidence interval; HR: hazard ratio; MCI: mild cognitive impairment.

from 4 to 12 years. To resolve the uncertainties related to different follow-up periods, a meta-analysis of time-to-event outcomes estimated an ABI-associated all-cause mortality risk between 1.18 and 5.06 [30]. Furthermore, analyses based on data from sixteen population cohort studies showed that a low ABI (< or ≤ 0.90) was associated with approximately twice the 10-year total mortality [31]. No interaction was found suggesting a difference in risk of mortality between men and women with a low PAD. Unfortunately, there are no studies investigating the prognostic value of the Ankle-Brachial Index on this difference, it is therefore not possible to compare our results to the literature. Considering the 2-year follow-up time, the mortality risk estimated in our older population with PAD seems to be slightly higher compared to other population-based studies [5]. Most of these studies showed an estimated mortality relative risk below 1.7, for follow-ups ranging from 4 to 12 years [5]. Authors considered that the higher risk may be related to a higher mean age of the population, as evidence from epidemiological data showed increasing prevalence of PAD (ABI ≤ 0.90) with age: around 10% by the age of 65 and as high as 25% after 85 [32]. Our overall population was at a high risk, with a mean age (73.8 ± 6.8 years) exceeding the average life-expectancy in this country (64.1 years according to the World Bank data in 2015 [33]). Furthermore, prevalence of diabetes and hypertension was high, at 11% and 67% respectively. These characteristics may contribute to the high mortality rate in the cohort: the overall mortality was 9% after 2 years. In most studies, the annual mortality rate was lower than in our survey, between 1.18 and 5.06 [30]. The Republic of Congo, as well as most SSA countries, has limitations in financial resources and access to treatment or medical facilities (in rural areas), which can hinder medical care and lead to increased mortality. The stronger association between PAD and mortality may be partly explained by a lower quality of care, risk factors control and the socio-economic situation.

The ethnic influence on PAD prevalence was previously documented in the US population [29,34,35], the condition being more prevalent in African-Americans. In the Cardiovascular Health Study [29], a second cohort of 687 African-American participants was enrolled and followed-up during 2 years. The main characteristics of this population were very similar to our cohort. The proportion of African-American participants with low ABI and no history of clinical PAD was 16.5% (as compared to 14.7% in our study). After 2 years, death rates were 17.1% and 3.8% in case of low or normal ABI, respectively. The prevalence of high ABI (≥ 1.40) (2.8%) in our study is concordant with data from high income countries studies (1.4%–2.8%) [30,36]. In these studies, high ABI was associated with increased mortality [37,38]. This association was not statistically significant in our study. Although the limited number of participants with high ABI and shorter time of follow-up may explain these results.

The present study presents several limitations. As expected in a longitudinal study, fifteen participants (1.6%) were lost to follow-up. However, compared with previous cohort studies conducted in SSA, the study achieved an excellent follow-up rate. As these participants had similar characteristics to those followed-up, a systematic bias is unlikely. Our follow-up period (2 years) was short compared to comparable studies that had follow-ups up to 11 years. In spite of this, we were able to show a significant effect very similar to the one described in the second CHS cohort [29]. Yet, as we were unable to evaluate accurately all causes of death, our results are limited to the overall mortality risk. Medical care during follow-up could be a source of confounding, but due to limited access to healthcare, we are confident that this observation bias is unlikely here. Furthermore, we must acknowledge that the self-reported nature of some information represents another limitation of our study, with a possibility of a significant amount of wrong or missing information due to the lack of awareness or access to healthcare facilities in this context. Nevertheless, all the main variables used in our multivariate model were measured, limiting the use of self-reported covariates to description only. Finally, as data on triglyceride levels was not available in our population, the estimation of the metabolic syndrome, an important predictor of cardiovascular diseases, was not possible and adjustments of our models were limited in this regard.

Based on our results, measurement of ABI enables to identify a subgroup of population with an ABI ≤ 0.90, who is at high risk of mid-term (2 years) mortality. ABI is a simple and rapid test, which could be performed by trained healthcare workers in the general population. However, our study is limited to individuals aged ≥65 years and the results can therefore not be extrapolated to younger people. Considering that, like anywhere else, the prevalence of PAD booms after this age limit [39], this tool might be particularly useful in low- and middle-income countries with limited medical resources to identify people at high risk. Further research is therefore required to evaluate the input of ABI measurement in population-based prevention programmes in sub-Saharan Africa.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

HS, BNB, GK, PMB, MG, JFD, PMP and PL were involved in the study design and data collection. HS, MG and PL prepared the first draft. Other authors reviewed the manuscript, provided further contributions and suggestions. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.05.013.

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