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Factors associated with incidence of stroke and heart failure among people living with HIV in Ghana: Evaluating Vascular Event Risk while on Long-Term Antiretroviral Suppressive Therapy (EVERLAST) Study

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Abstract

People living with HIV (PLWH) have a two-fold higher risk of cardiovascular diseases (CVDs) compared with HIV-negative populations. Although 70% of the global HIV population reside in Africa, data on CVD outcomes among PLWH are scarce. We seek to evaluate factors associated with incidence of stroke and heart failure in a prospective cohort of Ghanaian PLWH. We followed up a cohort of PLWH on antiretroviral therapy for 12 months to assess rates of clinically adjudicated stroke, and heart failure. We calculated incidence rates of events/1000 person-years and fitted Cox proportional hazards regression models to identify factors associated with incident stroke and heart failure as a combined outcome measure and as separate outcome measures. Among 255 participants, the mean age was 46 years and 211 (82.7%) were female. The participants contributed 245 years of follow-up data with mean follow-up duration of 11.5 months. There were three incident strokes giving an incidence rate of 12.24 per 1000 person-years (95% CI: 3.13–33.33) and two heart failure events with an incidence rate of 8.16 (95%CI: 1.37–26.97) per 1000 py. The combined event rate was 20.41 (95% CI: 7.48–45.24) per 1000 py. Being hypertensive was associated with aHR of 8.61 (1.32–56.04) of the combined outcome while each 100 cells/mm^3 rise in CD4 count was associated with aHR of 0.56 (0.35–0.88). Carotid bulb intimal media thickness was independently associated with stroke occurrence with aHR of 12.23 (1.28–117.07). People living with HIV on long-term cART in this Ghanaian sample have high rates of clinically adjudicated cardiovascular diseases driven by uncontrolled hypertension and persisting immunosuppression. Integration of CVD care into routine HIV management may help alleviate this untoward confluence of rising CVDs among PLWH.

1 | INTRODUCTION

People living with HIV (PLWH) have more than twice an increased risk of cardiovascular disease (CVDs) compared with HIV-negative populations.[1,2] With a steady diminution in deaths attributable to opportunistic infections and malignancies due to widespread access to combination antiretroviral therapy, CVDs have now emerged as leading causes of mortality and morbidity among

PLWH.[3–5] Direct vascular inflammation, dyslipidemia, and insulin resistance are some of the mechanisms linking HIV with the development of both overt and covert CVDs.[6–8] Global estimates based on a meta-analysis of 793,635 PLWH with a total of 3.5 million person-years gave a crude incidence rate of CVD per 1000 person-years of 6.18 (95%CI: 4.58–8.34). However, almost all the data on CVD events in HIV have been reported from cohorts in Europe, Northern America, Israel, and Asian countries.[2] There were no data from sub-Saharan Africa (SSA) in this meta-analysis of 80 studies due to paucity of prospective studies evaluating CVD outcomes among PLWH.[2] Sub-Saharan Africa harbors 70% of the 37 million individuals living with HIV on the globe and has concurrently witnessed an unprecedented rise in CVD burden over the last three decades.[9,10] There are indications that a convergence of a steep rise in vascular risk factors such as hypertension, dyslipidemia, and obesity among a population of PLWH with heightened vascular inflammation may engender an increased incidence of CVD events.[11–14] We have recently reported very high incidence rates of hypertension, pre-diabetes, and diabetes mellitus among PLWH in Ghana.[15,16] Poor detection and control of major vascular risk factors which is rife in SSA may contribute to a higher burden of CVDs among PLWH.[17,18] Furthermore, the relatively younger age of HIV patients, less frequent use of cigarette, female predominance, and less substance abuse among PLWH in SSA constitute a differential risk factor profile to those observed in high-income countries.[19] We, therefore, sought in this study to assess the incidence rates of stroke and heart failure in a prospective cohort of Ghanaian PLWH.

2 | METHODS

2.1 | Study design & population

The Evaluation of Vascular Event Risk while on Long-term Antiretroviral Suppressive Therapy (EVERLAST) Study is a case-control study to assess the prevalence of CVD risk among PLWH compared with HIV-negative controls.[20,21] Ethical approval for the study was obtained from the Kwame Nkrumah University of Science and Technology Committee of Human Research Publications and Ethics. PLWH were included if they were ≥30 years and receiving cART for at least 1 year at the HIV clinic of the Komfo Anokye Teaching Hospital, a tertiary medical facility in Kumasi, Ghana. For the present analysis, we focus on 12-month prospective CVD outcomes (incident stroke, heart failure, and acute coronary disease) among PLWH on cART at enrollment. Although we enrolled PLWH who were cART naïve and HIV-negative controls in the EVERLAST study, their follow-up was less rigorous and has not been included in the present report. All participants provided written informed consent.

2.2 | Study evaluations

Data on socio-demographic characteristics, namely age, sex, and location of residence (rural, peri-urban, and urban), were collected. Among the PLWH, we collected data through interview and review of medical record chart extraction on HIV disease characteristics, such as current CD4 cell count, HIV-1 viral load, and past and current history of cART. We assessed the traditional vascular risk factors using history-taking, physical examination, and by analyzing blood samples for $HBA_{1c,}$ fasting blood glucose, and lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides).

2.3 | Prospective follow-up

People living with HIV on cART at enrollment were prospectively followed up for 12 months via clinic visits every 3 months. During the follow-up period, participants were assessed through use of clinical history and examination with diagnostic investigations were feasible for the presence of CVDs including incident stroke or heart failure.

The following definitions were used for vascular risk factors and the study outcomes of interest:

- Hypertension: Blood pressure (BP; mean of three measurements) was taken on each study participant following a standard protocol. A cutoff of at least 140/90 mmHg according to WHO definitions[22] or use of antihypertensive drugs was regarded as indicators of hypertension.
- Dyslipidemia was defined as a fasting total cholesterol concentration of ≥5.2 mmol/L, HDL cholesterol ≤1.03 mmol/L, LDL cholesterol ≥3.4 mmol/L, or serum triglyceride of ≥1.7 mmol/L, according to National Cholesterol Education Program guidelines.[23]
- Obesity was defined using the WHO guidelines with a waist-to-hip ratio (WHR) cutoff of 0.90 (men) and 0.85 (women) or body mass index (BMI) of 30 kg/m^2 for obesity.[24] WHR was used to assess burden of central adiposity, and BMI was used to further categorize participants into underweight, ideal weight, overweight, and obese.
- Diabetes mellitus was diagnosed based on self-report or HBA1c >6.5%.[25]
- Carotid doppler assessments: The average intimal media thickness (IMT) of the left and right common carotid arteries (CCA) obtained at three angles (anterior, lateral, and posterior bilaterally) at the optimum angle of insonation was reported as the overall CIMT for the CCA.[26] We also measured IMT of the carotid bulb and internal carotid arteries.
- Stroke: Stroke diagnosis was based on the World Health Organization definition,[27] if participant had ever experienced sudden onset of weakness or sensory loss on one side of the body, sudden loss of vision, or sudden loss of speech.[28]
- Heart failure: Congestive heart failure was defined clinically as a history of dyspnea on minimal exertion, paroxysmal nocturnal dyspnea or acute pulmonary edema or the presence of distended neck veins (in other than the supine position and in the absence of venous obstruction), bilateral ankle edema (not caused by a

condition other than cardiac failure), hepatomegaly, crepitations in the absence of pulmonary disease, positive S_3, or chest radiographic evidence of pulmonary congestion (pleural fluid, pulmonary venous congestion, and prominent pulmonary veins) with or without cardiomegaly.

2.4 | Statistical analysis

Crude incidence rates of stroke or heart failure during follow-up were calculated and expressed as events/1000 person-years of follow-up (PYFU) and 95% CI calculated using the mid-P exact test. Comparisons of demographic, lifestyle, and vascular risk factors among those who experienced combined incident stroke and heart failure versus those who did not experience any of these outcomes were performed using Student's *T*-test for continuous parametric variables and Fisher's exact tests for discrete variables. A multivariate Cox Hazards Proportion regression analysis was fitted to identify factors independently associated with the risk of incident stroke or heart failure (as a combined outcome measure, and then separate outcome measures). Independent variables evaluated included age (categorized as continuous per 10-year rise), sex, WHO clinical stage at diagnosis, current CD4 T-cell count, viral load (categorized as <20, 20–1000 or >1000 copies/ml), history of hypertension, diabetes mellitus, elevated total cholesterol, use of protease inhibitor, common carotid artery intimal media thickness, carotid bulb IMT, and internal carotid artery IMT. Patients were censored either the date of stroke or heart failure, at the last visit for those who died, were lost to follow-up, and at end of study follow-up for the remainder. Bivariate analyses carried out to identify predictors to include in the final multivariate model were set at a liberal *p*-value of <.10. In all analyses, two-tailed *p*-values <.05 were considered statistically significant. Model diagnostics and fit were assessed using residual plots analysis and visual inspection for collinearity of variables in the Cox models. Statistical analysis was performed using GraphPad Prism version 7 and SPSS version 21.

3 | RESULTS

We enrolled 261 PLWH who had been on cART for at least 12 months. We excluded six participants who had already previous diagnosis of stroke (*n* = 5) and heart failure, leaving 255 participants for the present analysis.

3.1 | Incidence rates of stroke or heart failure

The 255 participants contributed 2940 months (245 years) of follow-up data with mean follow-up duration of 11.5 months. There were five participants who did not complete month 12 follow-up. There were three cases of incident stroke giving an incidence rate of 12.24 per 1000 person-years of follow-up (95% CI: 3.13–33.33). For heart failure, there were two events with an incidence rate of 8.16 (95%CI: 1.37–26.97) PYFU. The combined event rate was 20.41 (95% CI: 7.48–45.24) PYFU. There were no STEMI on NSTEMI recorded.

3.2 | Clinical and demographic features of participants with combined incident stroke or heart failure

The demographic and clinical features are compared in Table 1. The mean age of those with the combined CVD outcome of 50.2 ± 9.6 years was non-significantly higher than 46.1 ± 9.1 years among those with no such outcomes. There were no differences between the two groups with respect to WHO clinical stage, viral load at baseline, or combination antiretroviral therapy. Those with CVD events, however, had significantly lower mean CD4 T-cell count at 270.2 cells/mm^3 compared with 649.4 cells/mm^3 among those with CVD events. Those with CVD events were more likely to be hypertensive (60% versus 16%) than those without. Lipid panel, renal function indices, body mass index, and waist-to-hip ratios were comparable between the two groups. The mean intimal media thickness of the common carotid artery and carotid bulb was significantly higher among those with CVD outcomes than those without (Table 1).

3.3 | Factors associated with incident stroke or heart failure

In unadjusted analysis, CD4 T-cell count, being hypertensive, common carotid artery IMT, and carotid bulb IMT were associated with the combined outcome of stroke or heart failure. In adjusted analysis presented as adjusted hazards ratio, aHR (95% CI), two factors were independently associated with the combined outcome (Table 2). Being hypertensive was associated with aHR of 8.61 (1.32–56.04) of the combined outcome while higher CD4 count was protective against the outcome with aHR of 0.56 (0.35–0.88). In a sensitivity analysis where diastolic blood pressure was included in the model instead of hypertensive status, the adjusted HR of diastolic BP for the combined outcome was 1.64 (95% CI: 0.93–2.88), $p = .08$.

A sub-analysis to assess factors associated with incident stroke is presented in Table 3 and for incident heart failure in Table 4. For stroke occurrence, carotid bulb intimal media thickness was independently associated with aHR of 12.23 (1.28–117.07). For heart failure, there were no independent predictors although common carotid artery IMT and internal carotid IMT were associated with this outcome in unadjusted analysis.

4 | DISCUSSION

The combined incidence rate of stroke and heart failure among PLWH established on cART in this sample of Ghanaians is 20.41

TABLE 1 Comparison of baseline characteristics of PLWH who experienced either incident stroke or heart failure

	Incident stroke/heart failure (*n* = 5)	No incident stroke/heart failure (*n* = 250)	*p*-value
Age, mean ± SD	50.2 ± 9.6	46.1 ± 9.1	.32
Male sex, *n* (%)	2 (40.0)	42 (16.8)	.17
Location of dwelling			
Urban	5 (100.0)	170 (68.0)	.31
Semi-urban	0 (0.0)	64 (25.6)	
rural	0 (0.0)	16 (6.4)	
Time since HIV diagnosis (years), mean ± SD	11.0 ± 9.6	8.5 ± 4.2	.20
WHO stage			
1	0 (0.0)	78 (32.0)	.21
2	1 (20.0)	53 (21.7)	
3	4 (80.0)	90 (36.9)	
4	0 (0.0)	23 (9.4)	
Current CD4 count, each 100 cells rise	270.2 ± 167.8	649.4 ± 329.5	.01
Current viral load			
<20 copies	3 (60.0)	166 (68.0)	.92
20–1000 copies	1 (20.0)	35 (14.3)	
>1000 copies	1 (20.0)	43 (17.7)	
Log viral load mean ± SD	2.2 ± 1.9	2.0 ± 1.4	.74
Nucleos(t)ide backbone			
AZT + 3TC/FTC	3 (60.0)	137 (55.9)	.99
TDF + 3TC/FTC	2 (40.0)	106 (43.3)	
D4T + 3TC	0 (0.0)	1 (0.4)	
ABC + 3TC	0 (0.0)	1 (0.4)	
Third agent			
EFV or NVP	4 (80.0)	229 (93.5)	.24
PI/r	1 (20.)	16 (6.5)	
Current/previous cigarette smoking	1 (20.0)	18 (7.2)	.28
Alcohol use			
Current	1 (20.0)	17 (6.9)	.51
Previous	2 (40.0)	101 (40.7)	
Never	2 (40.0)	130 (52.4)	
Known hypertensive	3 (60.0)	40 (16.0)	.009
Systolic BP (mmHg), mean ± SD	144.2 ± 33.2	126.8 ± 22.4	.09
Diastolic BP (mmHg), mean ± SD	93.8 ± 22.6	79.0 ± 13.2	.02
Known diabetic	0 (0.0)	5 (2.0)	.75
Hemoglobin A1c, mean ± SD	5.4 ± 0.4	5.3 ± 0.9	.65
Total cholesterol, mean ± SD	5.1 ± 0.7	5.3 ± 1.2	.68
LDL cholesterol, mean ± SD	3.2 ± 0.6	3.2 ± 1.0	.99
HDL cholesterol, mean ± SD	1.3 ± 0.1	1.5 ± 0.4	.34
Triglyceride, mean ± SD	1.2 ± 0.3	1.4 ± 0.9	.72
Estimated glomerular filtration rate, mean ± SD	87.6 ± 2.6	84.7 ± 11.1	.56
Body mass index, mean ± SD	28.9 ± 7.5	27.1 ± 5.7	.50
Waist-to-hip ratio, mean ± SD	0.86 ± 0.12	0.88 ± 0.08	.47
Physical inactivity, *n* (%)	3 (60.0)	155 (62.0)	.93

(Continues)

TABLE 1 (Continued)

	Incident stroke/heart failure (*n* = 5)	No incident stroke/heart failure (*n* = 250)	*p*-value
Common carotid artery intimal media thickness, mean ± SD	1.08 ± 0.29	0.92 ± 0.16	.03
Carotid bulb intimal media thickness, mean ± SD	1.29 ± 0.35	1.01 ± 0.24	.01
Internal carotid artery intimal media thickness, mean ± SD	1.03 ± 0.36	0.90 ± 0.19	.16
Time to event or censoring (months), mean ± SD	7.2 ± 4.6	11.5 ± 1.9	<.001

Abbreviations: 3TC, lamivudine; ABC, abacavir; AZT, zidovudine; D4T, stavudine; EFV, efavirenz; FTC, emtricitabine; NVP, nevirapine; PI/r, ritonavir-boosted protease inhibitor (such as lopinavir).

TABLE 2 Predictors of incident stroke and heart failure among PLWH in Ghana

	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Age, each 10-year rise	1.53 (0.64–3.64)	.34	–	–
Male sex	3.28 (0.55–19.65)	.19	–	–
Stage 3 or 4 disease	4.60 (0.51–41.11)	.17	–	–
CD4 count/100 rise	0.57 (0.38–0.89)	.01	0.56 (0.35–0.88)	.01
Hypertensive	7.70 (1.29–46.08)	.03	8.61 (1.32–56.04)	.02
Diabetes	0.00 (0.00–1.20)	.97	–	–
Hypercholesterolemia	0.62 (0.10–3.69)	.60	–	–
Use of protease inhibitor	3.50 (0.39–31.30)	.26	–	–
Common carotid artery intimal media thickness (mm)	21.6 (15.7–298.2)	.04	38.90 (0.76–1983.90)	.07
Carotid bulb intimal media thickness (mm)	6.85 (1.49–31.51)	.01	9.85 (0.90–107.99)	.06
Internal carotid artery intimal media thickness (mm)	14.52 (0.36–589.81)	.16	–	–

(95% CI: 7.48–45.24) per 1000 person-years. This incidence rate is partitioned into 12.24 (3.13–33.33) per 1000 person-years for stroke and 8.16 (95%CI: 1.37–26.97) per 1000 person-years for heart failure with no documented acute coronary event during follow-up. The crude incidence rate recorded in the present study is about 3× higher than the global estimate of 6.18 (95%CI: 4.58–8.34) which was stratified into 2.59 (2.03–33.0) per 1000 person-years for myocardial infarction and 1.79 (1.32–24.3) per 1000 person-years for stroke.[2] There is, however, an appreciable overlap in the confidence intervals of the incidence rates in our study and that from the global estimate.[2] The absence of acute coronary events in our study may be due to the overall mean young age of 46 years. The global estimate also did not include heart failure as an outcome measure.[2] However, data from 19,798 PLWH in a large health insurance database in the United States reported incidence rates of MI, heart failure, stroke, atrial fibrillation, and peripheral artery disease of 1.2, 1.7, 0.7, 3.0, and 0.8 per 1000 person-years, respectively.[29] These observations suggest that vascular events are now significant contributors to morbidity among PLWH in Ghana. We have similarly observed among a cohort of Ghanaian hypertensive patients without HIV that the incidence rate of stroke of 14.19 (10.77–18.38) per 1000 person-years[30] was higher than reported for most studies available to comparative analysis.

Two factors were independently predictive of the occurrence of stroke or heart failure. Of foremost importance, we identified a potent association between prior diagnosis of hypertension and CVD outcomes. We have previously reported a high hypertension prevalence of 37% among PLWH on cART in Ghana.[31] People living with HIV with hypertension in this study had an eightfold higher risk of incident CVD than those without hypertension. This risk was largely observed for stroke occurrence where hypertension was associated with nearly 11-fold higher hazards than non-hypertensive PLWH. These findings resonate with epidemiological data from West Africa where the population attributable risk of hypertension for stroke occurrence is 90.8% (95% CI: 87.9%–93.7%), an indication of the pervasive contribution of hypertension to CVD incidence in the region.[32] Furthermore, we observed that a higher CD4 T-cell count was associated with a relative risk of a CVD, with each 100 cells/mm^3 rise accompanied by a 44% lower hazard of the combined outcome. Interpreted conversely, a lower CD4 T-cell count is associated with a higher relative risk of experiencing a stroke or heart failure. Depletion of CD4 T-cells which occurs through the gut mucosa among PLWH is linked to higher risk of atherosclerotic CVD events such as MI, strokes, and peripheral vascular disease via a cascade of chronic immune activation, inflammation, and alterations in cholesterol metabolism with atherogenic lipid profiles.[33–35] Furthermore,

TABLE 3 Predictors of incident stroke among PLWH in Ghana

	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Age, each 10-year rise	1.18 (0.36–3.85)	.79	–	–
Male sex	9.79 (0.89–107.96)	.06	Not included	–
CD4 count/100 rise	0.60 (0.35–1.04)	.07	Not included	–
Hypertensive	10.28 (0.93–113.37)	.06	11.31 (0.88–144.80)	.06
Diabetes	0.00 (0.00–4.39)	.97	–	–
Hypercholesterolemia	1.85 (0.17–20.43)	.61	–	–
Use of protease inhibitor	6.96 (0.63–76.76)	.11	–	–
Common carotid artery intimal media thickness (mm)	2.00 (0.00–1770.81)	.84	–	–
Carotid bulb intimal media thickness (mm)	8.10 (1.32–49.59)	.02	12.23 (1.28–117.07)	.03
Internal carotid artery intimal media thickness (mm)	0.44 (0.00–188.02)	.79	–	–

TABLE 4 Predictors of incident heart failure among PLWH in Ghana

	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Age, each 10-year rise	2.17 (0.58–8.17)	.25	–	–
Male sex	0.00 (0.00–8.52)	.95	–	–
CD4 count/100 rise	0.54 (0.26–1.13)	.10	–	–
Hypertensive	4.99 (0.31–79.77)	.26	–	–
Diabetes	0.00 (0.00–7.14)	.97	–	–
Hypercholesterolemia	0.00 (0.00–1.82)	.95	–	–
Use of protease inhibitor	0.00 (0.00–2.54)	.96	–	–
Common Carotid artery intimal media thickness (mm)	4.45 (1.41–6635.11)	.008	1.91 (0.00–10.87)	.13
Carotid bulb intimal media thickness (mm)	4.87 (0.27–88.38)	.28	–	–
Internal carotid artery intimal media thickness (mm)	5.00 (4.87–5144.29)	.02	3.79 (0.00–9584.71)	.74

the HIV virus itself may be implicated in cardiac failure by direct infection of cardiac myocytes.[36]

While some cross-sectional and few prospective studies[37–40] have demonstrated associations between HIV infection, its treatment, and carotid atherosclerosis, very few have found associations with incident CVD events.[41] Presently, the association between markers of carotid artery atherosclerosis and combined CVD outcomes of stroke and heart failure was attenuated into non-significance upon adjustment for confounders. Nonetheless, we noted that carotid bulb intimal media thickness was independently associated with stroke occurrence in our population. The one previous US study which reported associations between carotid atherosclerosis and atherosclerotic CVD found that incidental carotid plaques detected on CT scan were associated with a fourfold increased risk of stroke specifically among PLWH.[41] In our study, carotid bulb intimal media thickness was associated with a 12-fold increased risk of stroke for a millimeter rise in carotid IMT after adjusting for hypertension in the model.

The implications of our study findings are that cardiovascular events are more common among a female-dominated and younger population of PLWH than perhaps appreciated by clinicians and policy makers. Attention to the detection and control of hypertension among PLWH is paramount in mitigating this risk. There are indications from this study and our previous report that carotid atherosclerosis is rampant in the HIV population but not a part of routine workup for PLWH in our settings.[21,42] Therefore, in addition to hypertension control,[43–46] implementation of interventions to reduce atherosclerotic risk such as institution of statin therapy[47–49] as well as non-pharmacological therapies such as physical activity, health eating, and cigarette cessation are urgent priorities as PLWH live longer on cART.

Our study has a number of limitations. Similar to the meta-analytic data,[2] we relied on physician diagnosis or the International Classification of Diseases coding system to define cardiovascular disease. There was no funding for diagnostic workup of study participants using neuroimaging to confirm and type clinically diagnosed strokes. However, specialists at the HIV clinic (BN), cardiologist (LTA), and neurologist (FSS) supervised the assessment and adjudication of clinical events. Because this is a single-center study conducted in a tertiary medical facility, the findings are not generalizable to a wider PLWH population who receive care in primary health centers and community health posts in Africa. However, the prospective study design is a strength, and the follow-up rate over 12 months of over 95% completion enabled us to rigorously assess clinical outcomes of interest.

In conclusion, PLWH on long-term cART in this Ghanaian sample have higher rates of clinically adjudicated cardiovascular diseases driven by uncontrolled hypertension and persisting immunosuppression. Integration of CVD care into routine HIV management may help alleviate this untoward confluence of rising CVDs in PLWH.

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CONFLICT OF INTEREST

All authors have no conflicts to declare.

AUTHOR CONTRIBUTIONS

Fred Stephen Sarfo and Bruce Ovbiagele contributed to conceptualization, methodology, and supervision. Fred Stephen Sarfo contributed to data curation, formal analysis, project analysis, and writing—original draft. Fred Stephen Sarfo, Betty Norman, and Lambert Appiah contributed to investigation. Fred Stephen Sarfo, Betty Norman, Lambert Appiah, and Bruce Ovbiagele contributed to writing—review and editing.

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