RESEARCH ARTICLE

Differential pricing of medicines to improve access to medicines for hypertension and diabetes control in Ghana: The Ghana Access and Affordability Program, a multi-center prospective trial [version 1; peer review: 2 not approved]

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Abstract

Background: Access to medicines for hypertension and diabetes mellitus (DM) management is challenging in resource-limited countries. We sought to assess whether differential pricing of medicines based on socio-economic status would improve affordability of antihypertensive and anti-diabetic medications. A quasi-experimental, prospective cohort study was implemented at five Ghanaian health facilities, using medicines differentially priced by three pharmaceutical companies.

Methods: Adult patients ≥18 years with hypertension or DM were enrolled and assigned to a lower tiered differential price (DP arm) or market price (MP arm) based on minimum wage earning or a score >6/18 on a multi-dimensional poverty index scale. Study medicines were purchased at either the DP or MP when prescribed. Participants were followed for 18 months to assess blood pressure (BP) and

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glycemic control. Predictors of ability to purchase study medicines were assessed using parsimonious logistic regression models.
Results: 3,296 participants were enrolled with mean age of 57±12.7 years, 76.6% females. 1,869 (56.7%) had hypertension, 422 (12.8%) had DM, and 1,005 (30.5%) with both hypertension and DM. Average follow-up was 14 months. There were prescriptions of study medications for 526 participants of which 238 (45.2%) were able to make purchases at DP 60.9% versus MP 39.1%. Independent predictors of purchasing ability were higher income, MP arm, willingness to purchase additional medicines, and being at tertiary level institution.
Conclusions: Approximately 45% of Ghanaians could afford prescribed study medicines provided at a differential pricing mechanism albeit at an unsustainable basis. Further price reductions are expected to enhance access to medicines for hypertension and DM control.

Keywords
Differential Pricing, Access, Affordability, Hypertension, Diabetes, Control

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Low-and-middle income countries (LMICs) are experiencing an epidemiologic transition characterized by a dramatic rise in the burden of non-communicable diseases (NCDs)[1–6]. Hypertension and diabetes mellitus (DM), two of the principal risk factors for cardiovascular diseases (CVDs), are under recognized, untreated or under-treated in these regions resulting in considerable morbidity and mortality[7]. Many factors including low literacy rates, non-adherence, therapeutic inertia, and systemic factors such as challenges in access and affordability of medicines have been ascribed as reasons for poor disease control[8–11].

Affordability of quality assured, innovator medicines for the management of hypertension and DM in resource-limited settings is challenged by low income[10,12–14]. As populations age and disease prevalence increases, innovative and cost-effective interventions are urgently needed to improve access to these medicines for sustained and life-long management of these conditions. Differential pricing (DP) of medicines is a promising and viable approach to improve access and affordability. DP is an approach by which manufacturers price their medicines to reflect patients' ability to pay and has been successfully deployed to increase access to quality assured anti-malarials and vaccines for immunization[15–18]. However, such an approach has hitherto not been explored for the management of non-communicable diseases. To test DP as an intervention for improving access to innovator medicines for the control of hypertension and DM, the Bill and Melinda Gates Foundation working with three pharmaceutical companies made differentially priced medicines for these conditions for this study in Ghana. Our hypothesis is that by offering innovator medicines at a two-tier pricing system, i.e. market price and a lower tiered differential price based on socio-economic status, we could in a systematic fashion test whether a DP scheme improves access and affordability of medications. Furthermore, we sought to assess whether purchasing innovator medications was associated with better control of hypertension and DM.

Methods

The study protocol has been published previously[19].

Ethical permission

This study protocol was approved by the Committee on Human Research Publications and Ethics of the Kwame Nkrumah University of Science and Technology (CHRPE/AP/298/14) and the Ghana Health Services Ethical Review Committee (GHS-ERC: 12/07/14). It was declared exempt by the Institutional Review Board at the Johns Hopkins Bloomberg School of Medicine. Written informed consent was obtained from all study participants before enrollment into the study. All relevant data are included in the manuscript and as *Underlying* and *Extended data.*

Study design

The Ghana Access and Affordability Program (GAAP) study is a quasi-experimental study with a pragmatic trial design to examine the effect of DP on improving access to innovator medicines for control of hypertension and diabetes in a multi-center, prospective Ghanaian cohort.

Study sites

The GAAP study was conducted at five hypertension and diabetes specialty and general clinics in urban, semi-urban and rural locations in Ghana. The study was conducted at two tertiary institutions - Komfo Anokye Teaching Hospital (KATH) and Tamale Teaching Hospital (TTH) - two secondary level health institutions - Agogo Presbyterian Hospital (APH) and Atua Government Hospital (AGH) - and one primary level health institution - Kings Medical Center (KMC).

Participant recruitment

Participants were eligible if they were ≥18 years with known diagnosis of hypertension and/or type II diabetes presenting for routine care at either a general polyclinic (AGH, KMC, TTH) or a dedicated diabetes/hypertension clinic (KATH, APH). During the period of the study, consecutive potential participants were invited to participate after study nurses had explained the objectives of study. Participants meeting eligibility criteria were enrolled after written informed consent had been obtained by trained research assistants.

Allocation to Market Price (MP) or Differential Price (DP) Arm

At enrollment participants were assigned to DP by research assistants if their monthly household income was <210 Ghana Cedis (i.e. minimum wage) or had a multidimensional poverty index score ≥ 6/18[20]. Study participants whose physicians prescribed study medications were to purchase them at either DP or MP from the hospital pharmacy. However, when participants allocated to MP could not afford prescribed medicines at MP, they were offered pricing at the lower tiered DP at the pharmacy. Participants who could not purchase study medicines at either MP or DP were prescribed generic alternatives available on the National Health Insurance Scheme[21]. The decision tree is shown in Figure 1.

Participant evaluations and interviews

Trained Research Assistants interviewed participants and collected demographic and household information such as age, gender, educational attainment, employment status, monthly income and health expenditures. Study participants were also interviewed on their lifestyle behaviors such as alcohol use, diet, cigarette smoking and physical activity. We categorized alcohol intake and cigarette smoking status as never, former or current users. Physical activity was assessed by asking if participants frequently performed physical activities that caused a small increase in breathing or made their heart rate go up, such as (fast/brisk) walking, jogging, bicycling, and how much time they spent doing physical activity.

A detailed medical history including duration of hypertension or diabetes and medication used for treatment were obtained. Compliance to treatment was assessed using the 14-item

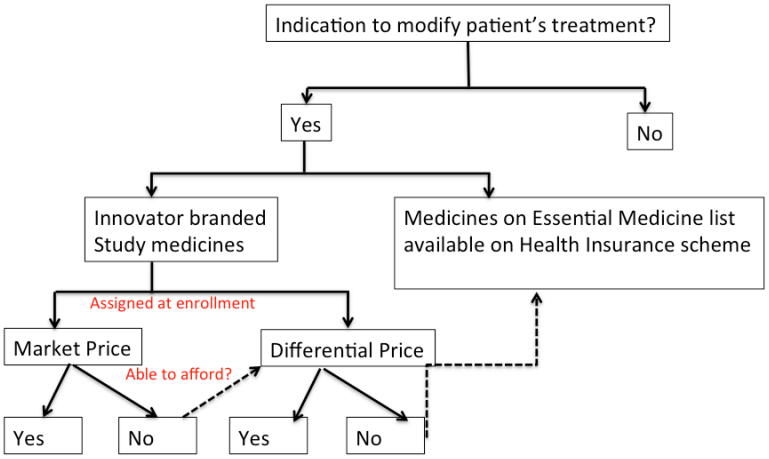

Figure 1. Decision algorithm for prescription of innovator brands of study medications for patients with hypertension and/or diabetes mellitus by study physicians. Physicians exercised their independent judgment in deciding on whether or not they would prescribe innovator brands of anti-hypertensive or anti-diabetic medicines at market price (MP), differential price (DP) or use generic alternatives where indicated. Participants prescribed innovator brands were asked to determine if they could purchase prescribed medicines within 2 days of prescription to avert leaving them uncontrolled for their medical condition. Participants assigned to MP but could not purchase prescribed medicines at MP, were offered the opportunity to purchase study medicines at DP. Participants who could not afford to purchase prescribed medicines at either MP or DP were offered generic alternatives of anti-hypertensive or anti-diabetic medications as indicated.

Hill-Bone compliance to high blood pressure therapy scale[22] and the 4-item version of Levine-Morisky Medication Adherence Scale[23] among diabetes patients. A past medical history of stroke was elicited by asking 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. Similarly, a history of heart failure was assessed by asking if participant had ever experienced shortness of breath on exertion, on lying down as well as swelling of both feet. Blood pressure and pulse rates were measured by study nurses following a standardized study protocol using an automated BP measurement device (Omron HEM-907XL). Two consecutive BP readings from the same arm taken 2 minutes apart was recorded and averaged for the present analysis. Anthropometric evaluations included measurements of weight and height for body mass index derivation and waist circumference.

Laboratory measurements

To ensure standardization across all study sites, an ISO-certified, quality-assured laboratory in Ghana was contracted to run all biochemical panels including creatinine, lipid profile and hemoglobin $A1_C$ for participants with diabetes. Samples were transported to the laboratory on the day of collection often within 4 hours or where not feasible (KMC and AGH sites), samples were frozen and delivered to the laboratory the next day.

Follow-up

Following enrollment, each participant was seen at two monthly intervals by their physician for 18 months to assess disease control. At enrollment and during follow-up physicians used their clinical judgment to make any changes in medicines they felt, including adding or discontinuing study medications (either at MP or DP).

Health systems strengthening activities

We developed a broad range of health systems strengthening activities, such as training of doctors on management of hypertension and diabetes using locally developed treatment guidelines (see supplementary material in 19) aligned with international guidelines, strengthening supply chain systems within health facilities to minimize important access barriers such as stock outs and medication expiry, and developing patient education leaflets on management of diabetes and hypertension[19].

Outcome variables

The following outcome variables were recorded:

- Decisions by physicians to prescribe study medicines at clinic visit
- Number of times out-of-pocket payments for study medications were made
- Blood pressure control: systolic and diastolic blood pressure readings taken at 2 monthly visits were averaged for each participant.
- Glycemic control: $HbA1_C$ measurements taken at 6-monthly were averaged with a target of <7.0%.

Statistical analysis

Means and medians were compared using either the Student's t-test or Mann-Whitney's U-test for paired comparisons or ANOVA or Kruskal Wallis tests for more than 2 group comparisons. Proportions were compared using the Chi-squared tests or Fisher's exact test for proportions with subgroupings <5. A multivariate logistic regression analysis was performed to identify factors associated with ability to purchase study medications. Predictors selected in this analysis include age,

gender, location of residence, educational status, employment status, monthly household income, price allocation (DP or MP), willingness to purchase study medications should they be prescribed and level of health facility. These factors were selected based on their known or predicted impact on ability to make out-of-pocket payments for medications. A parsimonious logistic regression model was constructed to determine the predictors of BP and glycemic control among participants who purchased study medicines compared with those who could not purchase prescribed study medicines. Variables included in these models included demographic variables, socio-economic indicators, level of healthcare institution, adherence to therapy and number of times purchases of innovator branded study medicines were made. In bivariate analysis, factors that attained a p-value of <0.05 were included in the multivariable model with two-tailed p-values <0.05 considered statistically significant. Statistical analysis was performed using SPSS version 19.

Results

Demographic and clinical characteristics of study participants

There were 3,296 participants enrolled into the study with a mean ± SD age of 57.5 ± 12.7 years and a preponderance of females comprising 76.6% of the study population. There were more urban dwellers (43.6%), followed by rural (33.7%) and semi-urban dwellers (22.6%). There were 1,869 (56.7%) participants with hypertension only, 422 (12.8%) with diabetes only and 1,005 (30.5%) with both hypertension and diabetes. Overall, mean ± SD duration of hypertension was 7.8 ± 7.3 years and DM was 9.4 ± 6.9 years, with 42.0% of participants with BP controlled and 29.8% with optimal glycemic control at enrollment into the study (Figure 2). Comparisons of baseline characteristics according to study site and pricing arm allocation are shown in *Extended data:* Tables S1 and S2.

Factors associated with ability to purchase innovator study medicines

At enrollment, all participants were on generic antihypertensive and anti-diabetic medicines available on National Health Insurance. A total of 24,632 patient clinic visits occurred over the course of the study with 2,469 (10.0%) decisions to modify treatment (Table 1). Average follow-up per participant was 14 months. There was a higher tendency for physicians to prescribe generic medicines for treatment modifications than with innovator medicines 76.2% vs 23.8% respectively (p<0.0001). Overall, 238 (45.2%) participants were able to afford prescribed study medicines while 288 (54.8%) were unable.

Table 2 shows a comparison of baseline demographic, socio-economic and clinical characteristics of participants who purchased prescribed study medicines (n=238), those who could not purchase prescribed study medicines (n=288) and those not prescribed any study medicines (n=2,770). These participants were able to access medicines on the National Health Insurance Scheme list[21]. Study medicines were considered mainly for participants whose BP and/or glycemic indicators were not optimally controlled at baseline. Several other differences observed between these three groups with regards to demographic and socio-economic characteristics, healthcare expenditures, lifestyle behaviors and disease control are shown in Table 2. Factors associated with ability to afford study medicines

Table 1. Main outcome measures for the study.

Characteristic	
Number of subjects recruited	3,296
Mean ± SD duration of follow-up per subject (months)	**14.2 ± 5.9**
Total number of clinic visits	24,632
Number (%) of decisions taken by physicians to modify patient's treatment at clinic visits[#]	**2,469 (10.0%)**
Decisions to use generic equivalents available on National Health Insurance scheme	1,882 (76.2%)
Decisions to use innovator branded medications	587 (23.8%)
Number of patients prescribed innovator branded medicines	**526**
Number of patients able to purchase innovator branded medicines at least once	238 (45.2%)
Number of patients who could not purchase innovator branded medicines	288 (54.8%)
Total number of prescriptions of innovator branded medicines presented at study pharmacy (n=1,681)	**1,681**
Total number of prescriptions of innovator branded medicines presented at pharmacy but not purchased	1,223 (72.8%)
Total number of prescriptions of innovator branded medicines presented at pharmacy and purchased	458 (27.2%)
Price tier innovator branded medicines were purchased (n=458)	
Market Price	179 (39.1%)
Differential Price	279 (60.9%)

[#]Common reasons recorded for treatment modifications were BP or glycemic control not optimal (n=875), side effects (n=90), other reasons not stated (n=1,504).

Table 2. Comparison of baseline characteristics of patients according to ability to access/purchase innovator branded study medicines.

Characteristic	Prescribed and able to access study medicines	Prescribed but could not access study medicines	Not prescribed study medicines	Overall (n=3,296)	P-value ANOVA	P-value A vs B	P-value A vs C	P-value B vs C
	n= 238 (7.2%)	n= 288 (8.7%)	n= 2,770 (84.0%)					
	Group A	Group B	Group C					
Age, mean ± SD	57.1 ± 12.5	57.1 ± 12.8	57.6 ± 12.7	57.5 ± 12.7	0.65	0.99	0.52	0.47
Female, n (%)	173 (72.7)	210 (72.9)	2143 (77.4)	2,526 (76.6)	0.08	0.95	0.10	0.09
Location of residence					**0.003**	0.16	**0.0006**	0.30
Urban	83 (34.9)	127 (44.1)	1226 (44.3)	1,436 (43.6)				
Semi-urban	77 (32.4)	73 (25.3)	594 (21.4)	744 (22.6)				
Rural	77 (32.4)	87 (30.2)	946 (34.2)	1,110 (33.7)				
Missing	1 (0.3)	1 (0.4)	4 (0.1)	6 (0.1)				
Highest educational status					**0.007**	0.10	**0.005**	0.14
No formal education	84 (35.3)	90 (31.3)	1053 (38.0)	1,227 (37.2)				
Primary level	30 (12.6)	45 (15.6)	463 (16.7)	538 (16.3)				
Secondary level	80 (33.6)	117 (40.6)	958 (34.6)	1,155 (35.0)				
Tertiary level or more	44 (18.5)	36 (12.5)	295 (10.6)	375 (11.4)				
No response	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)				
Employment status					**<0.0001**	0.09	**<0.0001**	**0.004**
Unemployed	47 (19.7)	76 (26.4)	674 (24.3)	797 (24.2)				
Retired	34 (14.3)	25 (8.7)	194 (7.0)	253 (7.7)				
Self-employed	69 (29.0)	63 (21.9)	671 (24.2)	803 (24.4)				
Farming	12 (5.0)	19 (6.6)	390 (14.1)	421 (12.8)				
Trading	41 (17.2)	64 (22.2)	483 (17.4)	588 (17.8)				
Government employee	23 (9.7)	28 (9.7)	200 (7.2)	251 (7.6)				
Others	12 (5.0)	13 (4.5)	158 (5.7)	183 (5.6)				
Monthly household income					**0.03**	0.06	**0.008**	0.53
>1,000 GHS	30 (12.6)	26 (9.0)	204 (7.4)	260 (7.9)	**0.01**	0.19	**0.004**	0.31
500-1,000 GHS	25 (10.5)	30 (10.4)	252 (9.1)	307 (9.3)				
300-500 GHS	32 (13.4)	26 (9.0)	313 (11.3)	371 (11.3)				
210-300 GHS	12 (5.0)	15 (5.2)	172 (6.2)	199 (6.0)				
<210 GHS	66 (27.7)	116 (40.3)	1042 (37.6)	1,224 (37.1)	**0.005**	**0.003**	**0.002**	0.38
No response/unknown	73 (30.7)	75 (26.0)	787 (28.4)	935 (28.4)				
Multi-dimensional poverty index score, mean ± SD	4.1 ± 3.0	4.0 ± 2.5	4.2 ± 2.7		0.27	0.90	0.30	0.19
Pricing arm allocation					**0.002**	**0.008**	**0.0005**	0.93
Market Price	139 (58.4)	135 (46.9)	1,291 (46.6)	1,565 (47.5)				
Differential Price	99 (41.6)	153 (53.1)	1,479 (53.4)	1,731 (52.5)				
Level of Health Institution					**<0.0001**	**<0.0001**	**<0.0001**	0.60
Tertiary level	89 (37.4)	170 (59.0)	1,639 (59.2)	1,898 (57.6)				
Secondary level	124 (52.1)	100 (34.7)	995 (35.9)	1,219 (37.0)				
Primary level	25 (10.5)	18 (6.3)	136 (4.9)	179 (5.4)				

Characteristic	Prescribed and able to access study medicines	Prescribed but could not access study medicines	Not prescribed study medicines	Overall (n=3,296)	P-value ANOVA	P-value A vs B	P-value A vs C	P-value B vs C
	n= 238 (7.2%)	n= 288 (8.7%)	n= 2,770 (84.0%)					
	Group A	Group B	Group C					
Vascular risk factors					**<0.0001**	**0.008**	**0.03**	**<0.0001**
Known Hypertensive only, n (%)	129 (54.2)	122 (42.4)	1,618 (58.4)	1,869 (56.7)				
Known Diabetic only, n (%)	22 (9.2)	47 (16.3)	353 (12.7)	422 (12.8)				
Known Hypertensive & Diabetic, n (%)	87 (36.6)	119 (41.3)	799 (28.8)	1,005 (30.5)				
Duration of hypertension, (years)	8.2 ± 8.6	8.5 ± 7.0	7.7 ± 7.3	7.8 ± 7.3	0.25	0.63	0.43	0.12
Duration of diabetes mellitus, (years)	9.9 ± 7.5	9.9 ± 7.0	9.3 ± 6.8	9.4 ± 6.9	0.46	0.97	0.39	0.32
Average Systolic Blood Pressure at enrollment (mmHg), mean ± SD	144.1 ± 21.6	145.9 ± 23.5	140.5 ± 22.0	141.2 ± 22.1	**<0.0001**	0.38	**0.02**	**<0.0001**
Average Diastolic Blood Pressure at enrollment (mmHg), mean ± SD	84.5 ± 14.3	84.5 ± 15.2	81.5 ± 12.9	82.0 ± 13.3	**<0.0001**	0.94	**0.0006**	**0.0003**
Medical co-morbidities								
Self-reported previous stroke diagnosis	11 (4.6)	20 (6.9)	128 (4.6)	159 (4.8)	0.21	0.26	1.00	0.08
Self-reported heart failure	28 (11.8)	13 (4.5)	141 (5.1)	182 (5.5)	**<0.0001**	**0.002**	**<0.0001**	0.67
Self-reported coronary artery disease	34 (14.3)	24 (8.3)	245 (8.8)	303 (9.2)	**0.02**	**0.03**	**0.006**	0.77
Lifestyle/behavioral factors								
Current alcohol use	26 (10.9)	23 (8.0)	197 (7.1)	246 (7.5)	0.09	0.25	**0.03**	0.58
Current cigarette smoking	3 (1.3)	2 (0.7)	11 (0.4)	16 (0.5)	0.16	0.51	0.06	0.46
Regular Physical activity	131 (55.0)	170 (59.0)	1724 (62.2)	2,025 (61.4)	0.06	0.36	**0.03**	0.29
Health expenditure indicators								
Monthly expenditure on antihypertensive/ antidiabetic medicines, mean ± SD (GHS)	28.2 ± 64.2	21.5 ± 44.8	21.4 ± 48.2	21.9 ± 49.3	0.12	0.16	**0.04**	0.96
Monthly expenditure on travel cost to hospital, mean ± SD (GHS)	8.0 ± 21.2	9.5 ± 19.4	7.6 ± 13.9	7.8 ± 15.1	0.13	0.41	0.68	**0.04**
Monthly expenditure on health, mean ± SD (GHS)	61.8 ± 87.6	38.7 ± 61.1	35.8 ± 55.5	37.7 ± 58.9	**<0.0001**	**0.002**	**<0.0001**	0.46
Average number of dependents on monthly household income, mean ± SD (GHS)	5.9 ± 4.7	5.4 ± 3.7	5.6 ± 4.0	5.6 ± 4.1	0.36	0.17	0.35	0.33
Willingness to purchase additional medicines if indicated/prescribed (yes)	230 (96.6)	262 (91.0)	2,527 (91.2)	3,019 (91.6)	**0.01**	**0.009**	**0.004**	0.88
Laboratory Indicators								
Serum creatinine, mean ± SD	79.0 ± 31.3	82.6 ± 39.7	81.8 ± 55.4	81.7 ± 52.6	0.72	0.29	0.46	0.83
eGFR, mean ± SD	77.6 ± 14.8	75.6 ± 17.7	76.7 ± 16.2	75.6 ± 16.2	0.41	0.19	0.40	0.35
HBA1C, mean ± SD	8.6 ± 2.6	9.2 ± 2.4	8.6 ± 2.5	8.7 ± 2.6	**0.03**	0.06	0.93	**0.008**
Serum total cholesterol, mean ± SD	5.45 ± 1.49	5.34 ± 1.10	5.41 ± 1.39	5.41 ± 1.37	0.90	0.66	0.88	0.68
LDL cholesterol, mean ± SD	3.35 ± 1.05	3.34 ± 1.12	3.44 ± 1.21	3.42 ± 1.19	0.71	0.95	0.58	0.50
HDL cholesterol (mmol/l), mean ± SD	1.36 ± 0.55	1.27 ± 0.38	1.35 ± 0.56	1.35 ± 0.54	0.52	0.32	0.95	0.26
Triglyceride (mmol/l), mean ± SD	1.53 ± 0.84	1.52 ± 0.65	1.58 ± 0.94	1.57 ± 0.91	0.85	0.91	0.74	0.63

GHS= Ghana Cedis

with their adjusted OR (95% CI) include monthly household income >1,000 GHS, 2.90 (1.13 – 7.43) [1USD = 4.5 GHS]; allocation to MP arm at enrollment, 1.62 (1.06 – 2.47); willingness to purchase additional medicines for disease management, 2.59 (1.00-6.77); and tertiary level healthcare seekers, 0.29 (0.14-0.59), as shown in Table 3.

Sustainability of affordability of study medicines

Of the 238 participants, 97 (40.8%) assigned to DP arm purchased study medicines at differential price while 141 (59.2%) assigned to MP arm purchased at the market price (n=91), but the remainder could only purchase at differential price (n=50) although they were assigned to MP arm. In total, 177 (74.4%)

Table 3. Predictors for ability to afford innovator medicines based on clinical indication.

Characteristic	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age, each 10-year increase	1.01 (0.89-1.16)	0.85	-	
Gender		0.95		
Female	0.99 (0.67-1.45)		-	
Male (referent)	1.00		-	
Location of residence				
Urban	0.74 (0.49-1.12)	0.15	-	
Semi-urban	1.19 (0.77-1.86)	0.44	-	
Rural (referent)	1.00			
Highest educational status				
Tertiary level or more	1.31 (0.77-2.23)	0.32	-	
Secondary level	0.73 (0.49-1.11)	0.14	-	
Primary level	0.71 (0.41-1.24)	0.23	-	
No formal education (referent)	1.00			
Employment status				
Employed	1.05 (0.73-1.50)	0.80	-	
Unemployed/Retired (referent)	1.00			
Monthly household income				
>1,000 GHS	2.03 (1.11-3.72)	0.02	2.90 (1.13 – 7.43)	0.03
500-1,000 GHS	1.46 (0.80-2.70)	0.22	0.58 (0.23-1.46)	0.25
210-500 GHS	1.89 (1.12-3.18)	0.02	0.93 (0.46-1.94)	0.87
Don't know	1.71 (1.10-2.66)	0.02	1.29 (0.78 – 2.14)	0.33
<210 GHS (referent)	1.00		1.00	
Pricing arm allocation				
Market Price	1.59 (1.13 – 2.25)	0.009	1.62 (1.06-2.47)	0.03
Differential Price (referent)	1.00		1.00	
Monthly expenditure on health, each 50 GHS higher	1.18 (1.03 – 1.35)	0.02	1.13 (0.98 – 1.31)	0.09
Willingness to purchase study medicines should they be prescribed at enrollment into the study				
Yes	3.51 (1.41 – 8.74)	0.007	2.59 (0.99-6.77)	0.05
No	1.00		1.00	
Level of Health Institution				
Tertiary level	0.38 (0.20-0.73)	0.004	0.29 (0.14-0.59)	0.0006
Secondary level	0.89 (0.46-1.73)	0.89	0.75 (0.37-1.52)	0.42
Primary level (referent)	1.00		1.00	

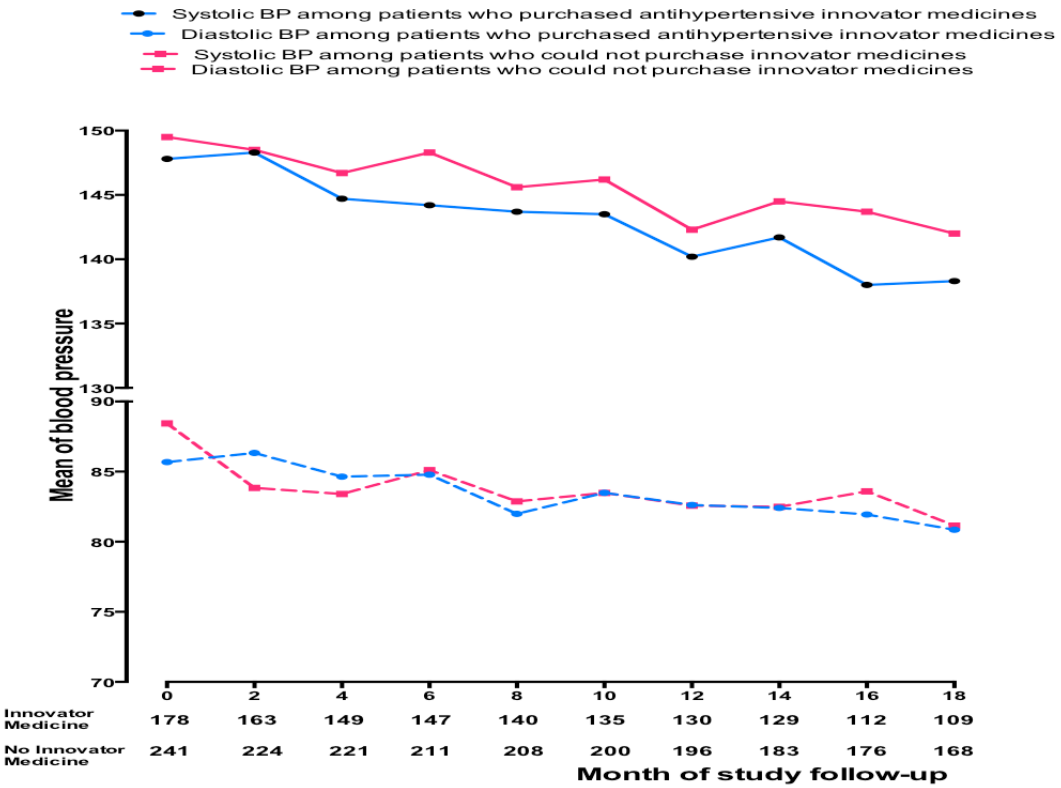

Figure 2. The impact of study medications purchases on disease control. Systolic and diastolic BPs over time among participants with hypertension who purchased innovator medicines versus those prescribed innovator medicines but could not purchase.

participants purchased innovator antihypertensive medicines and 61 (25.6%) bought anti-diabetic medicines. Overall, of the 458 study medicines purchases made by the 238 participants, 39.1% were at MP and 60.9% at the DP. However, the ability to afford study medicines were not sustained as 66% of participants could procure them just once (*Extended* data: Figure S1). The mean ± SD number of purchases/refills of innovator medicines among those assigned to MP arm who purchased at MP was 1.7 ± 1.4, those assigned MP arm but purchased at DP was 2.4 ± 2.2 and finally those assigned DP who purchased at DP (n=96) was 1.8 ± 1.4, p=0.03 (by ANOVA). Each medication purchase was made for two months of supply.

Disease control

Among participants who purchased innovator antihypertensive medicines, systolic BP declined from a baseline 147.8 ± 21.7mmHg through to 138.3 ± 22.5mmHg at month 18, (p=0.0007 by ANOVA). Among those who could not purchase prescribed study medicines, systolic BP decreased from 149.5 ± 22.8 to 142.0 ± 26.6mmHg at month 18 (p=0.02, by ANOVA) (Figure 2). Similar trends were also observed in diastolic BP over time. Proportion of diabetics with $HbA1_C$ <7% increased from 23% at baseline to 39% at month 18 among participants who purchased study medicines for diabetes control, (p=0.10) and from 30% at baseline to 40% at month 18 (p=0.25) among those prescribed but could not purchase (Figure 3). In a parsimonious multivariate logistic regression model where age, gender, location of residence, duration of disease, income level and adherence were accounted for, purchase of antihypertensive medications for 6 or more times was associated with an adjusted OR of 4.09 (1.02-16.29) of achieving averaged BP<140/90mmHg during follow-up compared with those unable to purchase prescribed study medicines (Table 4). Similarly, purchase of study anti-diabetic medications for 5 or more times was associated with an adjusted OR of 6.73 (1.11-40.84) of achieving averaged HbA1c <7% (Table 5).

Discussion

We have for the first time evaluated the effect of differential pricing on access to and affordability of innovator medicines for the control of hypertension and diabetes mellitus in a LMIC setting. Almost all study participants enrolled were already established on generic antihypertensive and or antidiabetic medicines. Hence study medications used to test the research hypothesis were prescribed when there was a therapeutic indication in accordance with physicians' judgment. Modifications of existing medications were undertaken in approximately 10% of 24,632 clinic visits and physicians had a proclivity towards the use of generic branded medicines which were available on the Ghana National Health Insurance. Consequently, study medicines

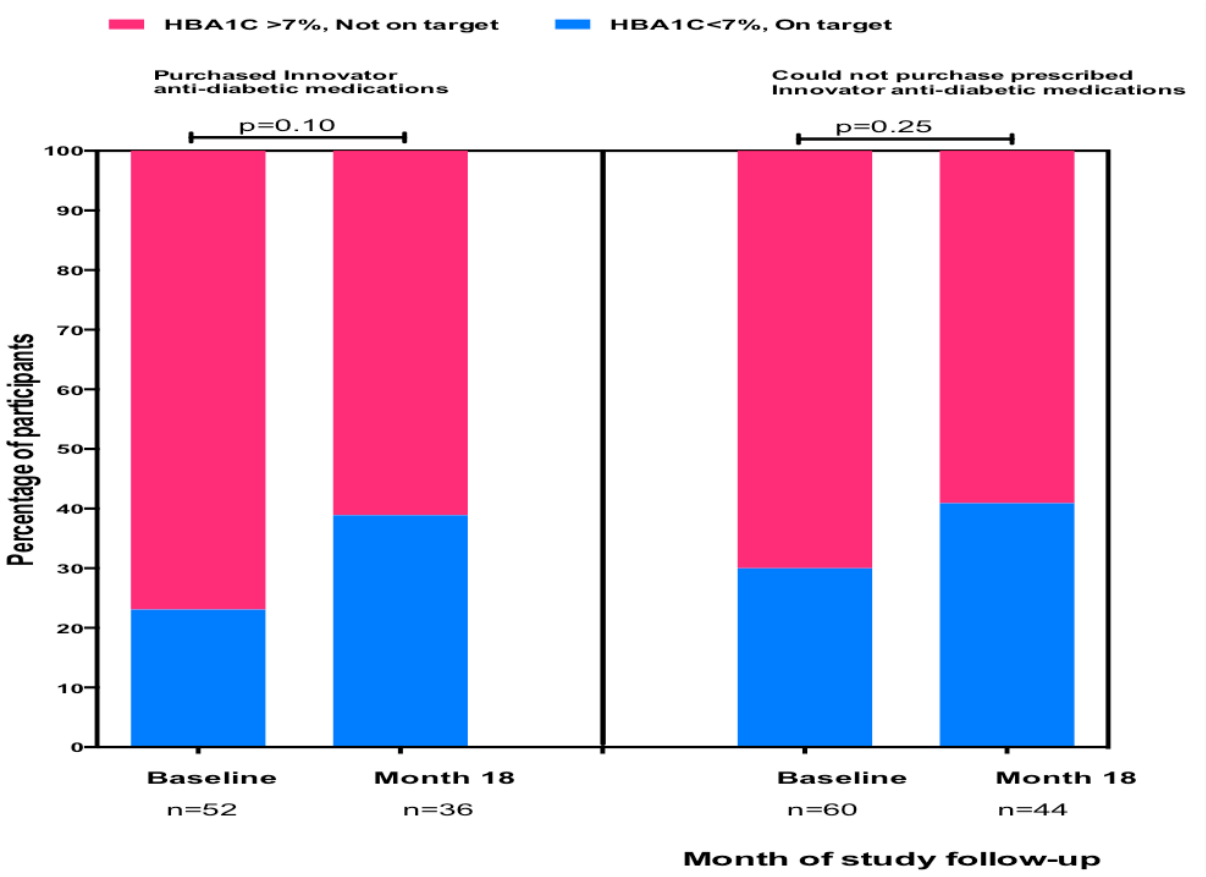

Figure 3. The impact of study medications purchases on disease control. Comparison of proportion of participants with diabetes mellitus whose $HbA1_c$ <7% at baseline and at month 18 according to those who purchased innovator anti-diabetic medications and those who could not afford to purchase prescribed innovator medicines.

were prescribed for 526 (16%) study participants overall, of which about 45% were able to afford the prescription. However, <40% of study participants prescribed study medicines were able to purchase more than one prescription. Indeed, three fifths of all study medication purchases were at the lower DP tier for those assigned to DP arm and also for the significant majority who were assigned to higher tier MP arm but could only afford medications at DP. Hence, three out of the four factors independently associated with ability to purchase study medicines, namely MP arm allocation, willingness to make out-of-pocket payments and higher income levels, reflected higher purchasing ability of purchasers. However, the differential pricing intervention was intended to improve access for participants with lower income levels.

There are several possible explanations for the less than expected patronage of study medicines. First, the extent of reductions in prices of study medicines at the DP tier was not substantial enough to enhance its affordability in a resource-limited setting. The impact of price reductions by the participating pharmaceutical companies was also compromised by the various levies and mark-ups by distributors and hospitals resulting in a differential price for study medicines ranging between 20–40%, compared with the market price. Thus, the cost of study medications even at the differential price tier was beyond the means of many participants including those assigned to MP arm purported to have sufficient income levels to support out-of-pocket payments. In support of this, we found household income above 1,000 Ghana Cedis to be the only income bracket independently associated with ability to afford study medicines. Second, the Ghanaian National Health Insurance scheme covers the cost of most essential medicines for hypertension and diabetes for an annual premium of <USD5[24]. There was a 98% subscription rate by study participants to this scheme. Thus, the proposition of making additional payments for medications was not popular. We found willingness to make out-of-pocket payments for study medicines as a factor associated with ability to purchase study medicines. Third, the range of study medicines used to test the study hypothesis had generic equivalents covered by National Health Insurance and might have obviated the need to prescribe them. Indeed, almost all study participants were already established on generic branded medications for hypertension and diabetes control at enrollment. For patients well controlled or not experiencing

Table 4. Predictors of poor blood pressure control during follow-up among hypertensive subjects for which study medicines were prescribed.

Characteristic	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age, each 10-year increase	0.93 (0.80 – 1.09)	0.39	-	-
Gender				
Female	1.49 (0.96 – 2.31)	0.08	-	-
Male	1.00			
Location of residence				
Rural	1.03 (0.65 – 1.62)	0.90	1.06 (0.66 – 1.71)	0.81
Semi-urban	1.68 (1.04 – 2.69)	0.03	1.50 (0.92 – 2.44)	0.11
Urban	1.00		1.00	
Highest Educational status			-	-
Tertiary level or more	1.20 (0.67 – 2.14)	0.54		
Secondary level	0.96 (0.61 – 1.50)	0.84		
Primary level	0.96 (0.52 – 1.76)	0.89		
No formal education	1.00			
Employment status			-	-
Employed	0.98 (0.63 – 1.54)	0.94		
Retired	0.92 (0.47 – 1.82)	0.82		
Unemployed	1.00			
Monthly Household income			-	-
>1,000 GHS	1.23 (0.61-2.50)	0.56	1.04 (0.49 – 2.22)	0.92
210-999 GHS	1.20 (0.73 – 1.96)	0.47	1.10 (0.66 – 1.83)	0.71
No response/unknown	1.89 (1.16 – 3.08)	0.01	1.78 (1.08 – 2.93)	0.02
<210 GHS	1.00			
Level of Health Institution			-	-
Tertiary level	0.69 (0.35 – 1.35)	0.27		
Secondary level	0.66 (0.33 – 1.29)	0.22		
Primary level	1.00			
Duration of hypertension, each year longer	0.96 (0.90 – 1.02)	0.17	-	-
Number of purchases of Antihypertensive innovator Study medications during follow-up				
6 times or more	4.68 (1.21 – 18.12)	0.03	4.09 (1.02 – 16.29)	0.05
3 to 5 times	0.73 (0.33 – 1.60)	0.43	0.69 (0.31 – 1.53)	0.69
1 to 2 times	1.44 (0.96 – 2.16)	0.08	1.39 (0.92 – 2.09)	0.12
Not able to afford	1.00		1.00	
Adherence to Treatment*				
Less than optimal score >14	0.61 (0.30 – 1.23)	0.61	-	-
Optimal score of 14	1.00			

adverse reactions, physicians and patients may have not sensed a need for change to a costlier medicine. In spite of these challenges, we observed a trend towards improved control of hypertension and diabetes among the few participants able to afford study medicines on a more sustained basis.

Implications of our results

It is estimated that approximately 90% of individuals in LMICs use their own funds to purchase medicines[25]. The out-of-pocket expenditures for medicines are second to food, making government subsidies for medicines not realistic[25]. Differential pricing

Table 5. Predictors of poor glycemic control during follow-up among participants with diabetes mellitus for which study medicines were indicated.

Characteristic	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age, each 10-year increase	1.63 (1.26 – 2.12)	0.0003	1.86 (1.38 – 2.52)	0.0001
Gender				
Female	1.19 (0.62 – 2.27)	0.61	-	-
Male	1.00			
Location of residence				
Urban	0.45 (0.22 – 0.93)	0.03	0.70 (0.14 – 3.53)	0.67
Semi-urban	1.43 (0.67 – 3.04)	0.35	3.08 (1.01-9.37)	0.05
Rural	1.00		1.00	
Highest Educational status			-	-
Tertiary level or more	0.86 (0.37 – 2.03)	0.73		
Secondary level	0.69 (0.34 – 1.43)	0.32		
Primary level	0.42 (0.17 – 1.03)	0.06		
No formal education	1.00			
Employment status			-	-
Employed	0.61 (0.32 – 1.17)	0.14		
Retired	1.64 (0.64 – 4.20)	0.31		
Unemployed	1.00			
Monthly Household income			-	-
>1,000 GHS	1.43 (0.58 – 3.55)	0.44		
210-999 GHS	0.55 (0.26 – 1.16)	0.12		
No response/unknown	0.91 (0.43 – 1.91)	0.80		
<210 GHS	1.00			
Level of Health Institution				
Tertiary level	0.35 (0.19 – 0.63)	0.0004	0.81 (0.23 – 2.90)	0.75
Primary/Secondary level	1.00		1.00	
Duration of diabetes mellitus, each year longer	0.95 (0.91 – 1.00)	0.04	0.93 (0.88-0.98)	0.010
Number of purchases of innovator branded anti-diabetic medications				
>5 times	8.71 (1.75 – 43.48)	0.008	6.73 (1.11 – 40.84)	0.04
3 to 4 times	1.42 (0.40 – 5.09)	0.59	1.60 (0.41 – 6.22)	0.50
1 to 2 times	1.00 (0.47 – 2.11)	0.99	0.70 (0.30-1.69)	0.43
Not able to afford	1.00		1.00	
Adherence to Treatment*				
Excellent	0.76 (0.29 – 2.01)	0.59		
Moderate	1.68 (0.55 – 5.19)	0.36		
Poor	1.00			
Interaction between location of residence and healthcare facility	0.55 (0.40 – 0.76)	0.0003	0.66 (0.26 – 1.67)	0.48

may potentially contribute to attaining the sustainable development goal of Universal Health Care by assuring access to safe, effective, quality and affordable essential medicines[26]. However, as a strategy, differential pricing of essential medicines places the burden of medication purchases on the patient. This burden is dependent on the cost of medicines, the purchasing power of patients and the extent of price reduction on the product by the pharmaceutical company and the size of government taxes, levies, and mark-ups by distributors and health facilities. In LMICs purchasing power of the majority of patients

living with NCDs requiring life-long treatment is low. Our findings would support the need to find additional ways to reduce prices of cardiovascular medicines for LMICs which currently bears the greatest burden of CVD on the globe[27,28]. Furthermore, in LMICs where national insurance policies are in existence, co-payment mechanisms for differentially priced innovator medicines to be shared between patients and national health insurance schemes would contribute to mitigating the financial burden on patients. Alternative price reduction mechanisms such as high-volume purchasing, reliable and adequate financing, public advocacy, negotiation, and market competition could contribute to further price reductions[15–18]. Further advantages could come through an integrated approach that addresses supply chain and weak health systems to improve access and affordability of quality assured innovator medications in LMICs. Governmental reduction or elimination of tariffs and charges on medicines together with hospitals dropping pharmacy mark-ups would also be helpful.

Strengths and limitations

A major strength of this pragmatic study is the enrollment of participants at primary, secondary and tertiary health institutions situated in rural, semi-urban and urban settings to enhance generalizability of our findings. Our study is among the few from sub-Saharan Africa to prospectively evaluate BP and glycemic control and we found evidence of modest improvements in disease control (Figure 2 and Figure 3). Detailed analysis of determinants of disease control for the entire cohort is beyond the scope of the present report. We however exercise caution in over-interpretation of disease control rates in this prospective cohort in the light of high attrition rates during follow-up, which may have been influenced by survivorship bias. Also parsimonious logistic regression models were used to assess the impact of access to study medicines on disease control using a minimalistic set of covariates empirically known to be associated with disease control but not specified *a priori*.

Future directions and conclusion

Our findings have policy implications for pharmaceutical industry and governments. Strategic public-private partnerships and advocacy will be critical to the roll-out of differential pricing as a strategy to assure improved access and affordability of essential medicines for non-communicable diseases in LMICs. Health system strengthening activities such as regular and more frequent hospital visits as done in the present study, together with patient education and training of physicians at study sites may have contributed to different extents in the overall improvements in BP and glycemic control in this cohort. Undoubtedly, efforts at further improvements in hypertension and diabetes control are still urgently needed to avert the rising burden of CVDs and its accompanying unacceptably high morbidity and mortality from CVDs in this region[29–40]. Furthermore enhancing adherence to CVD medicines through mobile health technology as has been shown in the context of stroke in Ghana may be worth pursing further to prevent major adverse cardiovascular events from uncontrolled hypertension and diabetes mellitus[41–43].

In conclusion, although purchases of study medicines were limited by cost even at differential price, sustained purchases of these quality assured medicines were associated with improved blood pressure and glycemic control. Further price reductions of study medicine below those in the present study are expected to lead to improved access and affordability of life saving cardiovascular preventive medications in LMICs.

Data availability

Underlying data

Open Science Framework: Differential pricing of medicines to improve access to medicines for hypertension and diabetes control in Ghana: The Ghana Access and Affordability Program, a multi-center prospective trial, https://doi.org/10.17605/OSF.IO/C97HZ[44].

This project contains the following underlying data:

- Final Outcomes Paper_Database
- Final Dataset_Codebook

Extended data

Open Science Framework: Differential pricing of medicines to improve access to medicines for hypertension and diabetes control in Ghana: The Ghana Access and Affordability Program, a multi-center prospective trial, https://doi.org/10.17605/OSF.IO/C97HZ[44].

This project contains the following extended data:

- Table S1: Baseline characteristics of study participants according to study site.
- Table S2: Baseline characteristics of study participants according to price allocation.
- Figure S1: Percentage of number of times innovator brands of medicines were purchased per participant.

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The NVF is a not-for-profit organization exempt as a public charity under section 501(c)(3) of the United States Internal Revenue Code of 1986 and assumes financial management of the study as a fiduciary agent and primary contractor for the Funders.

The participating pharmaceutical companies (Participant Companies) independently chose which innovator medicines to make available and the differential prices. Otherwise they had no role in the study design, data collection, data analysis, data

interpretation, writing of the report, or in the decision to submit for publication. FSS had final responsibility for the decision to submit for publication.

Consistent with anti-trust laws that govern industry interactions, each Participant Company independently and voluntarily will continue to develop its own marketing and pricing strategies reflecting, among other factors, the Company's product portfolios and the patients it serves. For the avoidance of doubt, the Participant Companies committed not to: (i) discuss any price or marketing strategy that may involve any Project-related product; or (ii) make any decision with respect to the presence, absence or withdrawal of any Participant Company in or from any therapeutic area; or (iii) discuss the launching, maintaining or withdrawing of any product in any market whatsoever. Each Participant Company is solely responsible for its own compliance with applicable anti-trust laws.

The Funders were kept apprised of progress in developing and implementing the study programs in Ghana but had no role in study design, data collection, data analysis or in study report writing.

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Version 1

Reviewer Report 13 February 2020

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This manuscript describes a study that is designed to test whether offering purchase of medicines based on differential pricing to patients with hypertension and/or diabetes in health facilities in Ghana will improve '*access*' and '*affordability*' of '*innovator*' medicines. (My emphasis in italics.) The study population is a cohort of 3296 adult patients, who needed medication and in the opinion of the treating physician needed possible change of treatment. The outcomes reported are proportion of patients purchasing medicines at the different prices (provided for free through the National Health Insurance Scheme, at the market price, at the differential price), clinical outcomes (control of blood pressure and glycemic control) and number of times out of pocket payments for medicines were made.

My review will focus on the principles underlying the study, the discussion and the conclusions drawn from the results. Salim Yusuf *et al* have provided a detailed critique of the methods, reporting and analysis; I agree with their comments and suggested amendments.

Differential pricing has been proposed for many years as a strategy to improve access to medicines. It has been particular espoused by pharmaceutical companies as a way of recouping R&D costs (eg. Danzon and Towse Int J Health Care Finance Econ. 2003 Sep;3(3):183-205[1].) Therefore studies that try to assess whether differential pricing can truly improve access are welcome and rare and the investigators are to be commended for attempting to do so.

However, the study is supported by 4 multinational R&D based pharmaceutical companies as well as the Gates Foundation, and I believe that this pharmaceutical company support has resulted in a fundamental problem with the framing and design, which is the designation of so called 'innovator' medicines for differential pricing. The medicines in question are listed in Table 2 in the protocol on line and I have reproduced that table below. With the exception of the combination product containing sitagliptin and metformin, ALL products are in fact off patent in the originator countries and are available as multiple generics, including biosimilars for insulin glargine. I think therefore that use of the language 'innovator' is misleading and should be removed. I presume that what in fact is being supplied is the originator brand product (at a high price) versus generics

at variable prices. As good quality generics are the mainstay of many countries' policies (including high income countries) to improve access to medicine, implicitly promoting the idea that these branded products are superior as 'innovator products' is potentially a dangerous and misleading frame for this study. Statements such as 'sustained purchases of these quality assured medicines' in the discussion raise further questions about the influence of the pharmaceutical companies on this study and reporting of it and I am concerned that this point may have not been considered adequately by the ethical review process.

Secondly, the differential price vs market price to be charged was apparently set by each company and these actual prices do not appear to be disclosed. Other literature on pharmaceutical pricing and access has used either international reference price as a benchmark or compared the prices paid by patients to their daily or monthly incomes as a measure of affordability. This paper uses an absolute daily value of income to determine the eligibility of patients to be asked to pay market or differential price- but does not report the prices of the medicines. Understanding the results and comparing them to other studies would be easier if this information were provided. It would also allow a proper assessment and discussion of whether the market prices were in fact 'affordable'. A comment is made in the discussion that 'the impact of price reductions by the participating pharmaceutical companies was also compromised by the various levies and mark-ups by distributors and hospitals'; do the authors have data to support this statement? As the majority of patients made only one purchase I have to assume that prices were in fact not affordable and or the differential pricing did not in fact exist.

A further issue is the co-intervention that was provided for the study, described in the methods as ' health systems strengthening activities'. These are listed in some length in the protocol. While the authors interpret their findings as showing that patients who purchased 'innovator medicines' had better disease control, the differences are small and I note the overall improvement in disease control could be a result of the training of health care workers in diagnosis and management.

In summary, it is important that the data in this study are fully published and presented correctly. This will require revision of the results as already suggested by Yusuf et al, addition of the pricing information and complete revision of the discussion and conclusions.Depending on the actual pricing of the products, it may be that this should be most reasonably presented as a negative paper. In my opinion the findings are mostly like to suggest that within-country differential pricing is difficult to implement and not effective and should not be presented as policy option to improve access.

Table of medicines – Table 2, protocol[2].

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacoeconomics, pharmaceutical policy, and public health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 06 February 2020

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Summary:
The primary aim of this study was to test the following question: would access and affordability of

innovator medicines, (i.e., medicines not listed on the essential medicine list), improve if they were offered using a two-tiered pricing system whereby those from lower socioeconomic backgrounds purchase the medicines at a lower price and everyone else at the market price? To answer this question, the authors recruited 3296 patients with self-reported hypertension and/or diabetes from 5 hypertension and/or diabetes clinics. At the time of enrollment, all patients were using generic antihypertensives/anti-diabetics listed available on the National Health Insurance scheme. Eligibility for the reduced price (differential price: DP) innovator medicines was determined based on patients self-reported household income (if it was less than minimum wage), and/or their multi-dimensional poverty index score. Mean follow-up time was 14 months.

Of the 3296 patients, 526 (16%) were prescribed the innovator medicines: 238/526 purchased the innovator medicines at least once and 288/526 were unable to purchase the innovator medicines. Of the patients that purchased the innovator medicines, 97/238 patients were assigned to the lower tiered price (differential price: DP) and purchased at DP, 91/238 were assigned to market price (MP) and purchased at MP, and 58/238 were assigned to MP but purchased at DP. The remaining patients (N=2,770/3296) continued to use medicines listed on the National Health Insurance scheme. The authors also examined whether the purchase of innovator medicines resulted in improved hypertension/diabetes control. The authors concluded that use of innovator medicines resulted in improved hypertension/diabetes control.

The authors present a manuscript outlining a quasi-experimental, prospective cohort study of 3296 participant with hypertension, diabetes or both, that was implemented at five Ghanaian health facilities, using non-generic, “innovator” medicines differentially priced according to the patient’s socio-economic status. It was hypothesized that differential pricing would mitigate barriers to care, thus resulting in the improved management of CVD risk, particularly hypertension and diabetes. Essentially, this study demonstrated that only a small proportion of patients were prescribed the “innovator” medications by their physicians (16%) and of these only 45% could afford them despite the differential pricing, with 66% only filling the prescription once (2 out of 18 month follow-up).

We appreciate the difficulties involved with conducting research in resource constrained environments. The authors are therefore commended for their work. Below we offer some suggestions for improving readability, transparency, and reproducibility.

Major comments:

- It appears that the authors deviated from their study protocol in several respects. For transparency, these deviations and their reasons should be reported. For instance, many outcomes listed in the protocol are not reported, particularly outcomes related to the health system strengthening interventions. The methods for analysing the data reported in the protocol are also different from those used in this study.

The study results could be presented more clearly and accurately. Specifically:

- The authors should consider defining the term ‘innovator medicines’. Are these the brand version of medicines that also have generics, or are these medicines with active patents and so generics are not yet available? The innovator medicines that were part of the study should also be listed.

- Since the primary aim of the study was to examine whether differential pricing improves access and affordability, the unit prices of the medicines for the MP and DP arms, and their

total costs to patients (unit price + mark-ups + professional fees etc.) should be presented.

- Given the primary aim of the study, results should be presented by pricing arm allocation (DP vs MP)

- Table 1 Main outcome measures for the study: Some of the information in the columns could be modified to improve presentation and communication of study results. For instance, rather than presenting "total number of clinic visits" the authors could present mean or median number of clinic visits per patient. This more useful to the reader especially since patients are meant to have 2 clinic visits per month. Similarly, "number of decisions taken by physicians to modify patients treatment at clinic" is not helpful. Instead, the proportion of patient for whom physicians altered treatment (which in this case implies that patients are prescribed innovator medicines) is more helpful to a reader. Presenting the denominators in the columns would also make the table easier to follow.

- The following sentence: "overall, 238 (45.2%) patients were able to afford prescribed study medicines while 288 (54.8%) were unable" is misleading for two reasons. First, 'affordability' if never defined, what the authors report is whether the patients *purchased* medicines or not. Second, the vast majority of the patients only made 1 purchase during follow-up (Supplemental Figure 1), only ~10% of patients made 2 purchases, and even fewer made more than 2 purchases. Therefore, the study medicines do not appear to be affordable.

- Table 2 Comparison of baseline characteristics of patients according to ability to access/purchase innovator medicines: The headings are unclear. What does it mean to be able to 'access study medicines'. Does 'access' encompass availability of medicines? If this column presents results for patients that purchased study medicines then perhaps the heading should state 'Prescribed and purchased study medicines'. In Group C, 'Not prescribed study medicines', why are there patients in this group that received the study medicines?

- Figure 2 The impact of study medications purchased on disease control: It is unclear which patients are in the 'no innovator medicine' group. These numbers do not add up to the numbers reported in Tables 1 and 2. Are these the patients that were prescribed but did not purchase? Also there appears to be significant loss to follow-up (i.e., 419 patients at month 0 and 277 patients at month 18), could the authors provide reasons for loss-to follow-up. It would also be helpful if the total number of patients are presented.

- Figure 3 Impact of study medications purchases on disease control: Patients in 'baseline' are not all included in 'month 18' thereby making it difficult to determine whether purchase of innovator medicines improved HBA1C levels. We recommend that the authors present the information only for those patients that are included in baseline *and* month 18. The lower proportion of patients with target HBA1C levels in 'baseline' could be driven by patients that are lost to follow-up.

- Tables 4 and 5, The authors should present the sample sizes and indicate what variables were included in the adjusted columns as a note below the table. The wide confidence intervals for 'number of purchases' could be driven by a small number of patients that were able to afford the innovative medicines.

- Study methods: The authors state they used a parsimonious logistic regression model to determine the predictors of blood pressure control and glycemic control among patients who purchased study medicines. What criteria did the authors use to judge parsimony? Was parsimony based on p-values only, or did the authors also incorporate other criteria (e.g., AIC, BIC)?

- The authors conclude that 45% of Ghanaians could afford the prescribed study medicines and that price reductions are expected to enhance hypertension and diabetes control. However, these results do not appear to be supported by the data presented. A significant proportion of the patients were only able to make 1 purchase of the innovator medicines, suggesting that the medicines were not priced according to patients ability to pay. Furthermore, it remains unclear whether differential pricing improved hypertension and diabetes control. Importantly, differential pricing did not appear to improve use of innovator medicines in patients with low socioeconomic status. The authors should consider rewording their conclusions.

- The results in the abstract do not reflect the main goals of the study, “Participants were followed for 18 months to assess blood pressure (BP) and glycemic control.” The clinical outcomes (BP and glycemic control results) should be included in the results and conclusion.
- In the second paragraph of the introduction, the authors suggest that price adjustments for the management of NCDs has not been evaluated to date. We would argue that mitigating cost barriers in NCDs and specifically cardiovascular risk has been evaluated and demonstrated to be successful in LMIC and HIC (Schwalm et al, Lancet 2019 and Persaud et al, JAMA 2019, respectively).

- The authors suggest that essential medicines were available through the National Health Insurance Scheme and were used if DP or MP “innovator brands” could not be afforded or were not prescribed. The authors need to better explain the differences in medications available free under national insurance versus the innovator brands used in this study. The majority of physicians prescribed generic brands.

- Within the health system strengthening activities, it is not clear if measures were only taken to improve stock and access to innovator brands? Did this also include stocking of generic medications. It would be helpful to understand the length of prescription participants were given on average as this may affect long-term adherence and add barriers to repeat filling. Two month supply was mentioned but was this the case for the generic brands?

- Some explanation as to the high proportion of females in the study would be useful. Is this representative of the population with CVD risk in Ghana or did bias play a role?

- Limitations in CVD risk control seem to extend beyond affordability of the medications. This should be highlighted in the discussion.

- The goal of this study remains in question. Is it to increase the use of non-generic medications? How does this translate into better outcomes if cost is still a factor (i.e. minimal reduction in medication costs as outlined, even with differential pricing given levies

and mark-ups). Would this not have been known before starting the study? It is stated that, the range of study medicines used to test the study hypothesis had generic equivalents covered by National Health Insurance and might have obviated the need to prescribe them." This seems obvious and would wonder why the study was undertaken given comparable generic meds are available and covered by insurance. This needs to be better explained.

- The authors need to better justify why this study was not simply an exercise to decrease generic brand use and increase comparable non-generic "innovator" medication sales in a country whose population is significantly resource constrained. Concerns regarding this exercise is warranted in HIC, let alone LMIC.

- The following statement in the Implications section, "The out-of-pocket expenditures for medicines are second to food, making government subsidies for medicines not realistic" does not align with the findings in the paper as the majority of participants had medications covered by universal coverage.

- "Our study is among the few from sub-Saharan Africa to prospectively evaluate BP and glycemic control and we found evidence of modest improvements in disease control (Figure 2 and Figure 3)." Based on the findings presented, there were no significant differences in glycemic control and the difference in change in SBP from baseline to 18 months between the two groups does not appear to be significant (but not provided-only change within group).

Minor comments:

1. The abstract describes the study design as a 'quasi-experimental prospective cohort study' whereas the methods section describes the study design as 'quasi-experimental study with a pragmatic trial design'. The title also includes the word trial. However, the intervention was not randomly assigned, therefore, 'quasi-experimental prospective cohort' seems more appropriate. The abstract and method sections should use consistent terminology and the use of 'trial' should perhaps be avoided.

2. Patient enrollment dates should be reported in the results section.

3. Figure 1 should include the sample size affiliated with each box.

4. The Tables and Figures are not always presented in the same order as the description of results. For instance, the authors begin with describing patient demographic and clinical characteristics, however these results are presented as part of Table 2 rather than Table 1.

5. Access and affordability should be defined.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiovascular Prevention

We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.