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Original Research

Impact of a clinical pharmacist on a cardiovascular surrogate endpoint: a pilot study

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ABSTRACT[*]

Utilizing a multidisciplinary approach to management of patients with certain chronic cardiovascular diseases (CVD) has been shown to improve treatment outcomes. The role of clinical pharmacists in comprehensive outpatient CVD management has not been evaluated.

Objective: The objective of this pilot study was to evaluate the impact of a clinical pharmacist added to cardiologist care on blood pressure (BP), a key surrogate marker of CVD, in outpatients with CVD compared to cardiologist care alone.

Methods: A retrospective, matched-control study was conducted in patients established in a cardiovascular clinic. The intervention was referral to a pharmacist clinic; control was usual care from the cardiologist. The surrogate marker evaluated was the change in BP.

Results: Patients in the pharmacist-intervention (n=57) experienced significant reductions in diastolic BP (-2.6 mmHg, p=0.05) and non-significant reductions in systolic BP (-4.3 mmHg, p=0.16) compared to baseline, whereas patients in the control group experienced non-significant increases in both systolic and diastolic BP (+1.6/+0.7 mmHg, p=NS). Similarly, there were significant reductions in diastolic BP and non-significant reductions in systolic BP for the intervention group when compared to controls (difference 3.3 mmHg, p=0.04 and 5.9 mmHg, p=0.1, respectively). Lastly, the proportion of patients categorized as having Stage 2 BP was significantly reduced in the intervention group (p=0.02), but not in the controls (p=0.5).

Conclusions: The multidisciplinary model of care that included a clinical pharmacist reduced BP more than usual care by a cardiologist alone. This benefit was demonstrated in complex patients with CVD who were already receiving specialized care. The impact of this model on clinical outcomes requires further evaluation and should be a high priority given the burden of CVD in the population.

Keywords: Hypertension. Blood Pressure. Pharmacists. Patient Care Team. Cooperative Behavior. United States.

IMPACTO DE UN FARMACÉUTICO CLÍNICO SOBRE UN RESULTADO INTERMEDIO CARDIOVASCULAR: UN ESTUDIO PILOTO

RESUMEN

Utilizar un abordaje multidisciplinar para el manejo de pacientes con determinadas enfermedades cardiovasculares (CVD) ha demostrado mejorar los resultados del tratamiento. No ha sido evaluado el papel del farmacéutico clínico en manejo ambulatorio completo de las CVD.

Objetivo: El objetivo de este estudio piloto fue evaluar el impacto del farmacéutico clínico añadido al cardiólogo en los cuidados de la presión arterial (BP), marcador intermedio clave de CVD, en pacientes ambulatorios con CVD comparando con el cardiólogo solo.

Métodos: Se realizó un estudio retrospectivo de control emparejado en pacientes atendidos en una clínica cardiovascular. La intervención era la remisión a un farmacéutico clínico; el control fue la atención habitual del cardiólogo. El marcador intermedio evaluado fue el cambio en BP.

Resultados: Los pacientes en el grupo intervención-farmacéutica (n=57) experimentaron reducciones significativas en la BP diastólica (-2.6 mmHg, p=0.05) y reducciones no significativas en la sistólica (-4.3 mmHg, p=0.16) comparadas con el inicio mientras que los pacientes en el grupo control experimentaron aumentos no significativos tanto en las BP sistólica como diastólica (+1.6/+0.7 mmHg, p=NS). Asimismo, hubo reducciones significativas en al BP diastólica y no significativas en la BP sistólica para el grupo intervención comparado con el control (diferencia 3.3 mmHg, p=0.04 y 5.9 mmHg, p=0.1, respectivamente). Por último, se redujo significativamente la proporción de pacientes en el grupo intervención clasificados como teniendo un estado 2 de BP (p=0,02) pero no en el grupo control (p=0,5).

Conclusiones: El modelo multidisciplinario de cuidados que incluía un farmacéutico clínico redujo la BP más que el modelo habitual de cuidados con el cardiólogo solo. Este beneficio fue demostrado en pacientes con CVD compleja que ya estaban recibiendo cuidados especializados. El impacto de este modelo sobre los resultados clínicos requiere

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más evaluaciones y debería darse alta prioridad al daño de las CVD en esta población.

Palabras clave: Hipertensión. Presión Arterial. Farmacéuticos. Equipo de Atención al Paciente. Conducta Cooperativa. Estados Unidos.

INTRODUCTION

Although advancements in the management of cardiovascular disease (CVD) have led to reduced death rates, the prevalence of CVD remains high, with more than 82 million people in the United States having at least one form of CVD.[1] Furthermore, the prevalence is predicted to increase by 1-2% annually over the next 10-20 years due to the rapid growth of the population over the age of 65.[2] The consequences of this are substantial: in 2008, CVD accounted for one out of every three deaths, was the most common hospital discharge diagnosis, was responsible for more than 94 million outpatient visits, included three of the top 15 conditions causing disability, and cost more than USD297 billion.[1] Further, CVD prevalence and costs are expected to increase substantially; a recent report by the American Heart Association estimated that total direct medical costs for CVD will triple by 2030 (USD818 billion, in 2008 dollars).[3]

Utilizing a multidisciplinary approach to manage patients with CVD is endorsed by the American Heart Association[3] and may be one mechanism to improve treatment outcomes. Several studies have shown that pharmacists can reduce clinical events[4-7] and adverse drug reactions[8], improve medication adherence[9], and lessen health care costs[5-7] in patients with CVD. However, these benefits were achieved with interventions that focused on a specific issue within CVD (e.g., medication adherence, prevention of adverse events) or on one discrete cardiovascular diagnosis (e.g., heart failure, anticoagulation). To our knowledge, no study has evaluated the effectiveness of including a clinical pharmacist in comprehensive cardiovascular care compared to cardiologist management alone.

The University of Oklahoma Health Sciences Center Heart, Lung, and Vascular Clinic (HLV Clinic) is an academic cardiovascular and pulmonology clinic that is the practice site for attending cardiologists, vascular physicians, and pulmonologists. A pharmacist-managed clinic was established within the HLV Clinic in February 2009. The pharmacist clinic is available to the attending cardiologists/vascular physicians for pharmacotherapy management of diverse cardiovascular diagnoses including hypertension, dyslipidemia, heart failure, coronary artery disease, arrhythmias, thrombosis, and medication related issues (e.g., adverse drug effects, medication adherence). Patients are required to be established with a physician in the HLV Clinic prior to referral. The referring physician defines which condition(s) the pharmacist is authorized to manage at the time of referral; additional authorizations can be given during the course of care if indicated. The pharmacist functions relatively independently such that drug therapy decisions are implemented and monitored by the pharmacist within the defined referral and scope of practice. Further, decisions are not pre-specified by a formalized protocol and do not mandate physician consultation if decisions are within the context of the referral, though referring physicians are available if needed. A written scope of practice agreement defines the authorities delegated to the pharmacist in the delivery of care; the pharmacist is required to consult the referring physician for needs outside the referral and scope of practice. A medical director serves to assess the knowledge and skills of the pharmacists and to provide back-up consultation if the referring physician is not available.

A pilot study was conducted to evaluate the effectiveness of pharmacists' care on blood pressure (BP) and cholesterol parameters as established surrogate markers of CVD in preparation for a more robust study to assess the impact on CVD clinical outcomes. The objective of this study was to evaluate the impact of a clinical pharmacist added to cardiologist care in outpatients with diverse cardiovascular diseases compared to usual care by a cardiologist alone. We hypothesized that incorporating a clinical pharmacist into direct patient management would improve CVD surrogate markers and clinical outcomes. This study adds to the published evidence of pharmacist care in CVD in the following ways: (1) Patient management is comprehensive and not limited to a single CVD diagnosis; (2) The control group consists of patients managed by cardiologists; and (3) Patients in the intervention group are referred by specialists.

METHODS

A pilot, retrospective, matched-cohort study was conducted to assess changes on BP and cholesterol among patients referred to the pharmacist clinic. The pilot design was employed to allow for evaluation of effect size differences so that an accurate power calculation could be applied to follow-up investigations. Patients were eligible for inclusion if they were ≥18 years old, had a diagnosis of hypertension and/or dyslipidemia, and had a minimum two BP results and/or cholesterol panels, respectively, at least 3 months apart between February 1, 2009 and November 30, 2010. Patients in the pharmacist group were comprised of referrals to the clinical pharmacists during the defined study period and meeting the pre-specified inclusion criteria. Eligibility also included authorization from the referring physician for management. Five attending cardiologists were solicited to participate as the matched cohort. Age-matched patients (within 1 standard deviation) not referred for pharmacist management were consecutively identified from clinic records for the five clinic cardiologists to serve as controls using a 2:1 match, determined *a priori*. The two co-primary endpoints were the changes in BP and cholesterol parameters (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides) between two visits. This was evaluated by comparing the changes between the

intervention and control groups; within group changes were also evaluated. The results obtained closest to the beginning and end dates within the study period were compared (identified as "Visit 1" and "Visit 2", respectively). Neither patients in the intervention nor in the control group were required to have uncontrolled hypertension or dyslipidemia as the primary basis for care.

The planned per protocol analysis in December 2010 showed lower enrollment in the intervention group than predicted, owing to the initiation of the pharmacist clinic in February 2009; providers in the control group each had established practices by this time. Therefore, to achieve enrollment goals, the study investigators increased the time of inclusion for the intervention group by five additional months; the follow-up period for the control group was unchanged. This analysis also revealed discordant cholesterol data that precluded proper analysis both within and between the intervention and control groups. Therefore, the planned assessment of cholesterol parameters was terminated, leaving BP change as the primary endpoint. Using BP alone as a single marker of CVD progression is reasonable for preliminary investigations due to the convenient and standardized sampling, the clear evidence of a linear relationship between BP and cardiovascular events, and the ability of the BP to be used a guide to track therapeutic efficacy.[10,11]

Statistical analysis

Descriptive statistics (means, standard deviations, and percentages) of patient demographics were calculated at baseline for each group. Results were analyzed using paired and independent t-tests. Z-tests of proportions were used to assess differences in proportions, both within and between groups. Linear regression was used for post-hoc analysis. Data management and analysis was conducted using Stata v10, with the alpha set at 0.05 a priori. This study was approved by the local Institutional Review Board.

RESULTS

A total of 360 patients were screened for participation during May 2011 for both groups. One hundred twenty-nine patients were screened in the intervention group. Seventy-two patients were excluded (incomplete data [n=48], hypertension management not authorized [n=21], no hypertension diagnosis [n=3]), leaving 57 patients in the final analysis for the intervention group. Two hundred thirty-one patients were screened for the control group. Ninety-three patients were excluded (age >1 standard deviation [n=78], no hypertension diagnosis [n=9], incomplete data [n=6]), leaving 138 in the final analysis for the control group.

Patients in the pharmacist-intervention group were more likely to have heart failure, venous thromboembolism, and sleep apnea compared to the cardiologist-control; other characteristics were similar between groups (Table 1). Follow-up time between Visit 1 and Visit 2 was similar between the intervention and control (mean 348 days versus 371 days, respectively, p=0.38). However, there were more visits for the intervention group than the controls (mean 9.3 visits versus 3.4 visits, p<0.01).

Compared to the control group, patients in the intervention group experienced significant reductions in diastolic BP (Δ 3.3 mmHg; p=0.04) and non-significant reductions in systolic BP (Δ 5.9 mmHg; p=0.1) (Table 2). Compared to baseline, patients in the intervention group experienced significant reductions in diastolic BP (mean: -2.6 mmHg, p=0.05) and non-significant reductions in systolic BP (mean: -4.3 mmHg, p=0.16) from Visit 1 to Visit 2 (Table 2). Conversely, non-significant increases in both systolic and diastolic BP (mean: +1.6/+0.7 mmHg, respectively) were observed within the control group during the study period (Table 2).

Patients in the intervention group were taking significantly more anti-hypertensives at Visit 1 and 2 compared to the controls (3.5 SD=1.5 versus 2.6 SD=1.3, respectively for Visit 1; 3.6 SD=1.6 versus 2.8 SD=1.3, respectively for Visit 2; p<0.01).

An *ad-hoc* analysis was conducted to explore differences in BP distribution between the groups, as well as to identify which patients experienced BP changes. Patients were categorized according to

Table 1 – Participants' demographics

	Intervention (n=57)	Control (n=138)
Mean age	69.4 (SD=11)	68.7 (SD=7.0)
Hypertension, % (number)	100% (57)	100% (138)
Dyslipidemia	71.9% (41)	81.2% (112)
Coronary Artery Disease	54.4% (31)	55.8% (77)
Cerebrovascular accident/ Transient Ischemic attack	14.0% (8)	8.0% (11)
Diabetes Mellitus	33.3% (19)	31.2% (43)
Peripheral Vascular Disease	15.8% (9)	13.0% (18)
Chronic Renal Insufficiency	17.5% (10)	10.1% (14)
Current tobacco use	7.0% (4)	8.0% (11)
Heart failure, total [8]	49.1% (28)	13.0% (18)
Heart failure, type not specified	19.3% (11)	11.6% (16)
Heart failure, systolic	15.8% (9)	1.4% (2)
Heart failure, diastolic	14.0% (8)	0% (0)
Venous Thromboembolic Disorder [8]	7.0% (4)	0.7% (1)
Valvular disease	8.8% (5)	5.1% (7)
Atrial Fibrillation	10.5% (6)	18.8% (26)
Chronic Obstructive Pulmonary Disease	17.5% (10)	10.1% (14)
Sleep apnea [8]	15.8% (9)	6.5% (9)

[8] $p < 0.05$

Table 2 – Mean Blood Pressure Comparisons between Intervention and Control			
	Intervention (n=57)	Control (n=138)	Between group difference
Systolic BP, mmHg, Visit 1	140.8 ± 21.5	136.2 ± 20.6	4.6
Systolic BP, mmHg, Visit 2	136.6 ± 16.3	137.8 ± 18.8	1.2
Δ systolic BP, mmHg	-4.3 ± 22.8	+1.6 ± 22.3	5.9
Diastolic BP, mmHg, Visit 1	75.6 ± 11.4	75.2 ± 10.7	0.4
Diastolic BP, mmHg, Visit 2	73.0 ± 10.0	75.8 ± 9.7	2.8
Δ diastolic BP	-2.6 ± 9.9	+0.6 ± 10.2	3.2 *
*P = 0.04			

Controlled BP (<140/90), Stage 1 (140/90 – 159/99), or Stage 2 (≥160/100) at Visit 1 and Visit 2. The proportion of patients in these categories was similar between the groups at both time points (p=NS). However, the proportion of patients with Stage 2 hypertension at Visit 1 was significantly reduced by Visit 2 for patients in the intervention group (p=0.02) but not in controls (p=0.5) (Table 3). No other changes in the proportion of patients in the BP categories were significant.

An *ad-hoc* analysis was also conducted to evaluate BP changes in the group of patients with uncontrolled BP at baseline (defined as BP≥140/90). In this cohort, both the intervention (n=30) and control (n=56) groups exhibited significantly reduced systolic BP (mean: -14.0 mmHg and -9.8 mmHg, respectively; p<0.01 for both); however, only the intervention group experienced significant diastolic BP reductions compared to baseline (mean: -5.2 mmHg for intervention, p<0.001 and -1.5 mmHg for control, p=0.25) (Table 4). No significant difference was detected between the intervention and control groups for either systolic or diastolic values.

A linear regression analysis was conducted to explore the causal role for the pharmacist's intervention on BP. No association was found for systolic BP between the intervention and control groups (p=NS); however, the intervention group was associated with greater reductions in diastolic BP than those not managed by the pharmacist (p=0.005).

DISCUSSION

Including a pharmacist in comprehensive outpatient cardiovascular management was associated with improved BP, a key surrogate marker of cardiovascular morbidity and mortality, more than usual care by a cardiologist alone. The current study demonstrated these improvements in a complex and diverse cohort of patients receiving management of multiple cardiovascular diseases in a specialty clinic. Significant improvements in diastolic BP were observed (-2.6 mmHg) in patients receiving care from a pharmacist in addition to their cardiologist. The severity of hypertension was also improved, where the proportion of patients with BP exceeding 160/100 mmHg was significantly reduced (from 19.3% to 3.5%). Reductions in systolic BP (-4.3 mmHg) were also observed, but did not achieve significance, possibly due to insufficient statistical power. This contrasts with patients in the matched cohort who were receiving standard care by a cardiologist alone and did not demonstrate reductions in BP or improvements in BP severity. Similar results were observed in the cohort of patients with uncontrolled BP, with the intervention group experiencing a larger BP reduction than the control group in both systolic and diastolic BP (difference 4.2 mmHg and 3.7 mmHg, respectively; Table 4), though statistical differences were not detected in this small sub-group analysis.

BP reduction achieved through collaborative management by a clinical pharmacist is well-established.[12] Studies have demonstrated significant improvements in BP or proportion of patients achieving their goal BP with pharmacist co-management.[12-15] However, several notable differences exist between the populations in these studies and our study. First, patients referred for pharmacist management in the studies conducted to date were managed for uncontrolled hypertension only and were not referred for management of multiple cardiovascular conditions. In our study, patients with hypertension were eligible even if their BP was at guideline-defined goals. This cohort was included because the risk of CVD begins to increase at BP≥115/75 mmHg[16] and because the study objective was to evaluate BP as a surrogate for cardiovascular risk, not to evaluate achievement of BP goals. The model of pharmacist care was also unique compared to other published studies, since a patient was often referred for longitudinal and comprehensive medication management of all of his/her cardiovascular conditions (e.g., heart failure, coronary artery disease, cardiovascular risk management, thrombosis) rather than for one specific diagnosis. Further, the patients in this study were referred to the pharmacist by a cardiologist, not a primary care provider. Lastly, the patients in this analysis were more complex, with two-thirds of the pharmacists' cohort having either established coronary artery disease or heart failure and one-third with both coronary artery disease and heart failure. Therefore, our study findings suggest that the benefits of pharmacist management may be

Table 3 – Classification of Hypertension Severity				
	Intervention (n = 57)		Control (n = 138)	
	Visit 1	Visit 2	Visit 1	Visit 2
Controlled (<140/90 mmHg)	27 (47.4%)	33 (57.9%)	82 (59.4%)	76 (55.1%)
Stage 1 (140/90 – 159/99 mmHg)	19 (33.3%)	22 (38.6%)	36 (26.1%)	45 (32.6%)
Stage 2 (>160/100 mmHg)	11 (19.3%)	2 (3.5%)*	20 (14.5%)	17 (12.3%)
*P=0.02 for comparison to proportion of patients in this category at Visit 1; P=NS for all others				

Table 4 – Comparison of patients with BP ≥ 140/90				
Intervention (n=30)				
	Visit 1	Visit 2	*Delta*	
Systolic BP (mmHg)	154.8 ± 19.3	140.8 ± 14.4	14.0 ± 20.6	P = 0.001
Diastolic (mmHg)	77.5 ± 13.9	72.3 ± 10.2	5.2 ± 11.4	P = 0.015
Control (n=56)				
	Visit 1	Visit 2	*Delta*	
Systolic (mmHg)	155.2 ± 16.3	145.4 ± 17.3	9.8 ± 19.5	P < 0.001
Diastolic (mmHg)	80.7 ± 11.1	79.2 ± 10.5	1.5 ± 9.5	P = 0.25
P>0.05 for between group comparisons				

extended to the comprehensive management of complex CVD patients and remains beneficial even when added to specialist care. To our knowledge, this is the first report showing a reduction in BP, an important surrogate marker of CVD, by including a clinical pharmacist compared to cardiologist management alone utilizing a comprehensive model of care rather than a disease-specific model.

Although no study to date has evaluated the impact of pharmacist management on clinical outcomes utilizing this comprehensive approach, studies within discrete cardiovascular diagnoses have consistently shown that clinical pharmacists improve outcomes. A 78% relative risk reduction in the combined endpoint of all-cause death and nonfatal cardiovascular events was achieved in a randomized, prospective controlled study when a clinical pharmacist was included on a specialized heart failure management team (odds ratio 0.22; 95% confidence interval 0.07-0.65, p=0.005); the benefit was largely driven by a reduction in hospitalization or emergency department visits for heart failure.[4] Pharmacists have also improved medication adherence in patients with heart failure and reduced adverse drug events in patients with hypertension and heart failure.[8-9] Improved anticoagulation control, fewer thrombotic and bleeding events, and reduced cost have been observed when pharmacists managed anticoagulation.[5-7] The partnership of specialized cardiovascular care including both cardiologists and clinical pharmacists has led to important improvements in patient care in discrete cardiovascular diagnoses, such as heart failure, hypertension, or anticoagulation. The results of our study demonstrate that benefits of this collaboration may not be limited to selected cardiovascular indications, but may be additionally applied to comprehensive cardiovascular care.

The rationale behind the improved outcomes demonstrated with clinical pharmacists may be related to the increasing complexity of medical therapy, especially in chronic CVD. Patients with chronic heart failure or coronary artery disease can be taking a minimum of 5-7 medications for their primary cardiovascular diagnosis. Medication management is further complicated when coupled with treatment for other common comorbidities (e.g., diabetes, chronic renal insufficiency). Age- and disease-induced changes in volume of distributions, metabolism, and clearance lead to altered pharmacodynamics and pharmacokinetics. Indeed, in our study, 63% of patients in the pharmacist cohort were 65 years of age or older, 49% had heart failure, and 17% had chronic renal insufficiency. Access to medications, drug interactions, safety monitoring, and adverse event prevention and management (e.g., hypokalemia, renal dysfunction) are frequent management issues. Clinical pharmacists are a sub-group of pharmacists with post-graduate residency or fellowship training that enables them to manage complicated medication issues common in patients with CVD.

It is recognized that BP change alone cannot fully capture the global impact of an intervention on reducing overall cardiovascular risk. In a cohort of patients with diverse cardiovascular diseases, no universal surrogate marker adequately quantifies CVD progression or risk.[17] Evaluation of cholesterol parameters, another well-established cardiovascular biomarker[17], was terminated in this study. The lack of standardized collection of lipid parameters and relatively short follow-up time led to incongruent data that limited a quality analysis in the two study arms. Other surrogates (e.g. endothelial function, arterial compliance) could not be evaluated due to limited resources. Blood pressure was sampled at each visit uniformly in both groups and provided a standardized metric such that a preliminary comparison between treatment groups could be conducted. Therefore, in the absence of a universal marker for CVD risk, BP is a reasonable proxy[11], especially in patients with a hypertension diagnosis since there is a well-established association between increasing BP and risk of cardiovascular events.[10] The findings from this study represent an important first-step in examining the effect of this multidisciplinary model on CVD outcomes and will aid in the design of continued studies to rigorously assess the true impact on important CVD endpoints, such as cardiovascular events, mortality, hospitalizations, and cost-effectiveness of care.

This study has several important limitations. First, the primary endpoint assessed was a single surrogate marker of CVD; a composite endpoint including multiple surrogates would be more sensitive and specific (e.g., cholesterol parameters, endothelial function, arterial compliance).[11] Further, clinical outcomes were not evaluated in this pilot study and require further investigation to establish the overall clinical benefit, as discussed above. Group assignment was not randomized, so it is foreseeable that differences could exist between the intervention and standard care groups that could have influenced the results despite our efforts to consecutively select matched controls. Indeed, patients in the intervention group were more likely to have heart failure, venous thromboembolism, sleep apnea, and were receiving more anti-hypertensives. Patients in the intervention group were also seen more frequently; therefore, it is possible that the benefits observed occurred due to increased patient

engagement. However, this could reflect inherent selection bias in the intervention group, as patients seen in the pharmacist clinic may have been referred specifically because they required more engagement due to instability of disease, close titration of medications, or other issues (e.g. medication adherence). The study design limits conclusions about causation and the influence of confounders such as these, though our linear regression analysis suggests pharmacist management was responsible for the improved BP values. Sample size and the retrospective design also place limitations on statistical power and the ability to draw definitive conclusions from the study. Finally, it is possible that an impact on systolic BP might have been observed in the intervention group or in the sub-group analyses with a larger sample size.

CONCLUSIONS

A multidisciplinary model that added a clinical pharmacist to cardiologist management resulted in reduction of BP, a well-established CVD surrogate marker, in a diverse group of patients with complex CVD. Clinical pharmacists have unique knowledge and skills that consistently provide benefits when they are included as a member of the health care team. Further evaluation is needed to determine the impact of this model on clinical events (e.g., cardiovascular hospitalizations, adverse drug events) and should be a high priority given the critical prevalence and economic projections for CVD in the United States.

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CONFLICT OF INTEREST

The authors have no financial disclosures or conflicts of interest.

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