
Clark


Khan


Dooley-Wood


Moore

Clinical Inertia

A Retrospective Review of Medication Treatment Plans in Patients with Type 2 Diabetes and Cardiovascular Disease

Meredith N. Clark, PharmD
PGY2 Pharmacy Resident
Penn Medicine Lancaster General Health

Nafisa Khan, PharmD
Andrea Dooley-Wood, PharmD, BCACP
Mara Moore, PharmD, BCACP
Ambulatory Pharmacist Clinicians
Penn Medicine Lancaster General Health

INTRODUCTION

The incidence of Type 2 diabetes mellitus (T2DM) has remained steady at about 6% while the age-adjusted prevalence of total diabetes among adults aged 18 years or older has increased steadily to more than 13% over the past 20 years.[1] The management of diabetes and its complications is responsible for significant health care costs every year.[1,2] The macrovascular complications of uncontrolled diabetes, such as atherosclerotic cardiovascular disease (ASCVD), are a focal point of pharmacotherapy selection and intensification.[2]

Patients with diabetes are at an increased risk of experiencing major adverse cardiovascular events, such as myocardial infarction and stroke. Therefore, antihyperglycemic medication classes with proven cardiovascular benefit, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RA), should be prioritized. The American Diabetes Association (ADA) recommends these agents be utilized in patients with ASCVD or at high risk of ASCVD regardless of their A1C due to proven cardiovascular risk reduction.[2] Patients may require multiple antihyperglycemic medications to effectively lower blood glucose levels and to achieve their goal A1C; however, many patients remain on suboptimal medication regimens.

Clinical inertia, or the lack of appropriate treatment alteration or escalation to evidence-based regimens despite risk factors or not achieving treatment goals, can be a common and detrimental problem with chronic disease state management.[3] A cohort study of U.S. patients demonstrated that from 2015 to 2019, SGLT2 inhibitor use had increased overall, yet utilization was still not optimized among patients who would benefit from this class of medications.[4]

A key consideration in medication optimization and diabetes control is ensuring that when indicated, agents with protective effects are being utilized first. This includes the addition of an agent — or transition to an agent — even if patients have achieved their individualized glycemic goals.[2] For example, antihyperglycemic regimens in T2DM patients with ASCVD or at high risk of ASCVD that include sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors, or multiple daily insulin injections should be optimized to regimens with cardiovascular benefit even if glycemic goals are already being met.

In patients with T2DM and an A1C not at goal, the ADA guidelines recommend treatment initiation or intensification within three months of findings.[2] However, a systematic review of therapeutic inertia in T2DM found the median time-to-treatment optimization was 0.3 to 2.7 years following an A1C above target.[5] This inaction could be due to many factors, including patient preference or non-adherence, provider preference or knowledge, system or cost barriers, competing demands, or time constraints.[4,6-9]

The ADA guidelines suggest a patient-centered, collaborative, multidisciplinary care team that consists of pharmacists, nurses, or dieticians, among other

health care professionals, and prioritizes timely follow-up and medication adjustments to avoid clinical inertia.[2] Penn Medicine Lancaster General Health is unique in that it has 15 primary care sites with clinical pharmacists who practice under collaborative drug therapy management (CDTM) agreements to manage many chronic disease states, including diabetes.

Clinical pharmacists play a critical role in the multidisciplinary care team, given their medication knowledge, ability to assist providers in achieving patient care goals, and potential to assist in increased GLP-1 RA and SGLT2 inhibitor use.[10] This study was completed to evaluate the utilization of medications with cardiovascular benefit in patients with T2DM and established ASCVD to identify patient populations where future care team collaboration with clinical pharmacists could be beneficial.

METHODS

Study Design

This study was a retrospective, descriptive cross-sectional study conducted in March 2023 using the electronic health record (EHR) looking at charts dated from October 2020 to March 2023. Patients were identified for inclusion if they were 1) managed within an LGHP practice, and 2) diagnosed with T2DM and established ASCVD. The former was defined as having two consecutive A1C values >8% at any point within the study period. The most recent A1C was collected at the time of chart review and reported as >7% or >8% only for the patients not prescribed an SGLT2 inhibitor or GLP-1 RA. A1C values were not trended in this study.

ASCVD was defined as either coronary heart disease (coronary artery disease, coronary atherosclerosis, angina, ischemic heart disease), cerebrovascular disease (ischemic stroke, transient ischemic attack, cerebral vascular accident, cerebral infarction), or peripheral artery disease (atherosclerosis of arteries of extremity with or without claudication, artery occlusion). Patients were excluded if they were younger than 18 years old, pregnant, or on hemodialysis.

Demographics, insurance, A1C values, estimated glomerular filtration rate (eGFR), and LGHP practice location were also collected. Past medical history was obtained via diagnosis codes or International Classification of Diseases, 10th revision (ICD-10) codes within the EHR and included chronic kidney disease, heart failure, pancreatitis, medullary thyroid cancer, multiple endocrine neoplasia syndrome type 2, and diabetic ketoacidosis. The past medical history was chosen by the investigators, as it was hypothesized that

ABSTRACT

Purpose: This study was completed to evaluate the use of medications with cardiovascular benefit in patients with type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) in the Penn Medicine Lancaster General Health system.

Methods: A retrospective, descriptive cross-sectional study was conducted in March 2023 using the electronic health record (EHR) looking at charts dated from October 2020 to March 2023. Patients were 18 years of age or older, diagnosed with both T2DM and ASCVD, had two consecutive glycosylated hemoglobin (A1C) values >8% at any point within the study period, and managed within Lancaster General Health Physicians (LGHP) practices. The primary endpoint of this study was to determine the percentage of patients with T2DM with an A1C >7% or >8%, based on their most recent A1C, and established ASCVD who were not on a sodium-glucose cotransporter-2 (SGLT2) inhibitor or glucagon-like peptide-1 receptor agonist (GLP-1 RA). Secondary endpoints included the percentage of that subset who were not currently prescribed an SGLT2 inhibitor or GLP-1 RA and on both basal and bolus insulin, the percentage of patients meeting the diagnostic criteria on three or more oral agents, and the percentage of patients meeting the diagnostic criteria who have Medicaid as their primary insurance coverage. The percentage of patients currently prescribed each antihyperglycemic pharmaceutical subclass was also evaluated.

Results: A total of 1,507 patients were included in this study. Of these, 1,102 patients (73.1%) were currently prescribed an SGLT2 inhibitor and/or GLP-1 RA. Of the 405 patients who were not currently prescribed either of these agents, 346 (85.4%) had an A1C >7% and 244 (60.2%) had an A1C >8%. Of the 405 patients not prescribed either an SGLT2 inhibitor or GLP-1 RA, 28.1% were prescribed a basal and bolus insulin regimen, 9.4% were prescribed three or more oral agents, and 4.2% had Medicaid as their primary insurance coverage. Metformin and insulin were prescribed most often among the 1,507 patients in the study, with 895 (59.4%) and 888 (58.9%) patients having active prescriptions for these agents, respectively.

Conclusion: Overall, there is utilization of SGLT2 inhibitor and/or GLP-1 RA agents in the majority of patients reviewed with T2DM and ASCVD within the LGHP practices. However, there are still many patients with diabetes and ASCVD who are not currently prescribed either medication class of interest.

different histories might affect the prescribing of either an SGLT2 inhibitor or a GLP-1 RA. The study was approved by the Lancaster General Health Institutional Review Board on December 12, 2022.

Study Outcomes

The primary endpoint of this study was a determination of the percentage of patients with T2DM and ASCVD who are not currently prescribed an SGLT2 inhibitor or a GLP-1 RA. We hypothesized that the majority of patients managed by LGHP practices would be prescribed an SGLT2 inhibitor and/or a GLP-1 RA. Secondary endpoints included the percentage of patients not prescribed an SGLT2 inhibitor or a GLP-1 RA who were prescribed a basal and bolus insulin regimen, which consisted of a basal insulin and up to four bolus insulin injections; the percentage of patients prescribed three or more oral agents; and the percentage of patients who had Medicaid as their primary insurance. The percentage of patients prescribed each antihyperglycemic pharmaceutical subclass was also analyzed.

Analyses

Descriptive statistics were used to report baseline characteristics and the percentage of patients currently prescribed either an SGLT2 inhibitor and/or a GLP-1 RA. Logistic regression modeling was performed to determine the odds of being prescribed either medication class of interest. The analysis included variables of interest, either demographic or related to the primary outcome, to determine the effect on the odds of being prescribed either of these agents. The significance level was set to $\alpha = 0.05$ for all statistical analyses. Multiple

Table 1. Baseline Characteristics Between Patients Prescribed a Drug Class of Interest vs. Not

	Prescribed an SGLT2 inhibitor and/or GLP-1 RA (n = 1,102)	Not prescribed an SGLT2 inhibitor and/or GLP-1 RA (n = 405)
Mean age — yr ± SD	66.5 ± 10.9	71.3 ± 12.1
Male sex — no. (%)	659 (59.8)	228 (56.3)
Race — no. (%)		
White	960 (87.1)	366 (90.4)
Black or African American	50 (4.5)	15 (3.7)
Other	92 (8.3)	24 (5.9)
Ethnicity — no. (%)		
Non-Hispanic/Latino	945 (85.8)	371 (91.6)
Hispanic/Latino	151 (13.7)	30 (7.4)
Not reported	6 (0.5)	4 (1.0)
Insurance — no. (%)		
Commercial	325 (29.5)	92 (22.7)
Medicaid	99 (8.7)	17 (4.2)
Medicare	664 (60.3)	287 (70.9)
Other	17 (1.5)	9 (2.2)
Past Medical History — no. (%)		
Chronic Kidney Disease	493 (44.7)	202 (49.9)
eGFR <30 mL/min/1.73²+	111 (10.1)	60 (14.8)
Heart Failure	397 (36.0)	134 (33.1)
Pancreatitis	38 (3.4)	15 (3.7)
History of Medullary Thyroid Cancer	8 (0.7)	6 (1.5)
Multiple Endocrine Neoplasia Type 2	0 (0.0)	0 (0.0)
Diabetic Ketoacidosis	45 (4.1)	21 (5.2)

+At any time within the study period.
SD = standard deviation; eGFR = estimated glomerular filtration rate; SGLT2 = sodium-glucose cotransporter-2; GLP-1 RA = glucagon-like peptide-1 receptor agonist

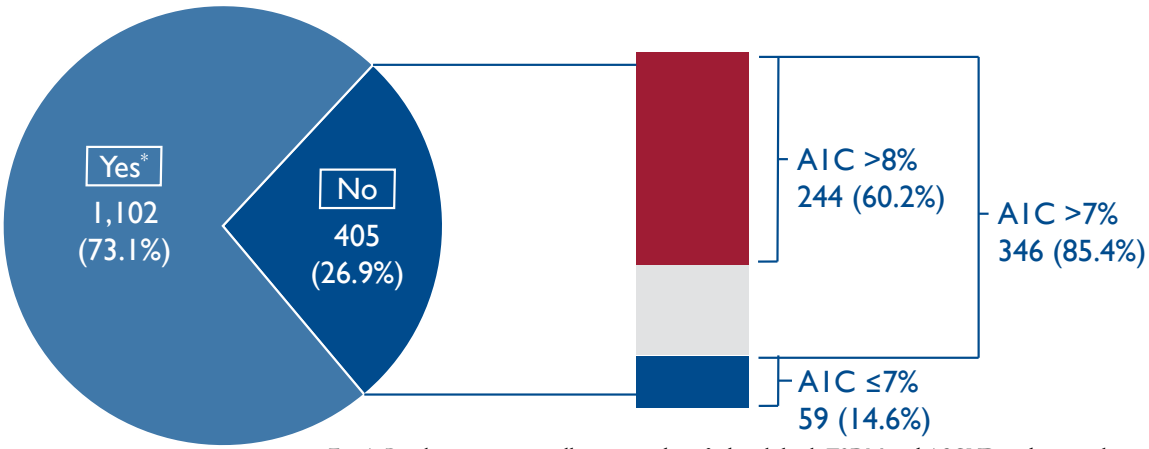

Fig. 1. Pie chart represents all patients identified with both T2DM and ASCVD and currently prescribed an SGLT2 inhibitor and/or GLP-1 RA. Stacked bar chart demonstrates that of the 405 patients not prescribed either an SGLT2 inhibitor or a GLP-1 RA during the study period, most had an A1C above 8% (n = 1,507).

models were performed to describe the adjusted odds ratio of the primary outcome. As this was an exploratory retrospective study, no sample size calculations were completed *a priori*.

RESULTS

Baseline Characteristics

Baseline characteristics are depicted in Table 1. Of the patients who were prescribed a GLP-1 RA or an SGLT2 inhibitor, most had either commercial insurance or Medicaid as their primary insurance carrier as opposed to Medicare. More patients who were prescribed an agent of interest had a diagnosis code consistent with heart failure than did those not prescribed an agent of interest. Patients who were not prescribed either agent of interest were more likely to have Medicare as their primary insurance carrier, a diagnosis code consistent with chronic kidney disease, and a history of an eGFR <30 mL/min/1.73 m^2.

Primary Outcome

Of the 1,507 patients included in this study, 1,102 (73.1%) were prescribed either an SGLT2 inhibitor and/or a GLP-1 RA. Of the 405 patients not prescribed either of these classes, 346 (85.4%) had an A1C >7% and 244 (60.2%) had an A1C >8% most recently (see Fig. 1).

For this analysis, two different A1C cutoffs were described because the quality metric goal in the LGHP organization is an A1C <8% for all patients; however, the ADA guidelines recommend an A1C <7% for most patients. Patient-specific A1C goals were not collected, so both cutoffs were reported.

Secondary Outcome

Of the 405 patients not prescribed either an SGLT2 inhibitor or a GLP-1 RA, 114 patients (28.1%) were prescribed a basal-bolus insulin regimen. Additionally, 38 patients (9.4%) were prescribed three or more oral antihyperglycemic agents, which most commonly included metformin, a sulfonylurea, a DPP-4 inhibitor, and/or pioglitazone. Finally, 17 patients (4.2%) had Medicaid as their primary insurance coverage.

Of the 1,507 patients with indications, not all were prescribed an antihyperglycemic medication. A total of 1,439 patients were prescribed at least one antihyperglycemic medication. Metformin and insulin were the most commonly prescribed medications, appearing in the charts of 895 (62.2%) and 888 patients (61.7%) respectively, followed by GLP-1 RAs and SGLT2 inhibitors in the charts of 767 (53.3%) and 637 (44.3%) patients respectively (see Fig. 2 on page 6).

An additional exploratory endpoint of patients not prescribed either medication class of interest revealed 74 patients (18.3%) were prescribed a DPP-4 inhibitor and almost 90% of this subset had an A1C >7% most recently.

Adjusted Analysis

Adjusted logistic regression analyses were performed to identify characteristics associated with an increased or decreased likelihood of being prescribed an SGLT2 inhibitor or GLP-1 RA while controlling for covariates (see Table 2 on page 7). There were two models performed for the final analysis.

For the first model, neither ethnicity nor type of insurance was associated with a difference in the likeli-

hood of being prescribed an SGLT2 inhibitor or GLP-1 RA when adjusted for age. When adjusted for ethnicity and insurance, each additional increase of one year in age was associated with a 7% decrease in the odds of a participant being prescribed either medication class of interest (OR 0.93; 95% confidence interval [CI] 0.92 to 0.94; p-value <0.005).

For the second model, age, eGFR <30 mL/min/m^2, a history of chronic kidney disease, and a history of heart failure were included as the variables of interest. When adjusted for age, neither having an eGFR <30 mL/min/m^2 nor a history of chronic kidney disease was associated with a likelihood of being prescribed either medication class of interest. Having a history of heart failure increased the odds of being prescribed either agent (OR 1.41; 95% CI 1.06 to 1.88; p = 0.019) when adjusted for age.

DISCUSSION

This study identified that the majority of patients with T2DM and ASCVD managed within the LGHP practices were prescribed an SGLT2 inhibitor and/or GLP-1 RA. However, there is still great potential to optimize therapy. Although the reasons for clinical inertia in this patient population were not explored in this study, previous studies have suggested this could be due to patient preference, comorbidities or risk factors, frailty of the patient, out-of-pocket medication costs, and provider preference or knowledge.[3-9] Based on the statistical analysis of this patient population, age seemed to correlate better than other variables with the odds of receiving either medication class of interest.

Clinical inertia may be due to patient preference. One hypothesis to explain this would be that patients may be reluctant regarding injectable medications.[3,5] However, we found that 30% of patients who were not prescribed an agent of interest were being prescribed an insulin regimen. By instead using a GLP-1 RA, patients might reduce the number of daily injections, their medication burden, and insulin requirements, while improving their cardiovascular risks.

Out-of-pocket costs may also be a barrier to initiation of these agents.[3,9] We could not prove this to be true, but did find that patients with Medicare had decreased odds of being prescribed either medication class of interest compared to patients who did not have Medicare. On the other hand, only 4% of patients who had Medicaid as their primary insurance coverage — and for whom the Pennsylvania Preferred Drug List covers these medications — were not prescribed one of these two classes. While only primary insurances were evaluated in this analysis, previous literature has demonstrated that patients with Medicaid as their secondary coverage may also have fewer out-of-pocket costs.[8]

An exploratory endpoint revealed 18% of patients not on either medication class of interest were

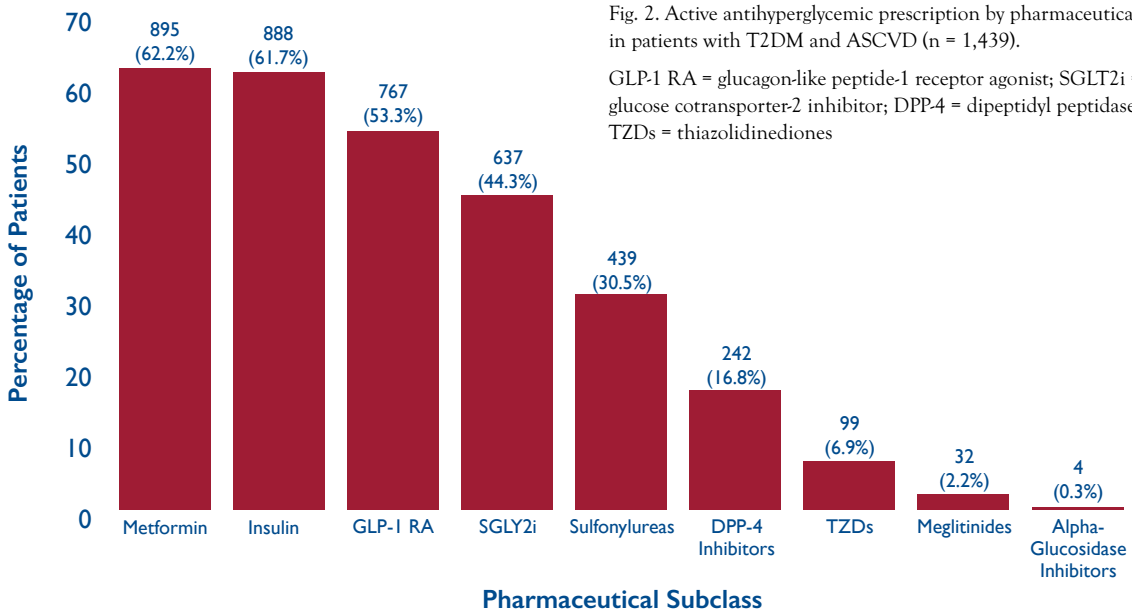

Fig. 2. Active antihyperglycemic prescription by pharmaceutical subclass in patients with T2DM and ASCVD (n = 1,439).

GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor; DPP-4 = dipeptidyl peptidase-4; TZDs = thiazolidinediones

Table 2. Unadjusted and Adjusted Logical Regression Model Showing the Variable Effect on the Odds of Being Prescribed Either an SGLT2 Inhibitor or a GLP-1 RA

Variable	Value	Unadjusted		Adjusted — Model 1		Adjusted — Model 2	
		OR [95% CI]	*p*-value	OR [95% CI]	*p*-value	OR [95% CI]	*p*-value
Age		0.93 [0.92, 0.94]	0.000*	0.93 [0.92, 0.94]	0.000*	0.93 [0.91, 0.94]	0.000*
Sex	Female	0.80 [0.63, 1.02]	0.075				
Race	Black or African American	1.39 [0.73, 2.65]	0.312				
	Other	1.71 [1.02, 2.88]	0.044*				
Ethnicity	Hispanic/Latino	2.06 [1.32, 3.20]	0.001*	1.50 [0.93, 2.35]	0.101		
Insurance	Commercial	2.09 [1.54, 2.83]	0.000*	0.90 [0.63, 1.30]	0.582		
	Medicaid	5.64 [2.58, 12.30]	0.000*	1.56 [0.64, 3.81]	0.329		
	Other	1.00 [0.41, 2.43]	0.997	0.50 [0.19, 1.34]	0.171		
eGFR <30 mL/min/1.73 m^2		0.60 [0.43, 0.85]	0.004*			0.73 [0.49, 1.09]	0.127
CKD		0.69 [0.55, 0.88]	0.003*			1.14 [0.85, 1.53]	0.389
Heart Failure		1.07 [0.93, 1.38]	0.597			1.41 [1.06, 1.88]	0.019*

**Statistically significant.*
OR = odds ratio; CI = confidence interval; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease

prescribed a DPP-4 inhibitor. This is notable because DDP-4 inhibitors do not have proven cardiovascular benefit and can be associated with higher costs. Patients could be transitioned to an SGLT2 inhibitor and/or GLP-1 RA and have improved glycemic control and additional cardiovascular benefit without incurring increased costs.

This study has some limitations. Since it is retrospective, data collection was limited to what was available in the EHR and therefore subject to recall bias. For patients prescribed an SGLT2 inhibitor or a GLP-1 RA, we were unable to confirm medication adherence. SGLT2 inhibitor and GLP-1 RA classes were analyzed as a whole rather than by the agents within these classes that have proven cardiovascular benefit. No power analysis was performed prior to this study for the statistical analysis, so it is unknown if this study was appropriately powered to detect a statistically significant difference; however, the odds ratio can provide trends in the data collected.

There are likely many patients with T2DM and cardiovascular disease who were not identified by the rather strict criteria used here, including a search for two consecutive A1C values above 8%. Finally, a history of allergic reaction or intolerance to SGLT2 inhibitors or GLP-1 RA was not analyzed in the patients who were not prescribed either of those agents.

The ADA guidelines recommend an SGLT2 inhibitor and/or GLP-1 RA should be utilized in all patients with established ASCVD or at high risk of ASCVD regardless of their A1C. Findings from this study showed clinical inertia may still be present in patients with T2DM and ASCVD regardless of glycemic control. Although not established during the course of this investigation, there could be several reasons for clinical inertia, including patient preference, provider preference, time constraints, or cost barriers, among others.[3-7]

The ADA recommends that a multidisciplinary team approach be employed to help achieve patient care goals and avoid clinical inertia.[2] Clinical pharmacists have the drug therapy knowledge and are uniquely positioned as part of the multidisciplinary team to focus on time-intensive management in between visits

with the patient's provider. Future research should be done to determine the benefit of a clinical pharmacist as part of the team-based care approach to assist in overcoming clinical inertia, increase access to these agents, and assist in the achievement of patient care goals.

CONCLUSION

Overall, the majority of patients within the LGHP practices diagnosed with T2DM and ASCVD were prescribed an agent with cardiovascular benefit. However, our study demonstrates clinical inertia is still present and identifies opportunities to optimize therapy with either an SGLT2 inhibitor or a GLP-1 RA.

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Meredith N. Clark, PharmD
Penn Medicine Lancaster General Health
555 N. Duke St.
Lancaster, PA 17601
717-544-8638
Meredith.Stoeckl2@pennmedicine.upenn.edu

Andrea Dooley-Wood, PharmD, BCACP
Penn Medicine Lancaster General Health
631 N. Duke St.
Lancaster, PA 17602
717-544-8633
Andrea.DooleyWood@pennmedicine.upenn.edu

Nafisa Khan, PharmD
Penn Medicine Lancaster General Health
555 N. Duke St.
Lancaster, PA 17601
717-419-8293
Nafisa.Khan@pennmedicine.upenn.edu

Mara Moore, PharmD, BCACP
Penn Medicine Lancaster General Health
631 N. Duke St.
Lancaster, PA 17602
717-544-4056
Mara.Moore@pennmedicine.upenn.edu