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Evaluating Cardiometabolic Risk Management in Multiethnic Adult Patients with Diabetes in the UCI Health System

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

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DEDICATION

To my parents

For always supporting me with unconditional love

To my friends

For reminding me to smile even during challenging times

To my mentors

For helping me achieve things that even I did not think were possible

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ABSTRACT OF THE THESIS

Evaluating Cardiometabolic Risk Management in Multiethnic Adult Diabetic Patients in the UCI Health System

by

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Master of Science in Biomedical and Translational Science

University of California, Irvine

Professor Nathan D. Wong, Chair

Atherosclerotic Cardiovascular Disease (ASCVD) remains the leading cause of death in diabetes mellitus (DM) adult patients. I investigated the current status of ASCVD and DM risk factor control for DM adult patients in the UCI health system, stratified by sex, race/ethnicity, and ASCVD status, A total of 34,207 DM adult patients were identified in the UCI electronic health records (EHR) through ICD-10 code during the timeframe of January 1st, 2022 – June 30th, 2023. Of these patients, within a year after their last DM diagnosis, while 91.3% received a blood pressure (BP) measurement, only 55.3% received a hemoglobin A1c (HbA1c) measurement and less than 50% received any kind of lipid profile measurement (total cholesterol, HDL-C, LDL-C, and triglycerides). Only 56.5% of patients were on any kind of DM drugs, with just 34.1% on metformin, even lower (29.6%) for patients with ASCVD. Only 15.6 % and 10.7% were on newer DM therapies of SGLT2i and GLP1-RA drugs, respectively. Only 46.6% were on statins, and non-statin use was infrequent (<3%). Statin usage was much higher in DM patients with ASCVD (72.5%) than those without (38.7%). 84.6% of DM patients reached control for BP. 94.0% of DM patients with ASCVD reached target control for BP, which was significantly higher compared to 81.6% for DM patients without ASCVD ($p<0.00001$). However, only 48.9% were at target control for HbA1c, 23.0% for LDL-C and 10.1% for composite control (HbA1c + BP + LDL-C). Some of these findings differed by race/ethnicity,

such as only 36.4% of Hispanic patients being at target control for HbA1c, compared to 48.9% for the overall sample. A substantial number of DM patients in the UCI EHR are not receiving recommended risk factor measurements and treatment. Improving the frequency of yearly testing and drug therapies in these patients could prove invaluable in optimizing care in DM patients.

CHAPTER 1: INTRODUCTION

Atherosclerotic Cardiovascular disease (ASCVD) events, including myocardial infarction, stroke, peripheral arterial disease, and heart failure, remain the leading causes of death in adult diabetes mellitus (DM) patients.[1] While glycemic control is frequently the key target of treatment for many with DM, other cardiometabolic risk factors, including lipid levels such as LDL-C and blood pressure (BP) frequently go inadequately addressed. Controlling these additional factors together with hyperglycemia can have a significant impact on improving cardiovascular outcomes.

In addition, the proportion of individuals receiving yearly testing of DM and ASCVD risk factors, such as BP, hemoglobin A1c (HbA1c), and LDL-C, must be increased.[2] Moreover, use of newer DM therapies including SGLT-2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP1-RA), which have been shown to improve cardiovascular outcomes more than the common DM therapy metformin, remain highly underutilized.[3] Many patients are not at target recommended levels for BP, LDL-C, and HbA1c as well.[4]

There also remain significant disparities, particularly across race/ethnicity in composite cardiovascular risk factor control and use of newer therapies for DM management. Asian, Black, and Hispanic patients tend to differ substantially from White patients in both DM and ASCVD prevalence.[5] The goal of this project is to examine the frequency of regular testing, drug therapies, and target control for ASCVD and DM risk factors within the UCI Health system. Furthermore, all these findings will be stratified by ASCVD status to examine any disparities. The target control findings will further be stratified by sex and race/ethnicity. This study can identify the current areas of improvement in DM treatment, and if addressed over the coming years, can significantly reduce ASCVD mortality in DM patients.

Specific Aim #1: Determine the proportion of adult DM patients who have received key ASCVD and DM risk factor measurements within a year after their last DM diagnosis and stratify by ASCVD status in the UCI Health system.

Hypothesis #1: A significant proportion of adult DM patients will not have received ASCVD and DM risk factor measurements within a year after their last DM diagnosis. There will be significant differences between patients with and without ASCVD.

Specific Aim #2: Quantify the prevalence of use of lipid-lowering drug and DM drug therapy in the sample of adult DM patients and stratify by ASCVD status in the UCI Health system.

Hypothesis #2: Many patients will not be on guideline-recommended statin therapy or newer DM therapeutic options (SGLT2-I or GLP1-RA). There will be significant differences between patients with and without ASCVD in the UCI Health system.

Specific Aim #3: Determine how many DM patients are at recommended LDL-C levels (<70 mg/dl, for without ASCVD or <55 mg/dl with), BP levels (<130/80 mmHg), and HbA1c targets (<7%) and stratify by ASCVD status in the UCI Health system.

Hypothesis #3: There will be suboptimal control of LDL-C, BP, and HbA1c individually. Furthermore, few patients will be at recommended levels for LDL-C, BP, and HbA1c simultaneously, known as target control. There will be significant differences between patients with and without ASCVD.

Specific Aim #4: Further stratify the target control findings by sex and race/ethnicity among DM patients in the UCI Health system.

Hypothesis #4: There will be significant sex/race/ethnicity disparities in the control outcomes.

CHAPTER 2: BACKGROUND

Diabetes mellitus (DM) is a metabolic condition that plagues more than 1 in 10 of the population worldwide. By 2045, it is projected to affect 1 in 8 people.[6] DM manifests in two types. Type 1 DM, which accounts for only about 6% of DM cases, involves an autoimmune reaction where the body destroys its own beta cells, the cells responsible for making insulin. Insulin is a vital hormone that helps control blood sugar. T1DM is often attributed to genetic or viral causes.[7] Type 2 DM, which accounts for the rest of DM cases, is characterized by insulin resistance, where the body requires higher than average levels of insulin to produce normal blood sugar control. Insulin resistance often develops due to high amounts of blood sugar entering the body over a long period of time, caused by poor eating habits or a lack of physical activity. As such, unlike T1DM, T2DM is largely preventable, and a healthy diet and proper exercise can help prevent the onset of insulin resistance.[8]

Patients with DM will tend to have excessive amounts of glucose in the bloodstream, known as hyperglycemia. This hyperglycemia weakens the body as whole and can lead to heart conditions. Atherosclerotic Cardiovascular disease (ASCVD), specifically myocardial infarction (MI), is the leading cause of death in DM patients.[1] An electronic health records (EHR) study conducted examined DM mortality over the last 11 years and found that 30.5% of the deaths were attributed to ASCVD, which was the highest of any individual cause.[9] Furthermore, an EHR study in the US found that DM patients have a 53% higher risk of MI compared to the non-DM population.[10] As such, proper treatment of DM may also involve the proper treatment of ASCVD as well.

ASCVD risk, which tends to increase with the onset of DM, is primarily associated with a high concentration of lipids in the bloodstream, namely low-density lipoprotein cholesterol

(LDL-C). An excess of lipids in the body is known as dyslipidemia. Chronic dyslipidemia can lead to the buildup of plaque in blood vessels. A completely blocked blood vessel can cut off blood flow to the heart, causing MI, also known as a heart attack.[11] A 2023 EHR study conducted in the US found that only 50.6% of DM patients had their LDL-C at recommended levels, and 55.2% of DM patients had LDL-C above the non-DM population.[12] In a similar study conducted by the Diabetes Collaborative Registry, only 48.6% of patients reached recommended LDL-C values.[13] This draws attention to the importance of evaluating ASCVD risk factors like LDL-C in DM patients. An EHR study conducted in the US Veterans Affairs Healthcare System found that ASCVD mortality was significantly higher in DM patients with hemoglobin A1c (HbA1c) that exceeded 7%.[14] As such, to effectively manage ASCVD-related mortality in DM patients, their cholesterol and glucose should both be effectively controlled.

To help control LDL-C and HbA1c levels in DM patients, drug therapy usage needs to be optimized. Statins are commonly prescribed cholesterol-lowering drugs that can reduce LDL-C levels in the bloodstream by more than 50%.[15] However, an EHR study of 2011-18 US patients found that only 51.1% of eligible patients were on any kind of statin therapy.[16] In terms of DM therapies, metformin is a common and effective therapy, prescribed to over 150 million patients worldwide. However, adherence to metformin is suboptimal, as a meta-analysis study examining 1.6 million DM patients found that it had the lowest adherence of any of several DM drug classes examined, including SGLT2i and GLP1-RA drugs, both of which are newer therapies. Lack of adherence in metformin was typically associated with side effects, notably diarrhea and flatulence.[17]

A meta-analysis among T2DM patients found that SGLT2i decreased fasting plasma glucose more significantly than metformin showed similar benefits for other DM criteria like

HbA1c. Furthermore, SGLT2i significantly reduced some ASCVD criteria like weight and blood pressure more than metformin. It was also shown to not cause the same kind of gastrointestinal side effects that metformin did.[18] Another meta-analysis was conducted in DM patients comparing GLP1-RA drugs to metformin, and the former was shown to significantly improve insulin sensitivity and lower BMI compared to the latter, while matching it in all other criteria.[19] Recent studies conducted at UCI can attest to the effectiveness of GLP1-RA drugs in not just DM factors, but also ASCVD risk. Our recent NHANES study examining patients from 2015-18 found that Semaglutide 2.4 mg weekly can prevent over 1.5 million ASCVD events across the US.[20] SGLT2i and GLP1-RA drugs, with their similar, if not superior benefits compared to metformin, also do not possess the same side effects, potentially leading to improved retention when prescribed. Despite this shining evidence however, SGLT2i and GLP1-RA use is only 5.8% and 4.4% in T2DM patients, respectively.[21] Increasing this prevalence could reduce ASCVD risk in DM patients as well as adherence to drug therapies.

In addition to the prescription of drug therapies, regular testing of DM and ASCVD risk factors is invaluable in effectively tracking changes in health over time. DM patients are recommended to obtain HbA1c measurements twice a year. However, the prevalence of DM patients who undergo HbA1c testing even once a year is only 64.6%.[22] Furthermore, DM patients who are at risk or have been diagnosed with ASCVD often do not undergo regular LDL-C testing. Cholesterol treatment guidelines recommend a regular lipid measurement at least yearly for those at high risk of ASCVD or with existing ASCVD. An EHR study conducted in the US examining DM patients from 2008-19 found that only around 52% of patients received any kind of LDL-C testing within a year of their latest DM diagnosis.[23] Blood pressure (BP) testing at least once a year is also essential, as 73.6% of DM patients are reported to have

hypertension (BP > 130/80 mmHg).[24] Testing of BP, HbA1c, and LDL-C at least once a year could ensure proper tracking of DM and ASCVD risk factors over time.

There exist large discrepancies in drug usage between DM patients who have ASCVD and those who do not. Roughly 70% of DM patients with ASCVD are on statins compared to only 37% of DM patients without ASCVD[3]. Comparing these two groups for numerous DM and ASCVD drug types could provide insight on the potential gaps in drug usage. Furthermore, more insight is required into the differences in yearly risk factor screening and target control between DM patients with ASCVD and those without.

Sex and race/ethnic disparities also exist among DM patients. Roughly 18 million more males have DM compared to females, but an EHR study conducted in the US in 2023 showed that female DM patients have a higher relative risk of ASCVD and ASCVD mortality compared to male DM patients.[25] Racial disparities are even more apparent. The prevalence of T2DM in Asian, Black, and Hispanic patients is 9.0%, 13.2%, and 12.8% respectively, all of which are higher than the non-Hispanic White prevalence of 7.6%. In certain Native American groups, DM prevalence can be as high as 24.1%.[26] In addition to the higher prevalence of T2DM in non-White racial groups, what makes these facts more concerning is data showing that very few studies exist that examine T2DM in these populations, with <20% having separately stratified data for Asian, Black, and Hispanic patients.[27] Due to variations in DM prevalence, it is essential to ensure that all studies investigating DM in diverse populations should be stratified by different racial groups.

Overall, the enhanced risk of ASCVD, the low use of drug therapies, the lack of regular testing, and sex/racial/ethnic disparities among DM patients must be addressed.

CHAPTER 3: METHODS

This project first identified the number of adult patients from the UCI electronic health records (EHR) with an ICD-10 code for DM in the time frame of January 1st, 2022 – June 30th, 2023. The sample was then stratified by patients who have ASCVD and those who do not. Thus, three groups were created: the overall sample, patients with ASCVD, and patients without ASCVD. Descriptive statistics were gathered for each of these groups, such as age, sex, and race/ethnicity, as well as the proportion of the comorbidities heart failure (HF) and chronic kidney disease (CKD).

This study looked exclusively at adult DM patients, within the timeframe of January 1st, 2022 – June 30th, 2023. Exclusion criteria were simply UCI EHR patients out of the timeframe, those who did not have DM, or those who were below 18 years of age. Analysis was performed using SQL programming, using the vocabulary SNOMED, following the guidelines of UCI OMOP. Specific concept codes were identified for various laboratory procedures, HbA1c measurement for example, and patients were identified who had a record of said concept codes.

We examined the proportion of patients who received blood pressure [including systolic (SBP) and diastolic (DBP)], serum glucose, serum creatinine, HbA1c, microalbumin, or lipid profile (triglycerides, total cholesterol, HDL-C, and LDL-C) measurements within a year after their last DM diagnosis. This was compared across all three groups, with p-values calculated using a Chi-square test of proportion to compare between patients with and without ASCVD. Furthermore, the number of patients on statins, non-statin ASCVD therapies (e.g. ezetimibe, fibrates), mainstream DM therapies, such as metformin and insulin, and newer DM therapies (SGLT2i or GLP1-RA) was calculated for each of the three groups. Similarly, the drug therapies prevalence was also compared between patients with and without ASCVD, with p-values calculated with a Chi-square test of proportions to determine statistically significant differences.

In addition, of those who had measurements within the last year, individuals with LDL-C, HbA1c, and BP levels at target control were identified, stratified by sex, race/ethnicity, and presence of ASCVD or not. LDL-C control was defined as <70 mg/dl, or <55 mg/dl if the patient has ASCVD, as established by recent ADA standards of care. HbA1c control was defined as <7.0%, and BP control was defined as <130/80 mmHg[28]. Lastly, the proportion of patients at composite control (at control for LDL-C, HbA1c, and BP) was determined. Once again, a chi-square test was performed to compare target control between patients with ASCVD and without.

To determine sex/ethnic/racial disparities in the target control data, all findings were stratified by sex/race/ethnicity, and p-values were calculated with a Chi-square test of proportions to determine statistically significant differences, to compare between sexes, and among ethnicity/race. For the ethnic/race comparisons, since multiple groups are being compared, a Bonferroni Correction was also made.

CHAPTER 4: RESULTS

Sample Selection:

The eligible sample was first determined (Figure 1). From an initial population of 278,474 UCI patients in the timeframe (January 1st, 2022 – June 30th, 2023), 34,207 (13.6%) adult DM patients were eligible for the study. The 13.6% prevalence of DM was slightly higher than the national average of 11.6%[1]. Patients excluded were simply those who were out of the timeframe, not adults (<18), or who did not have an ICD-10 Code for DM. The sample was further stratified by patients with and without ASCVD, resulting in 7,992 patients with ASCVD, and 26,215 without. This amounts to a 23.4% prevalence of ASCVD in DM patients, as well as a 42.8% prevalence of DM in ASCVD patients.

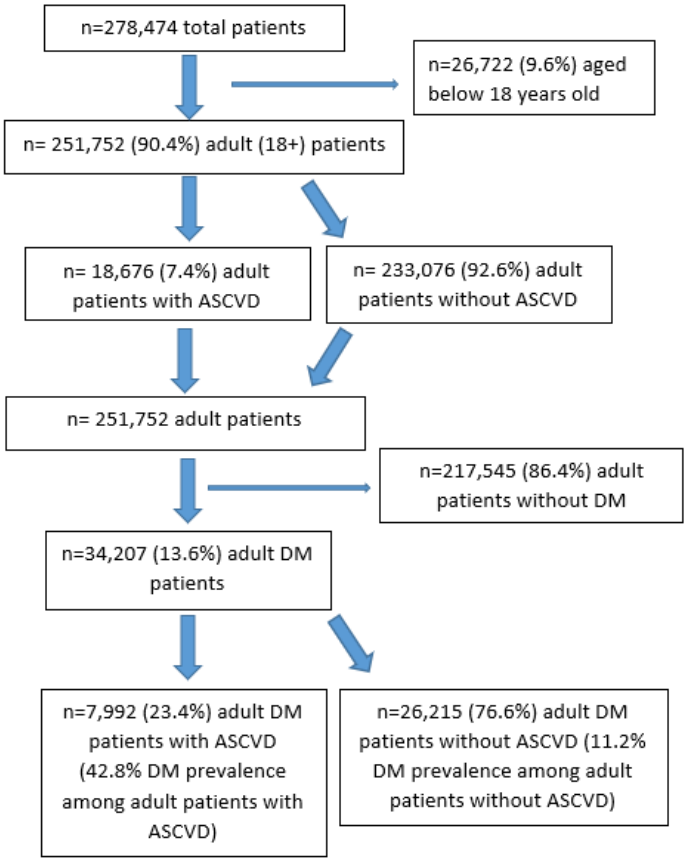


Figure 1. Eligible Sample Flowchart

Descriptive Statistics:

The mean age of the overall sample was 62±15.8 years, higher in ASCVD patients (69±12.4 years) and lower in those without (59±15.9 years) (Table 1). Male and female proportions were roughly equal in the overall sample and those without ASCVD but were not equal in the ASCVD sample (38.1% female proportion). White was the predominant race/ethnicity in the overall sample (52.9%), but a significantly higher percentage of Hispanic (37.4%) and Asian (18.3%) sample was noted, compared to the national average of 19.1% and 6.3%, respectively. A Black proportion of 2.9% was reported, much lower than the national average of 13.6%. This is due to variations in the racial makeup of Orange County and surrounding areas served by UCI Health, compared to the US population[27]. HF and CKD prevalence in the overall sample was 9.6% and 19.4%, respectively, the patients with ASCVD having higher prevalence of both conditions (26.4% and 36.7% respectively) comparatively. However, all of these were lower than the national averages of 15.5% and 38.3%, respectively.[29]

	Overall	ASCVD	No-ASCVD
Sample Size (n)	34,207	7.992	26,215
Age (yr)	62.0 ± 15.8	69.0 ± 12.4	59.0 ± 15.9
Female (%)	16,962 (49.6%)	3,043 (38.1%)	13,919 (53.1%)
Race (%)			
Whites	18,110 (52.9%)	4,136 (51.8%)	13,974 (53.3%)
Black or African American	986 (2.9%)	255 (3.2%)	731 (2.8%)
Asian	6,259 (18.3%)	1,704 (21.3%)	4,555 (17.4%)
American Indian or Alaska Native	100 (0.3%)	15 (0.2%)	85 (0.3%)
Native Hawaiian or Other Pacific Islander	206 (0.6%)	59 (0.7%)	147 (0.6%)
Multirace	1542 (4.5%)	400 (5.0%)	1,142 (4.4%)
Other Race	6,045 (17.7%)	1,301 (16.3%)	4,744 (18.1%)
Unknown	959 (2.8%)	122 (1.5%)	837 (3.2%)
Ethnicity (%)			
Hispanic or Latino	12,780 (37.4%)	2,460 (30.8%)	10,320 (39.4%)
Not Hispanic or Latino	20,569 (60.1%)	5,399 (67.6%)	15,170 (57.9%)
Unknown	858 (2.5%)	133 (1.7%)	725 (2.8%)
Comorbidity (%)			
Heart Failure	3,299 (9.6%)	2,133 (26.4%)	1,186 (4.5%)
Chronic Kidney Disease	6,647 (19.4%)	2,934 (36.7%)	3,713 (14.2%)

Table 1. Descriptive Statistics of Sample (n=34,207/7,992/26,215)

DM and ASCVD Risk Factor Screening:

For DM patients, it is recommended to receive DM and ASCVD risk factor testing at least once annually[30]. In the current sample, BP testing was managed effectively, as 91.3% of the overall sample (Figure 2) received at least one BP test and was even higher for patients with ASCVD (97.3%). Furthermore, serum creatinine and serum glucose were also tested in most patients (77.8% and 77.6% respectively). However, surprisingly, 55.3% of patients received a HbA1c test in the overall sample, even lower (50.6%) in patients without ASCVD, despite it being a principal standard for DM diagnosis. A higher 70.9% of patients with ASCVD had hbA1c testing. Even worse, less than 50% of patients in the overall sample received lipid profile measurements of any kind in the last year. Once again, lipid measurements were more prevalent (>60%) in those with ASCVD but were very low in those without. The reason for this discrepancy is likely due to lipid management being the standard of care in treating ASCVD. However, even for patients without ASCVD, lipids still need to be measured at least yearly to lower ASCVD risk in these patients[31]. Furthermore, patients without ASCVD had statistically significantly ($p<0.00001$) lower annual screening frequencies compared to those with ASCVD in nearly all criteria.

	Overall		ASCVD		No ASCVD		p-values
	n	%	n	%	n	%	
SBP	31,247	91.3	7,777	97.3	23,470	89.5	<0.00001
DBP	31,247	91.3	7,777	97.3	23,470	89.5	<0.00001
Serum Creatinine	26,617	77.8	7,220	90.3	19,397	74.0	<0.00001
Serum Glucose	26,557	77.6	7,222	90.4	19,335	73.8	<0.00001
Hba1c	18,921	55.3	5,667	70.9	13,254	50.6	<0.00001
Triglycerides	16,108	47.1	5,062	63.3	11,046	42.1	<0.00001
Total Cholesterol	15,870	46.4	4,970	62.2	10,900	41.6	<0.00001
HDL-C	15,793	46.2	4,948	61.9	10,845	41.4	<0.00001
LDL-C	15,545	45.4	4,891	61.2	10,654	40.6	<0.00001
Microalbumin	10,241	29.9	2,342	29.3	7,899	30.1	0.157

Table 2. Annual DM and ASCVD Risk Factor Screening Frequency (n=34,207/7,992/26,215)

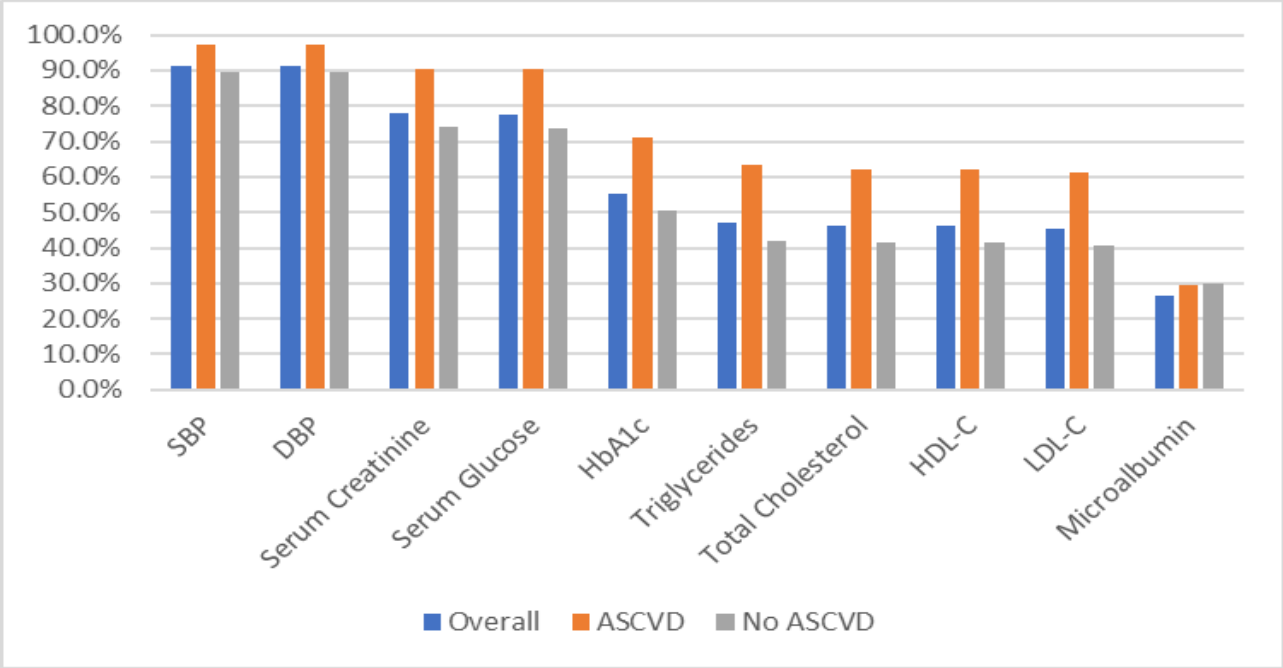


Figure 2. Annual DM and ASCVD Risk Factor Screening Frequency (n=34,207/7,992/26,215)

Drug Therapies:

Drug therapy frequency (Table 2) for the sample was also concerning. Only 56.5% of the patients in the overall sample were on any kind of DM drug: 34.1% were on metformin, 23.3% were on insulin, 15.6% and 10.7% were on newer DM therapies SGLT2i and GLP1-RA, respectively, and other therapies (e.g. sulfonylureas, DPP-4, MRA) had an even lower frequency (<10% for each). Interestingly, while patients with ASCVD generally had higher usage for most drugs compared to those without, their metformin usage was statistically significantly ($p<0.00001$) lower (29.6%) compared to the no ASCVD group (35.5%). This was contrasted by their much higher usage of insulin (34.4%) compared to the no ASCVD group (19.9%). As for lipid-lowering drugs, only 46.6% of the overall sample was on statins, and non-statin lipid lowering drugs were very infrequent (<3% for each). Unsurprisingly statin usage in patients with ASCVD was much higher (72.5%), due to it being the standard of care for ASCVD treatment. Conversely, only 38.7% of patients without ASCVD were on statins. Furthermore, patients without ASCVD had lower usage for all lipid-lowering drugs compared to those with ASCVD. The lack of use in drug therapies for both DM and ASCVD calls to attention a lack of efficient care management. Ensuring that all patients who are eligible for drug therapies receive their treatment would greatly improve both their DM and ASCVD treatment.

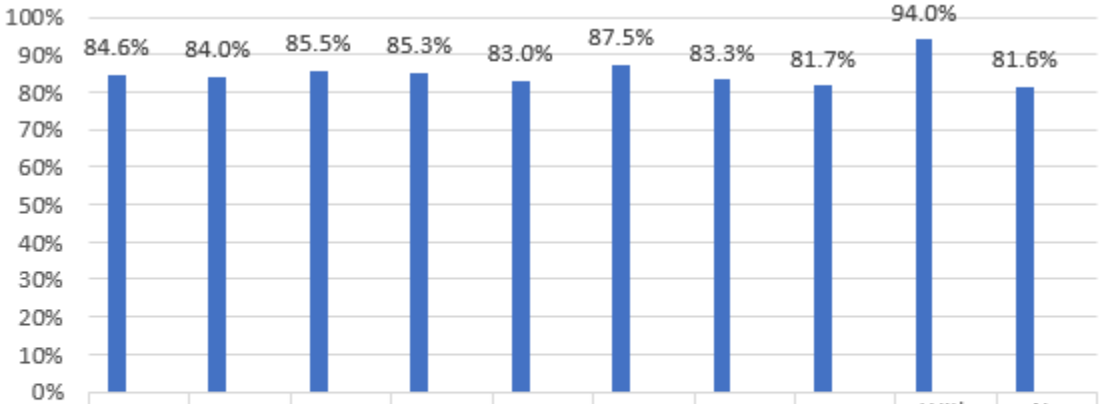
	Overall		ASCVD		No ASCVD		p-values
Diabetes Drugs	n	%	n	%	n	%	
Any Diabetes Drug	19,344	56.5	5,172	64.7	14,172	54.1	<0.00001
Metformin	11,663	34.1	2,363	29.6	9,300	35.5	<0.00001
Insulin	7,971	23.3	2,746	34.4	5,225	19.9	<0.00001
SGLT2i	5,342	15.6	1,675	21.0	3,667	14.0	<0.00001
GLP1-RA	3,654	10.7	876	11.0	2,778	10.6	0.356
Sulfonylureas	2,911	8.5	711	8.9	2,200	8.4	0.157
DPP-4	2,610	7.6	791	9.9	1,819	6.9	<0.00001
MRA	1,582	4.6	738	9.2	843	3.2	<0.00001
Thiazolidinediones	1,416	4.1	289	3.6	1,127	4.3	0.00729
Meglitinides	220	0.6	62	0.8	158	0.6	0.0902
AGI	83	0.2	22	0.3	61	0.2	0.0498
DRA	15	0.04	3	0.04	12	0.05	0.758
Lipid-Lowering Drugs							
Any Lipid-Lowering Drug	16,903	49.4	5,984	74.9	10,919	41.7	<0.00001
Statins	15,939	46.6	5,796	72.5	10,143	38.7	<0.00001
Ezetimibe	986	2.9	547	6.8	439	1.7	<0.00001
Fibrates	873	2.6	255	3.2	618	2.4	0.000035
Icosapent Ethyl	600	1.8	262	3.3	338	1.3	<0.00001
Pcsk9-i	299	0.9	210	2.6	89	0.3	<0.00001
Bile Acid Resins	88	0.3	32	0.4	56	0.2	0.00391
Niacin	53	0.2	21	0.3	32	0.1	0.00512
Bempedoic Acid	18	0.05	14	0.2	4	0.02	<0.00001

Table 3. Drug Therapies of Sample (34,207/7,992/26,215)

Target Control:

The final part of my analysis examined the proportion of patients in the sample that had reached proper control for BP, HbA1c, LDL-C, as well as composite control. LDL-C was chosen amongst the lipids as it is the most indicative of ASCVD risk[32]. These findings were stratified by sex, race/ethnicity, and ASCVD status.

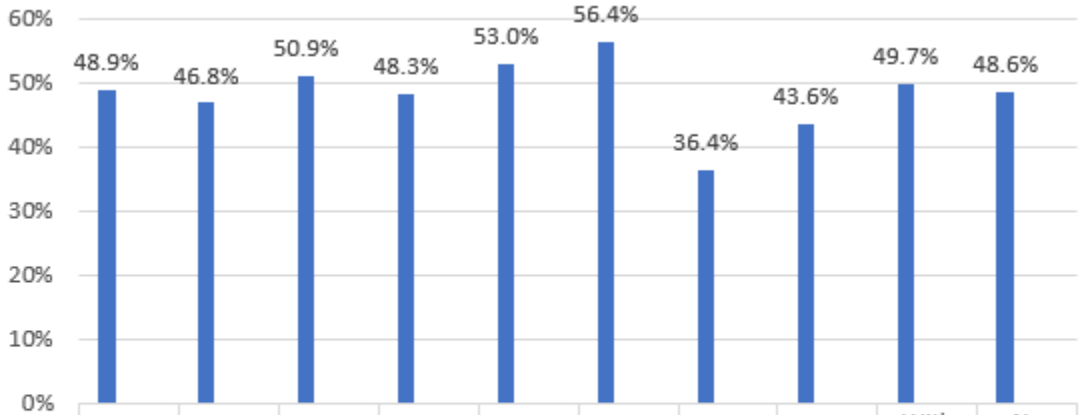
BP control (Figure 3a), defined as <130/80 mmHg, was effective, with 84.6% of the sample meeting the requirements, and was greater than 80% for all subgroups. Patients with ASCVD had an especially high BP control of 94.0%, statistically significantly ($p<0.00001$) higher than 81.6% control in patients without ASCVD, the lowest of any subgroup.



	Overall	Male	Female	White	Black	Asian	Hispanic	Other	With ASCVD	No ASCVD
% Control	84.6%	84.0%	85.5%	85.3%	83.0%	87.5%	83.3%	81.7%	94.0%	81.6%
n	31,579	15,977	15,615	16,673	902	5,905	12,141	8,112	7,777	23,802
p-value		0.00037		0.00001					0.00001	

Figure 3a. Blood Pressure Control (n=31,579)

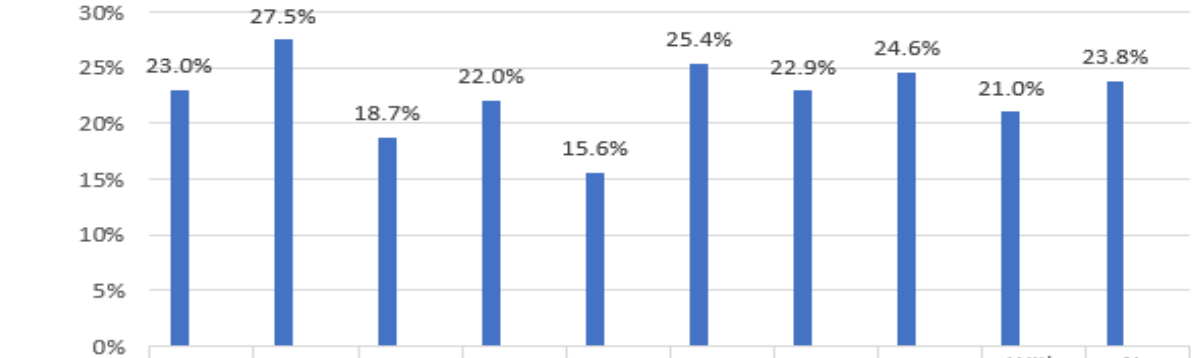
A patient is at target control for HbA1c if their reading is <7.0%. Real world data has shown that in the general populace, >70% of DM patients have HbA1c <7.0%[33,34]. The study sample was not as impressive however, with only 48.9% of patients at target control (Figure 3b). This could be attributed to the significant number of patients not on any kind of DM drug to help control their HbA1c levels. Variation existed between races, with Asian patients having a statistically significant ($p<0.00001$) higher control of 56.4%, and Hispanic patients having a statistically significant ($p<0.00001$) lower control of 36.4%. HbA1c control in patients with and without ASCVD was very similar to the overall, and there were no significant differences between the two groups. By ensuring proper prescribing of DM medication, these numbers could be significantly improved.



	Overall	Male	Female	White	Black	Asian	Hispanic	Other	With ASCVD	No ASCVD
% Control	48.9%	46.8%	50.9%	48.3%	53.0%	56.4%	36.4%	43.6%	49.7%	48.6%
n	20,071	10,248	9,853	10,814	562	3,875	8,297	4,850	5,667	14,404
p-value		0.00001		0.00001					0.13	

Figure 3b. Hemoglobin A1c Control (n=20,071)

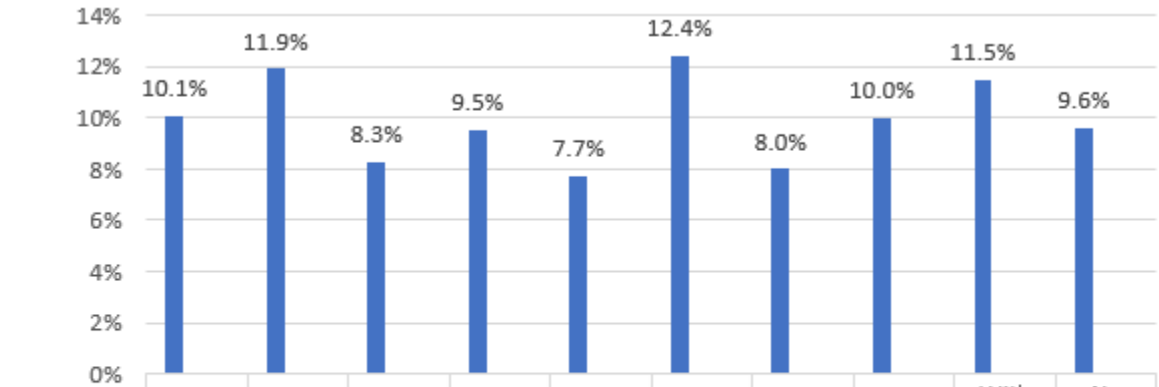
LDL-C control (<70 mg/dL, <55 mg/dL if with ASCVD) was even worse, with only 23.0% of the sample at control (Figure 3c). Black patients had an abysmally low control rate of only 15.6%. Female patients had a significantly ($p<0.00001$) lower control (18.7%) compared to males (27.5%). Patients with ASCVD had statistically significantly ($p<0.00001$) lower LDL-C control compared to those without ASCVD. A key reason for the very low target control % may lie in the recent change in cutoffs for LDL-C control. For example, a previous study conducted at UCI in 2019 investigating LDL-C control in DM patients found that 49% were at target control, significantly higher than that of this sample (23.0%).[35] However, in the previous UCI study, the target control cutoff was a more generous <100 mg/dL and <70 mg/dL if with ASCVD. More recent guidelines have set target control as <70 mg/dL and <55 mg/dL if with ASCVD. Applying the old target control cutoffs to this study sample, it was found that 47.5% were at target control, which waas not significantly different from the previous UCI study. While this serves as evidence that there is no significant negative change in LDL-C control since 2019, there has been no positive change either, and with the use of stricter target control cutoffs, treatment regimens need to be modified to aim for those.



	Overall	Male	Female	White	Black	Asian	Hispanic	Other	With ASCVD	No ASCVD
% Control	23.0%	27.5%	18.7%	22.0%	15.6%	25.4%	22.9%	24.6%	21.0%	23.8%
n	16,962	8,537	8,462	9,317	461	3,351	6,731	3,860	4,891	12,071
p-value		0.00001		0.00001					0.000077	

Figure 3c. LDL-C Control (n=16,962)

The composite control analysis evaluated patients who satisfied the control conditions for BP, HbA1c, and LDL-C. Unsurprisingly, this category had the lowest percentage of patients at control. Only 10.1% of the sample reached composite control (Figure 3d), and was even lower for subgroups, such as 7.7% for Black patients, and 8.0% for Hispanic patients. Patients without ASCVD had a statistically significant ($p<0.00032$) lower composite control compared to those with ASCVD. The low composite control values lie in the poor control of its components, namely HbA1c and LDL-C.



	Overall	Male	Female	White	Black	Asian	Hispanic	Other	With ASCVD	No ASCVD
% Control	10.1%	11.9%	8.3%	9.5%	7.7%	12.4%	8.0%	10.0%	11.5%	9.6%
n	15,988	8,062	7,926	8,737	431	3,136	6,531	3,684	4,663	11,325
p-value		0.00001		0.00001					0.000318	

Figure 3d. Composite Control (n=15,988)

Sex and race/ethnicity disparities were significant across the results. In terms of sex, females had significantly lower LDL-C control compared to males. In terms of race/ethnicity, for most criteria, Black and Hispanic patients had control significantly below the group average. Interestingly, Asian patients consistently had control above the average, and had the highest target controls percentages of any ethnic/race group in all categories.

In terms of disparities by ASCVD status, patients without ASCVD generally had worse target control compared to those with ASCVD, except for LDL-C. However, both groups followed similar trends of good BP control, subpar HbA1c control, and abysmal LDL-C and composite control.

CHAPTER 5: DISCUSSION

The findings of the study for annual testing are relatively consistent with national data. The high 91.3% of overall patients that received a yearly BP measurement in the sample is similar to the CDC reported prevalence of 96.8%.[36] Around 45.4% of the sample received a yearly test for LDL-C, which is relatively similar to an EHR study that found around 52% of patients obtained an annual LDL-C test.[23] Only 55.3% of patients received an annual HbA1c test, which is slightly below the national average of 64.6%.[22] However, worth noting is that our data could not capture certain HbA1c tests administered at home, such as the finger prick, and could only acquire data obtained from visits at the UCI medical center. Inclusion of those extra tests would likely equal a number closer to the national average.

In terms of drug therapies, 46.6% of the overall sample was on statins, which was relatively similar to the national average of 51.1%[16]. 72.5% of the patients with ASCVD were on statins, which was consistent with the national estimate of around 70% usage in DM patients[3]. Despite all patients in the overall sample being eligible for statins, only around half utilizing them seems surprisingly low. One potential reason for this may be due to recent evidence that shows that statins can actually raise HbA1c.[15] Biologically, this is theorized to be due to inhibition of glucose uptake caused by insulin, which in turns leads to more glucose in the bloodstream instead of stored in the tissues, and a higher HbA1c. Clinically however, the study reported only a 0.1% increase in HbA1c for those taking statins, contrasted to a 54% lower risk of heart attack, 20% lower risk of stroke, and 20% lower all-cause mortality in the same group. Ultimately, the study group itself concluded, despite the potential risk in taking statins of worsening T2DM, its benefits in lowering ASCVD risk factors - which are the primary cause of mortality in DM patients – far outweigh the risks. In addition, it was stated that these negative

effects were only reported in very high intensity statins, meaning that low-dose statins may not have the impact on HbA1c. Regardless, it is possible that new evidence like this could discourage physicians from prescribing statins to their DM patients from a perspective of strictly trying to treat their DM risk factors and not their ASCVD risk factors.

The use of other lipid lowering drugs in the sample was consistent with national data (<3%).[16] Use of certain DM drugs however, was unexpected, such as the 34.1% use of metformin, and even lower 29.6% usage in patients with ASCVD, which is lower than the national average of 52.0%.[17] This is likely due to cases where it was used in combination with another drug, such as metformin and sitagliptin (Janumet), and could not be included in our sample due to database limitations. In addition, the use of SGLT2i and GLP1-RA was 15.6% and 10.7% in the sample, which is objectively low, but is higher than the national average of 5.8% and 4.4%, respectively.

As for target control, the sample only had 23.0% of the sample reached LDL-C control with the new cutoffs, adjusted to 47.5% with the old cutoffs. The previous studies conducted in the *All of US* Research Program and the Diabetes Collaborative Registry evaluating LDL-C target control reported 50.6% and 48.6% respectively, both of which used the old cutoffs.[12,13] With the new cutoffs applied to the *All of US* Study, however, only 16.0% of the sample reached target control, even less than that of this study sample. This indicates that low LDL-C control is consistent across different US studies and must be addressed. The low LDL-C control in patients with ASCVD and without ASCVD (21.0% and 23.8%, respectively) was also concerning. For patients without ASCVD, this could be attributed to the lack of lipid-lowering drug usage. Only 41.7% of patients without ASCVD were on any kind of lipid-lowering drug, and if this was increased, a great deal more patients would be able to reach LDL-C target control.

In terms of sex and racial/ethnic disparities, female patients had a statistically significant ($p<0.00001$) lower control (18.7%) compared to males (27.5%). This is consistent with data that females have an increased relative risk of ASCVD and ASCVD mortality compared to males.[25] Hispanic and Black patients in the study sample had target control values lower than overall for most criteria, notably the very low Hispanic HbA1c control of 36.4%, compared to 48.9% for the overall. This is consistent with data that supports Hispanic patients have significantly lower glycemic control compared to average.[37] Interestingly, Asian patients were above the overall in all target control categories, which contrasts a study that posits Asian patients tend to have worse T2DM compared to whites.[38] However, it is worth noting that very same study states that Asian patients are highly underrepresented in DM studies, indicating that we may need to examine more on the exact differences between T2DM in Asian patients versus the general population.

There are many limitations to this study. As stated earlier, certain means of collecting laboratory data, such as finger-prick HbA1c tests cannot be accounted for in this data and can contribute to an underestimated yearly testing frequency. This also applies to BP testing, which is very commonly assessed at home, although the very high frequency of BP testing and high BP control indicates that there were likely no significant gaps for BP coverage in the data. Furthermore, certain types of drug data could not be obtained. As previously mentioned, the use of metformin in the sample was significantly below the national average. This is likely due to the exclusion of cases where it was used in combination with another drug. However, this is sadly not possible to track in UCI OMOP due to the limited drug options in the database.

As for other limitations, sample sizes varied significantly between groups. A very small sample of Black patients, especially apparent in target control analyses (431 in the composite control for example), compared to the sample size of the other groups (such as 8,737 for Whites),

could lead to a strong skewing of the overall toward those larger groups compared to smaller ones. Another limitation of the study was also mentioned earlier and is the use of the recent stricter LDL-C cutoffs for target control. As such, LDL-C control in this study is much less compared to other studies as well as the national average, leading to variations in the composite control compared to other data as well.

CHAPTER 6: SUMMARY AND CONCLUSIONS

The findings of the study are in strong support of the 4 hypotheses.

Hypothesis 1: A significant proportion of adult DM patients will not have received ASCVD and DM risk factor measurements within a year after their last DM diagnosis. There will be significant differences between patients with and without ASCVD.

For the overall sample, within a year after their last DM diagnosis, while most patients (91.3%) received regular BP testing, only 55.3% received an HbA1c measurement, and less than 50% received any kind of lipid profile measurement. Patients with ASCVD had statistically significantly ($p<0.00001$) higher risk factor screening frequencies for nearly all criteria compared to those without ASCVD. Of note is the higher screening frequency for HbA1c in patients with ASCVD (70.9%) compared to those without (50.6%).

Hypothesis 2: Many patients will not be on guideline-recommended statin therapy or newer DM therapeutic options (SGLT2-I or GLP1-RA). There will be significant differences between patients with and without ASCVD.

Only 46.6% of patients were on statins, and <3% were on any other lipid-lowering medication. Only 15.6% and 10.7% were on SGLT2i and GLP1-RA respectively, and other newer DM therapies had even lower usage (<10%). Furthermore, only 56.5% of patients were on any kind of DM drug, which is concerning, considering all patients have an ICD-10 code for DM. Patients with ASCVD generally had a higher prevalence of drug usage compared to those without ASCVD. Of note is the statistically significant ($p<0.00001$) higher percent of statin users in patients with ASCVD (72.5%) compared to those without ASCVD (38.7%).

Hypothesis 3: There will be suboptimal control of LDL-C, BP, and HbA1c individually. Furthermore, few patients will be at recommended levels for LDL-C, BP, and HbA1c

simultaneously, known as target control. There will be significant differences between patients with and without ASCVD.

BP control was impressive, with 84.6% of the sample reaching target control. HbA1c control, however, was lower, with only 48.9%, and LDL-C control was very low, only 23.0%. Due to these low percentages, especially LDL-C, the composite control was only 10.1% for the overall sample. Worth noting for LDL-C control is the newer definition for target control of <70 mg/dL (<55 mg/dL with ASCVD) compared to the older definition of <100 mg/dL (<70 mg/dL if with ASCVD), making LDL-C target control much harder to achieve. Patients with ASCVD generally had higher target control compared to those without ASCVD, except for LDL-C control. Noteworthy is a statistically significant ($p<0.00001$) higher BP control in patients with ASCVD (94.0%) compared to those without (81.6%).

Hypothesis 4: There will be significant sex/race/ethnicity disparities in the target control findings.

While relatively even for other criteria, males were shown to have statistically significantly ($p<0.00001$) higher LDL-C control (27.5%) compared to females (18.7%). Race/ethnicity disparities were very prevalent as well. For HbA1c target control compared to the overall sample, Hispanic patients had a statistically significant ($p<0.00001$) lower percentage (36.4%), and Asian patients had a statistically significant ($p<0.00001$) higher percentage (56.4%), leaving a large 20% gap in target control between both groups. Furthermore, Asian patients were shown to have the highest target control of any group among all 4 criteria. On the other end, apart from HbA1c, Black patients were shown to have target control percentages below the overall in most categories. In addition, Hispanic and Black patients were shown to have the lowest composite control percentages, being 8.0% and 7.7%, respectively.

This study served to call to light the current disparities in the UCI health system for adult DM patient care. While a largely grim perspective on UCI's quality of care, this study can also be taken in a positive light. My hope is that this data can serve to point out areas of improvement. In addition to implementing entirely new methods of care, or experimenting with newer, more powerful drugs, simply improving the efficiency of our existing system could improve health in countless DM patients. Ensuring that all DM patients receive yearly tests for their DM and ASCVD risk factors would provide valuable insight in the progression of their DM, as well as their potential (or existing) ASCVD. Furthermore, maximizing the use of drug therapies for patients that are eligible can accelerate the process of lowering the risk of potential ASCVD events. Lastly, the evident sex and racial/ethnic disparities in target control must be addressed as well. Due to the relatively high proportion of Hispanics in UCI's health system, and their relatively lower target control percentages in this study, future studies will further examine similar criteria to this one in comparing Hispanic vs. Non-Hispanic DM patients. Future studies will also examine whether various social determinants of health, such as income and insurance status might explain ethnic/racial disparities.

This project is also under a larger umbrella project called IMPROVE-DM, which aims to improve DM and ASCVD treatment in the UCI health system, based on the data collected from this study. The next step in that project involves implementing Best Practice Advisories (BPAs), messages sent to physicians informing them of any deficits in care, such as missing laboratory measurements or unprescribed drug therapies, when eligible. The results of these BPAs will be published in a future study.

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APPENDIX

	No Medication	Any Lipid-Lowering Drug	Any Statin	Low-Moderate Intensity Statin	High Intensity Statin
n	6,809	10,153	9,818	7,493	2,325
LDL-C >= 55 mg/dl	6,155 (90.4%)	8,247 (81.2%)	7,952 (81.0%)	6,230 (83.1%)	1,722 (74.1%)
LDL-C >= 70 mg/dl	5,525 (81.1%)	6,647 (65.5%)	6,373 (64.9%)	5,075 (67.7%)	1,298 (55.8%)
LDL-C >= 100 mg/dl	3,577 (52.5%)	3,595 (35.4%)	3,417 (34.8%)	2,812 (37.5%)	605 (26.0%)

LDL-C Levels by Drug Type (n=16,962)

	No Comorbidity	Heart Failure	Chronic Kidney Disease	ASCVD
n	7,464	2,272	4,209	5,102
LDL-C >= 55 mg/dl	6,260 (83.9%)	1,656 (72.9%)	3,272 (77.7%)	3,866 (75.8%)
LDL-C >= 70 mg/dl	5,299 (71.0%)	1,272 (56.0%)	2,605 (61.9%)	3,000 (58.8%)
LDL-C >= 100 mg/dl	3,061 (41.0%)	595 (26.2%)	1,320 (31.4%)	1,542 (30.2%)

LDL-C Levels by Comorbidities (n=16,962)

	No Medication	Any Lipid-Lowering Drug	Any Statin	Low-Moderate Intensity Statin	High Intensity Statin
n	1,082	4,020	3,885	2,056	1,829
LDL-C >= 55 mg/dl	855 (79.0%)	3,011 (74.9%)	2,897 (74.6%)	1,558 (75.8%)	1,339 (73.2%)
LDL-C >= 70 mg/dl	712 (65.8%)	2,288 (56.9%)	2,182 (56.2%)	1,183 (57.5%)	999 (54.6%)
LDL-C >= 100 mg/dl	414 (38.3%)	1,128 (28.1%)	1,065 (27.4%)	595 (28.9%)	470 (25.7%)

LDL-C Levels in ASCVD Patients (n=5,102)

	No Medication	Any Lipid-Lowering Drug	Any Statin	Low-Moderate Intensity Statin	High Intensity Statin
n	5,727	6,133	5,933	5,437	496
LDL-C >= 55 mg/dl	5,300 (92.5%)	5,236 (85.4%)	5,055 (85.2%)	4,672 (85.9%)	383 (77.2%)
LDL-C >= 70 mg/dl	4,813 (84.0%)	4,359 (71.1%)	4,191 (70.6%)	3,892 (71.6%)	299 (60.3%)
LDL-C >= 100 mg/dl	3,163 (55.2%)	2,467 (40.2%)	2,352 (39.6%)	2,217 (40.8%)	135 (27.2%)

LDL-C Levels in Patients without ASCVD (n=11,860)