ORIGINAL RESEARCH

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Sex/Gender -Based Pharmacology and Statin Utilization Amongst Elderly Patients with Diabetes

Abstract

Purpose: The purpose of this study was to explore the ten-year trends in utilization of bioequivalent doses of statin amongst elderly patients with diabetes according to sex/gender in Ontario, Canada.

Methods: A cohort of patients with diabetes (>65 years) was constructed using the Ontario Diabetes Database Statin utilization data (2003-2012) was obtained from the Ontario Drug Benefit Program for both women and men. Bioequivalent doses for statins were calculated according to the dosing conversion factor in therapeutic interchange programs in clinical practice. Utilization pattern of high potency (Atorvastatin and Rosuvastatin) *vs.* low potency statins (Simvastatin, Lovastatin, Fluvastatin, Pravastatin) were also analyzed.

Results: The average bioequivalent Simvastatin utilization in 2003 was 29.22 mg/day for women and 30.35 mg/day for men. By 2008, this gap in dosing was higher for both women and men and by 2013 it had increased to 47.75 mg/day for women and 52.98 mg/day for men. For average number of day supply per year, there was no significant trend of changes over the 10-year period, although the use of high potency statins increased significantly ($P<0.001$) for both women and men. No differences were seen for sex/gender; either for the 10-year period or for each year.

Conclusions: There has been significant increase in bioequivalent statin utilization amongst elderly patients with diabetes in Ontario; for both men and women. In a publicly-funded healthcare system such as Ontario, there were no sex/gender differences in the utilization of high potency statin (Atorvastatin and Rosuvastatin) amongst elderly patient with diabetes.

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Several large-scale randomized controlled trials and observational studies have demonstrated the efficacy of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) in preventing cardiovascular morbidity and mortality in patients with diabetes^{1,2}; therefore, statins have become the cornerstone of hypercholesterolemia pharmacotherapy in patients with diabetes^{1,2}. Statin therapy to reduce LDL-C levels for elderly patients with diabetes has been recommended by guidelines for decades [1,2]. The main goal in clinical practice for management of diabetes regarding blood glucose, lipid and blood pressure is to achieve predefined levels according to the practice guidelines to reduce the burden of illness and complications due to diabetes [1-3]. Numerous studies have demonstrated that a large proportion of patients with diabetes in the community do not reach the predefined goals for optimal management of blood glucose, lipids and blood pressure [4-6]. This failure to attain therapeutic goals has been reported in several studies from around the globe, despite different patient populations, different clinical practice guidelines and different time frames [7]. In clinical practice, when a patient with diabetes cannot attain the LDL-C goal, treatment strategies include up-titration of the statin dose or switching to a statin with higher potency [1,2].

There is a vast sex/gender disparity regarding the epidemiology and burden of illness of diabetes within a patient population [8] and differences in morbidity and mortality related to diabetes have been shown to be associated with sex/gender [9]. This pattern of morbidity and mortality is likely related to differences in glycemic and CVD risk factor control [9-11]. For dyslipidemia treatment in patients with diabetes, sex/gender disparities have been illustrated in several studies [12]. Sex/gender differences in dyslipidemia treatment with statins and the greater difficulty in reaching targets may be related to the use of a less aggressive approach in women, poorer adherence of women to statins or sex/gender physiopathological differences [13]. An example of pathophysiological data on sex/gender differences is diverse drug responses between women and men due to dissimilarities in pharmacodynamics and pharmacokinetics [14,15]; for instance, evidence supporting sex/gender-based differences in statin metabolism implicates differences in body-fat content between men and women [16]. Females tend to have a higher percentage of body fat than men, which affects the volume of distribution of some drugs and can significantly increase the half-life of a variety of medications, including the more lipophilic statins [16]. Furthermore, a clinical study reported that only 28.9% of diabetic women *vs.* 33.9% of diabetic men have received all five recommended services (HbA1c

testing, lipid profile, influenza immunization, eye and foot examination) in the appropriate time frame [17].

The objective of this study was to explore the ten-year trends in utilization of bioequivalent doses of statin amongst elderly patients with diabetes according to sex/gender in Ontario, Canada. This was to explore the implementation of clinical practice guidelines recommendations for more intensive treatment of dyslipidemia in diabetes for both men and women in real-world clinical settings [1-2].

Methods

A cohort of patients with diabetes aged 65 years and older was constructed using the Ontario Diabetes Database (ODD) for a ten-year period between the beginning of 2003 and the end of 2012. The index year was beginning of 2003 and continued for each year until end of 2013; therefore, each year included incidence (new patients) and prevalence of patients within the year. If a patient moved out of province or died, he/she was excluded from the cohort correspondent to the date of death or data of loss of OHIP (Ontario Health Insurance) benefits. This cohort included all statin users. Statin utilization data was obtained from the Ontario Drug Benefit (ODB) Program for the same period of time.

ODD was created at ICES and has been validated using chart reviews. It contains all Ontario diabetic patients identified since 1991 (defined as having one hospital admission with a diabetes diagnosis or an OHIP claim with a diabetes diagnosis, followed within two years by either an OHIP claim or a hospital admission with a diabetes diagnosis [in CIHI (Canadian Institute for Health Information) / DAD (Discharge Abstract Database)]). There are more than 50,000 new diabetic cases per year in this dataset. ODB program provides drug benefits for all adults aged 65+ and those receiving social assistance in Ontario. The pharmacist submits a claim for each prescribed drug that is covered under the ODB formulary. These claims form the basis of the ODB database. Information in the database includes: drug identification number, dispensing date, quantity of pills dispensed, number of days supplied, and cost, as well as encrypted patient and physician identifiers. ODB and ODD databases are robust and well-validated data source with high sensitivity (more than 90%) and specificity (more than 90%) for such a study [18].

Bioequivalent doses for statins were calculated according to dosing conversion factor in therapeutic interchange programs in clinical practice [19-21] as follows: Rosuvastatin, 5 mg = Atorvastatin, 10 mg = Simvastatin, 20 mg = Pravastatin, 40 mg = Lovastatin, 40 mg = Fluvastatin, 80 mg. According to the American College of Clinical Pharmacy's Guidelines

for Therapeutic Interchanges, “therapeutically equivalent drugs are chemically dissimilar but produce essentially the same therapeutic outcome and have similar toxicity profiles. Usually, these drugs are within the same pharmacologic class” [20,21]. All bioequivalent doses of different brands of statins were converted to bioequivalence of Simvastatin for this analysis. Utilization pattern of high potency statins (Atorvastatin and Rosuvastatin) *vs.* low potency statins (Simvastatin, Lovastatin, Fluvastatin, Pravastatin) for men and women was analyzed. The data were analyzed per year and by sex/gender. Statistical analyses were conducted using appropriate methods: the Wilcoxon test was utilized to compare the differences in mean doses as mg/day and mean days per year; the chi-square statistics and non-parametric methods for proportions were used for overall and annual comparisons for the total cohort and by sex/gender; and, the chi-squared statistics for trend and one-way ANOVA were utilized for trend analysis. SAS Software was utilized for statistical analysis.

As the sample size of this study was large, we emphasized on both statistical and clinical significance in our interpretations of the data. Studies with large sample sizes may identify differences that are statistically significantly but not necessarily clinically significant. Statistical significance measures how likely that any apparent differences in outcome between groups are real and not due to chance; however, hypothesis testing cannot establish the clinical implications of these results. Rather, clinical significance can be established once the magnitude of results is larger than the minimal clinically-important difference. Clinical significance measures how large the differences in treatment effects are in clinical practice [22-24].

Results

The average population sample size was $n=73,182$ patients per year, over a 10-year period (Appendix 1). Women comprised almost 45% of the total cohort (Appendix 1). Appendix 2 tabulates demographic and clinical data of the cohort over 10-year period by gender and age group. Standardized difference of the mean between men and women for age at index, age at diagnosis and Charlson Comorbidity Index were statistically significant but not clinically significant as average differences are too small for both age strata.

The average bioequivalent Simvastatin utilization in 2003 was 29.22 mg/day for women and 30.35 mg/day for men (Table 1; Figure 1). The average difference dose per milligram (mg) per day between men and women was approximately 1 mg/day. This difference was statistically significant (Wilcoxon 2 sided P-value less than 0.001); however, this difference was not clinically significant. In 2008, this gap in dosing was in-

creased 40.98 mg/day for women and 45.00 mg/day for men (an average of almost 4 mg/day difference) (Table 1; Figure 1). In 2013, the average bioequivalent Simvastatin utilization increased to 47.75 mg/day for women and 52.98 mg/day for men (an average gap of more than 5 mg/day) (Table 1; Figure 1). These results were both statistically and clinically significant. For the total cohort, the average dose per day increased per year constantly between 2003 and 2012 from 29.84 mg/day to 50.68 mg/day. This constant increase was both statistically and clinically significant (Table 1). These results illustrate that between 2003 and 2013, there was a clinical and statistical significant ($P<0.001$) increase in bioequivalent statin utilization (as mg per day) amongst elderly patients with diabetes in Ontario. The average dose (as per mg per day) almost doubled between 2003 and 2013; from 29 mg/day to 50 mg/day; however, observed statin bioequivalent doses between men and women demonstrated a constant statistical significant difference ($P<0.001$), but not clinically significant difference, between 2003 and 2007.

For average number of day supply per year (Table 2; Figure 2), there was no significant trend of changes over 10-year period for the total cohort, women or men. Also, no clinical significant differences between women and men were observed (Table 2). The average number of day supply per year was 260 - 280 days per year over the span of 10 years (Table 2; Figure 2). The use of high potency statins increased significantly ($P<0.001$) in the total cohort, both for women and men over the 10 year period (Table 3; Figure 3). In the total cohort, average utilization of high potency statins was 67% between 2002 and 2007 compared with 81% between 2008 and 2013 (Table 3; Figure 3). This trend of significant increase in high potency statins utilization started between 2007 and 2010 for both sexes/genders (Table 3; Figure 3). Comparison by sex/gender did not illustrate any significant difference for high potency statin use, both for an overall 10-year period (74% for men *vs.* 73% for women) and for each year (Table 3; Figure 3).

Discussion

Sex/gender disparities in diabetes care

Cardiovascular disease continues to be a significant factor for increased morbidity and mortality in people with diabetes [1,2,25,26] and disparities in outcomes for cardiovascular disease exist between men and women with diabetes [9,11,13,27,28]. A recent systematic review and meta-analysis of 64 cohorts, including 858,507 individuals and 28,203 coronary events, reported women with diabetes have more than a 40% greater risk of incident coronary heart disease compared

TABLE 1. Statin utilization per year

		2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
ATORVASTATIN	Female	17	18	19	20	21	22	23	24	25	25
	Male	18	19	20	21	23	25	26	27	28	28
	All	18	19	20	21	22	24	25	26	27	27
ROSUVASTATIN	Female	13	12	12	12	12	12	12	13	13	13
	Male	13	13	12	12	12	13	13	14	14	14
	All	13	12	12	12	12	12	13	13	14	13
FLUVASTATIN	Female	30	29	30	31	35	38	40	40	37	35
	Male	29	30	30	32	38	39	41	41	41	40
	All	30	30	30	31	37	39	40	41	39	37
LOVASTATIN	Female	24	24	25	25	25	26	25	26	26	27
	Male	25	25	25	25	26	27	27	27	27	27
	All	24	25	25	25	26	26	26	27	27	27
PRAVASTATIN	Female	24	25	25	25	25	26	26	26	26	26
	Male	25	26	26	26	27	27	28	28	28	28
	All	25	25	25	26	26	27	27	27	27	27
SIMVASTATIN	Female	23	24	24	25	25	26	26	26	27	27
	Male	24	25	25	26	27	27	28	28	28	28
	All	24	24	25	25	26	27	27	28	28	27
BIOEQUIVALENT of SIMVASTATIN	Female	29.22 (2.47)	32.42 (2.44)	34.24 (2.58)	36.26 (2.64)	38.62 (3.13)	40.98 (3.44)	43.35 (3.60)	45.42 (3.53)	46.84 (3.11)	47.75 (2.97)
	Male	30.35 (2.35)	34.01 (2.48)	36.57 (2.54)	38.99 (2.65)	41.96 (3.39)	45.00 (3.46)	47.89 (3.55)	50.46 (3.56)	52.19 (3.47)	52.98 (3.32)
	All	29.84 (2.41)	33.29 (2.45)	35.51 (2.55)	37.76 (2.64)	40.46 (3.24)	43.20 (3.44)	45.86 (3.56)	48.21 (3.51)	49.81 (3.25)	50.68 (3.10)

Average milligram per day

with men with diabetes [29]. The cause of these significant disparities may partially stem from lack of control for cardiovascular risk factors including low-density lipoprotein (LDL) cholesterol among female patients with diabetes [11,13,27,30,33]. A cross-sectional study of 680 patients with diabetes reported mean systolic BP and LDL cholesterol levels were significantly higher in women. Men were significantly more likely to have risk factor control (odds ratio 2.90; 95% confidence interval 1.37, 6.13) compared with women [24]. In a cohort of high-risk veterans, including 23,955 men and 1,010

women, LDL-C values were higher in women than men, with age-adjusted estimated mean values of 111.7 *vs.* 97.6 mg/dL ($p < .01$) [35]. A Spanish study, which included available data from electronic medical records for a total of 286,791 patients, reported although the proportion of women treated with lipid-lowering medications was similar to (with prior CVD) or even higher (without CVD) than men, LDL-cholesterol levels were remarkably uncontrolled in both women with and women without CVD [36]. A Chinese study explored the reasons for the disparity in the lipid-lowering treatment goal attainment

FIGURE 1. Simvastatin bioequivalent doses: statin use 2003-2012

FIGURE 2. Total average days of exposure per year: statin use 2003-2012

TABLE 2. Statin utilization per year

		2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
ATORVASTATIN	Female	273	270	277	280	281	286	285	282	273	260
	Male	274	272	279	281	282	287	285	284	277	262
	All	274	271	278	281	282	287	285	283	275	261
ROSUVASTATIN	Female	58	191	233	238	247	256	258	261	262	253
	Male	58	198	240	244	252	261	262	266	263	255
	All	58	195	237	242	250	259	260	264	263	254
FLUVASTATIN	Female	256	268	266	262	252	259	282	259	269	263
	Male	267	271	281	268	255	248	262	250	232	238
	All	262	269	273	265	253	254	273	255	253	252
LOVASTATIN	Female	302	294	297	301	288	286	279	281	283	259
	Male	297	287	293	291	283	287	284	294	273	247
	All	299	291	295	296	286	287	281	287	278	253
PRAVASTATIN	Female	280	279	286	287	281	277	275	273	261	258
	Male	282	279	288	289	278	280	283	278	268	257
	All	281	279	287	288	280	278	279	276	265	257
SIMVASTATIN	Female	274	279	284	288	286	286	287	284	277	258
	Male	277	284	290	290	288	290	287	285	276	260
	All	276	282	288	289	287	288	287	285	276	259
Total average number of day supply per year Mean (SD)	Female	269.28 (31.6)	267.03 (12.7)	275.68 (7.76)	277.61 (7.74)	277.35 (4.99)	280.56 (4.99)	279.27 (3.59)	277.05 (3.78)	270.61 (2.88)	258.45 (1.13)
	Male	270.15 (31.6)	269.70 (11.6)	278.87 (6.78)	279.08 (6.36)	278.47 (5.38)	282.29 (5.98)	280.09 (4.09)	279.80 (5.47)	272.77 (5.87)	259.98 (3.29)
	All	269.76 (31.6)	268.49 (12.1)	277.42 (7.16)	278.42 (6.98)	277.97 (5.81)	281.51 (5.36)	279.73 (3.37)	278.57 (4.40)	271.81 (3.42)	259.31 (1.33)

Average number of day supply per year

rates between women and men, and concluded that nearly half of the sex/gender disparity in lipid-lowering treatment goal attainment rates can be explained by the sex/gender differences in baseline lipid levels, socioeconomic status, cardiovascular comorbidities and associated risk factors, and the dosage of statin in high and very high CVD risk patients; however, the other half of the sex/gender disparity remains unexplained and requires further study to fully understand what other factors are at play [37].

Sex/gender disparities in statin utilization from clinical pharmacology perspectives

Differences in pharmacokinetics, pharmacodynamics and physiology contribute to the observation that women and men frequently respond differently to drugs [14,15]. Hormonal influences can play an important role [14,15]; for example, as a result of fluctuations in concentrations of sexual steroids, and subsequently changes in total body water, sex/gender-specific differences in the plasma levels of drugs can be observed [38]. Sex/gender differences in dyslipidemia treatment with statins

TABLE 3. Percentage of statin use according to generic name

Statin generic name		2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
ATORVASTATIN	All	54%	55%	58%	59%	59%	59%	58%	56%	55%	55%
ROSUVASTATIN	All	3%	9%	10%	12%	15%	18%	22%	25%	27%	29%
FLUVASTATIN	All	2%	1%	1%	1%	1%	1%	1%	1%	1%	1%
LOVASTATIN	All	4%	3%	3%	3%	3%	1%	1%	1%	2%	1%
PRAVASTATIN	All	11%	9%	8%	6%	5%	5%	4%	4%	3%	3%
SIMVASTATIN	All	26%	23%	20%	19%	17%	16%	14%	13%	12%	11%
ATORVASTATIN	M	54%	55%	58%	59%	59%	59%	58%	56%	55%	55%
ROSUVASTATIN	M	3%	9%	11%	13%	16%	19%	22%	26%	28%	30%
FLUVASTATIN	M	2%	1%	2%	2%	1%	1%	1%	1%	1%	1%
LOVASTATIN	M	4%	3%	2%	2%	2%	2%	2%	2%	2%	1%
PRAVASTATIN	M	11%	9%	7%	6%	5%	4%	4%	3%	3%	3%
SIMVASTATIN	M	26%	23%	20%	18%	17%	15%	13%	12%	11%	10%
ATORVASTATIN	F	54%	55%	58%	59%	59%	59%	58%	57%	56%	55%
ROSUVASTATIN	F	3%	9%	10%	12%	15%	18%	21%	24%	27%	29%
FLUVASTATIN	F	3%	2%	1%	2%	2%	1%	1%	1%	1%	1%
LOVASTATIN	F	4%	3%	3%	2%	2%	2%	2%	2%	1%	2%
PRAVASTATIN	F	11%	9%	8%	7%	6%	5%	5%	4%	4%	3%
SIMVASTATIN	F	25%	22%	20%	18%	16%	15%	13%	12%	11%	10%

and the greater difficulty in reaching the targets can be partially related to the sex/gender physiopathological differences [13]; for example, sex/gender differences is diverse drug responses between women and men due to dissimilarities in pharmacodynamics and pharmacokinetics [14,15]. Evidence supporting sex-based differences in statin metabolism implicates differences in body-fat content between men and women [16]. Females tend to have a higher percentage of body fat, which affects the volume of distribution of some drugs and can significantly increase the half-life of a variety of medications, including the more lipophilic statins [16]. A study investigated the effects of sex/gender on the pharmacokinetics of Atorvastatin after administration of 20 mg tablets [39]. The equivalent maximum concentration (C_{max}) of Atorvastatin was 17.6% higher in women than in men. In addition, the mean area under the concentration-time curve (AUC_{0-infinity}) and half-life (t_{1/2}) were 11.3% lower and 19.9% shorter, respectively, in women than in men [39]. In a Chinese study, a pharmacokinetic

study was conducted on 12 volunteers following a single dose of 1 mg, 2 mg and 4 mg of Pitavastatin [40]. The study illustrated that female SLCO1B1 521TT genotype subjects had higher C_{max} and AUC(0-infinity) of Pitavastatin compared with male 521TT genotype subjects; however, such sex/gender differences disappeared in 521 TC and 521CC genotype subjects [40]. Furthermore, another study concluded that SLCO1B1 polymorphism has a large effect on the pharmacokinetics of Pravastatin but not Fluvastatin [41]. This difference suggests that the lipophilic Fluvastatin can penetrate the hepatocyte plasma membrane via passive diffusion or that primarily uptake transporters other than organic anion transporting polypeptide 1B1 mediate its hepatic uptake [41]. Moreover, the results suggest that sex/gender may affect the pharmacokinetics of Pravastatin and possibly the functional consequences of SLCO1B1 polymorphism [41]. A meta-analysis of RCTs and observational studies on adherence to statins by men and women reported that women had a 10% greater odds of

Percent is calculated within variables.

Percent is calculated within variables.

FIGURE 3. Percentage of statin use according to generic name for all, female and male users

non-adherence (odds ratio 1.10, 95% confidence interval: 1.07-1.13) [42]; therefore, evidence supports sex-based evaluation and treatment for CVDs risk factors such as dyslipidemia. The current study illustrated that between 2003 and 2013, there has been a clinical and statistical significant ($P < 0.001$) increase in bioequivalent statin utilization amongst elderly patients with diabetes in Ontario. The average dose almost doubled between 2003 and 2013. The Canadian dyslipidemia guideline in 2006 changed the target for LDL-C level in patients with diabetes from a threshold of 2.5 mmol/l to 2.0 mmol/l; however, observed statin bioequivalent doses between men and women demonstrated a constant statistical significant difference ($P < 0.001$), but not clinically significant difference between 2003 and 2007. The average difference dose pre milligram (mg) per day between men and women was approximately 1 mg/day in 2003. This gap in dosing was increased to an average of almost 4 mg/day differences in 2008. In 2013, the average bioequivalent simvastatin utilization gap between women and men was more than 5 mg/day.

Sex/gender disparities in statin utilization from access to medication perspectives

This study demonstrated that in a publicly-funded healthcare system such as the one in Ontario, there were no sex/gender differences in the utilization of high potency statin (Atorvastatin and Rosuvastatin) amongst elderly patient with diabetes in Ontario by sex/gender. Also, this analysis illustrated that a significant increase in utilization of high potency statins was seen between 2007 and 2010, long before the expiration of the patents for Atorvastatin in July, 2010 and Rosuvastatin in July, 2012 in Ontario. This illustrates accessibility to patented high potency statins in a publicly-funded system; however, a cross-sectional study of veterans serviced by the Veterans Health Administration concluded that women with diabetes and hyperlipidemia received less aggressive lipid-lowering therapy than men, especially among the younger age groups⁴³. Women had higher LDL levels than men (110 *vs.* 101 mg/dL) and were less likely to be receiving lipid-lowering therapy (80% *vs.* 84%) or to be initiated on such therapy (37% *vs.* 42%). Differences were greatest in the youngest women (<45 years old) for any lipid-lowering therapy (61% *vs.* 75%) and for initiation of therapy (26% *vs.* 38%). This disparity is of concern, because early intervention to control hyperlipidemia can reduce the later burden of cardiovascular disease among diabetic women [43]. An Italian study reported that, amongst patients with type 2 diabetes, women were monitored less frequently than men, irrespective of age. Fewer women reached the LDL-C target as compared with men, particularly in the subgroup treated with

lipid-lowering medications. The between-sexes/genders gap in reaching LDL-C targets increased with age and diabetes duration, favouring men in all groups [44]. A retrospective cohort study, using Veterans Health Administration, illustrated that although there were no significant sex/gender differences in LDL-C testing, women were less likely to have LDL-C under 130 mg/dL (OR=0.77; 99% CI=0.69, 0.87) [45]. This study suggested that lower LDL-C control among women indicates areas of unmet needs for women and opportunities for future targeted quality improvement interventions at system and provider levels. Also, sex/gender disparities in performance indicators among persons enrolled in Medicare-managed care have been observed for dyslipidemia management in diabetes population [46]; poor cholesterol control in women suggests the possibility of less intensive cholesterol treatment in women. Another study concluded that sex/gender differences in the quality of cardiovascular and diabetic care were common and sometimes substantial among enrollees in Medicare and commercial health plans [47]. The largest disparity was for control of LDL-C among diabetics, where women were 19% less likely to achieve control among Medicare enrollees (relative risk [RR] = 0.81; 95% confidence interval [CI] = 0.64-0.99) and 16% less likely among commercial enrollees (RR = 0.84; 95%CI = 0.73-0.95).

Sex/gender disparities and future directions for dyslipidemia research

A study investigated the evolving pattern of sex/gender disparity in participants of RCTs on statins between 1990 and 2010 [48]. The RCTs on statins with more than 500 participants in the 1990s included, on average, 18.6% women; however, in the first decade of the 2000s, women comprised, on average, 31.45% of the total cohort of the RCTs with more than 500 participants. The study demonstrated a significant progress in the inclusion of women in RCTs on statins. This finding can reflect the efforts of different agencies and groups to increase the representation of women in clinical trials. Despite significant improvement in participation and recruitment of women into RCTs, additional clinical investigations of sex/gender differences are needed in order to eliminate fundamental inequalities between men and women in the treatment of disease. In the ideal situation, the proportion of enrollment for women in mixed-sex/gender trials should be 50% of the total cohort; however, the current enrollment number is still significantly below 50% despite recent improvements. As new classes of medications for dyslipidemia management, such as PCSK9 (proprotein convertase subtilisin/kexin 9) inhibitors, are in horizon [49], the RCTs should recruit sufficient numbers of

women to be included into the trials. The following recommendations were proposed for future cardiovascular trials in women [50]: include equal representation of women and men; limit exclusion criteria and remove the upper age limit to improve the generalizability of results and the projection of effectiveness in clinical practice; conduct and publish sex/gender-specific analyses for both efficacy and safety; conduct cost-effectiveness analysis for both sexes/genders; publish sex/gender-specific data; document non-adherence to interventions according to sex/gender; and, conduct sex/gender-specific power calculations.

Sex/gender-specific pre-clinical pharmacological testing has been proposed to enable adequate assessment of pharmacokinetic and pharmacodynamic actions of drugs and to enable an adequate sex/gender-specific clinical development plan [51]. Sex/gender-specific pre-clinical research will increase the sex/gender equity of care and will produce more evidence-based medicine [51]. Sex/gender gap has also been observed beyond clinical research in evidence-based guidelines development. The lack of incorporation of sex/gender data into evidence-based medicine is the next step to be addressed; for example, despite well recognized sex/gender differences in coronary heart disease management in UK critical care units, the UK NHS guidelines for management are not sex/gender-specific [52]. As another example, the 2007 American Heart Association guidelines for cardiovascular disease prevention in women were established on results from randomized clinical trials; however, of the 156 trials included in the guidelines, 20 trials enrolled only men [53]. Also, sex/gender-specific results were discussed in only 31% of the primary trial publications [53]. The level of representation for women in RCTs should be adequate to ensure that evidence-based sex-specific recommendations are applicable for women.

Strength and limitations

This study provided new data and insight into 10-year trends of bioequivalent statin utilization in elderly patients with diabetes and dyslipidemia, by gender. This is the strength and the value of this study and it is the first of such data to be analyzed and presented for this population in Ontario, Canada. In this context, this study is unique and novel, and provides new insight; however, the databases did not include any laboratory values, such as LDL-C levels for patients on statin therapy and comparisons of these data with previous published data were, therefore, limited by lack of data. Also, the results for average bioequivalent Simvastatin utilization were not adjusted for other confounding factors, such as age, medical history, disease severity and co-morbidities. The results of this study should be in-

terpreted with the recognition that this study has geographical limitations that limit the generalizability of the results to the Canadian population in other provinces.

In conclusion, the exploration of sex/gender differences is a driving force for ensuring that biomedical research is conducted on gender parity cohorts and for raising awareness about the biological and physiological differences between men and women [54]. In the era of personalized medicine, attention to sex/gender differences in drug disposition is crucial as a platform for therapeutics development and utilization [55]. At this juncture, attention to the impacts of the sex/gender differences on the pathophysiology and management of the prevalent diseases such as cardiovascular diseases and diabetes is needed. This calls for further studies to determine causes of possible sex/gender disparities to tailor interventions for each risk factor to address the impact of sex/gender differences. Also, it will be important to disseminate sex/gender-specific data to potentially reduce sex/gender disparities in preventive care and to improve clinical outcomes for women.

Acknowledgments/Disclaimers

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APPENDIX 1. Number of patients per calendar year

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Female	34265	37824	38174	38594	38595	36394	33592	29515	24155	18047
Male	40937	45335	46041	47018	47366	44941	41431	36485	30230	22883
All	75202	83159	84215	85612	85961	81335	75023	66000	54385	40930

APPENDIX 2. Demographic and clinical data of the cohort over 10-year period by gender and age group

VARIABLE	VALUE	Men ages between 65 and 75	Women ages between 65 and 75	STANDARDIZED DIFFERENCE OF THE MEAN	P-VALUE
		N=49,151	N=32,532		
Age at index	Mean $\pm$ SD	69.37 $\pm$ 3.05	69.59 $\pm$ 3.08	0.07	<.001
	Median (IQR)	69 (66-72)	69 (66-72)	0.07	<.001
Age at diagnosis	Mean $\pm$ SD	62.89 $\pm$ 6.36	62.92 $\pm$ 6.40	0	0.51
	Median (IQR)	63 (59-68)	63 (59-68)	0	0.426
Charlson Comorbidity Index	Mean $\pm$ SD	1.53 $\pm$ 2.00	1.47 $\pm$ 1.95	0.03	<.001
	Median (IQR)	1 (0-2)	1 (0-2)	0.03	<.001

VARIABLE	VALUE	Men older than 75	Women older than 75	STANDARDIZED DIFFERENCE OF THE MEAN	P-VALUE
		N=35,831	N=37,069		
Age at index	Mean $\pm$ SD	80.43 $\pm$ 4.05	81.27 $\pm$ 4.47	0.2	<.001
	Median (IQR)	80 (77-83)	80 (78-84)	0.2	<.001
Age at diagnosis	Mean $\pm$ SD	75.68 $\pm$ 6.51	76.28 $\pm$ 6.94	0.09	<.001
	Median (IQR)	76 (71-80)	76 (71-81)	0.09	<.001
Charlson Comorbidity Index	Mean $\pm$ SD	1.66 $\pm$ 2.04	1.45 $\pm$ 1.87	0.11	<.001
	Median (IQR)	1 (0-3)	1 (0-2)	0.11	<.001