RESEARCH ARTICLE

Diabetes Management

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Adherence to treatment guidelines in Type 2 diabetes patients failing metformin monotherapy in a real-world setting

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Summary points

Background

- The importance of proactive diabetes treatment has been reinforced by recent diabetes guidelines. Understanding the magnitude of clinical inertia in a real world cohort of patients with Type 2 diabetes mellitus, and understanding the factors affecting intensity of care may improve diabetes care.

Results

- Overall, 7705 patients were identified in a large computerized database of an Israeli HMO, in whom HbA1c >7% was measured for the first time following at least 90 days on metformin therapy. Of these, 56% (n = 4336) changed treatment within 1-year, by increasing metformin dose (36%), adding drugs (60%), or switching to other medications (4%).
- Strongest predictors of change were higher HbA1c, younger age and higher socioeconomic status (SES).

Conclusion

- In this cohort, the extent of inertia appears to be smaller than that reported in previous studies. The may be due to intensive implementation of guidelines.

SUMMARY **Aim:** To describe the drug management of T2DM patients in a real life cohort with suboptimal HbA1c after treatment with metformin monotherapy. **Methods:** we performed a retrospective cohort analysis of computerized medical records after measuring an HbA1c >7% for the first time following at least 90 days on metformin therapy. **Results:** Among 7705 eligible patients, 56% (n = 4336) changed treatment within 1-year, by increasing metformin dose (36%), adding drugs (60%), or switching to other medications (4%). Strongest predictors of change were higher HbA1c, younger age and higher socioeconomic status (SES). **Conclusion:** In this cohort, the extent of inertia appears to be smaller than that reported in previous studies. Nonetheless, disease management programs aimed at improving guideline adherence and reducing inertia are still warranted.

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KEYWORDS
- ADA/EASD guidelines
- clinical inertia
- personalized medicine

Type 2 diabetes mellitus (T2DM) is one of the most common diseases worldwide [1]. Diabetes is a progressive disease that causes microvascular and macro vascular complications [2]. These complications significantly decrease patient quality of life and increase morbidity and mortality. National and international diabetes management guidelines consistently emphasize the importance of glycemic control to prevent these complications.

Metformin, a biguanide, is considered the first choice for oral treatment of T2DM in patients without contraindications [3]. Metformin primarily decreases hepatic glucose output and increases insulin-mediated glucose utilization in peripheral tissues particularly after meals. Metformin also has an antilipolytic effect that lowers serum-free fatty acid concentrations, thereby reducing substrate availability for gluconeogenesis. In obese patients, treatment with metformin results in a modest weight reduction. In addition, metformin compared with other drugs used for treating T2DM is less likely to cause hypoglycemia. Metformin typically lowers fasting blood glucose concentrations by approximately 20% and HbA1c by 1.5% [4–6].

The American Diabetes Association (ADA) together with the American College of Cardiology and the American Heart Association, recommends HbA1c <7% as a reasonable treatment goal for patients with T2DM. If HbA1C target is not achieved by metformin monotherapy at the maximal tolerated dose after 3–6 months, a second oral agent, glucagon-like peptide 1 (GLP-1) receptor agonist, or insulin should be added to the treatment regimen. In addition to these specific recommendations, the guidelines do acknowledge that patients may differ in their personal goals and that co-morbidities may affect the risk of hypoglycemia. Therefore, the guidelines recommend personal tailoring of patients' HbA1c target taking into account patients' personal preferences as well as diabetes duration, age and co-morbidities [3].

In several observational studies, it has been demonstrated that many patients fail to achieve the recommended HbA1c treatment goals. A previous study that assessed 41,936 Israeli T2DM patients has shown that 41% of the patients did not reach the target of HbA1C <7.0% [7]. The Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) study reported in a European cohort of 2023 T2DM patients receiving metformin plus an additional antihyperglycemic drug that only 25.5% had adequate glycemic control [8]. Several studies have demonstrated that in more than 40% of patients who failed to reach target HbA1c, treatment change took more than 1 year [9,10]. The importance of proactive diabetes treatment has been reinforced by recent diabetes guidelines [3]. Understanding the magnitude of clinical inertia in a real world cohort of patients with T2DM, and understanding the factors affecting intensity of care may improve diabetes care.

The aim of this study was to describe treatment patterns of T2DM patients receiving care from a managed care organization in Israel during 12-months follow-up after a suboptimal HbA1c test result while they were on metformin monotherapy for at least 3 months. The study was performed in a leading Israeli Health Maintenance Organization (HMO), Maccabi Healthcare Services (MHS) using their large, comprehensive database. MHS registry of diabetes patients was constructed in 1999 by an automated search in the organizational computerized databases and currently includes over 100,000 patients. It is continuously validated by computerized feedback from practitioners and has been extensively used for clinical, epidemiological and pharmaceutical research [11,12].

Methods

For the present retrospective cohort study we have used the computerized medical records of members of MHS, the second-largest Health Maintenance Organization (HMO) in Israel, serving 25% of the total population countrywide (about 2 million members). The study was approved by MHS's ethics committee and performed in accordance with the Declaration of Helsinki, as revised in 2000.

Since 1997 MHS downloads all members' interactions (Drug purchases, laboratory results, physician visits, etc.) to a central computerized database and patients are gathered in validated computerized registries per major chronic diseases such as ischemic heart disease, oncological diseases and diabetes. To be included in the diabetes registry, which holds information for >100,000 patients, one has to have one or more of the following: HbA1c ≥7.25% (55.7 mmol/mol), blood glucose ≥200 mg/dL (11.1 mmol/l), a preceding diagnosis of diabetes according to any relevant International Classification of Diseases, ninth revision (ICD-9) codes and HbA1c ≥6.5%

or glucose >125 mg/dL (6.9 mmol/l), or had purchased antihyperglycemic medication twice within the last 2 months. Patients are identified by an automated database search and therefore the registry is not dependent on physicians actively reporting on the patient to the registry.

Electronic patient records of diabetic patients 18–89 years old who had a dispensed prescription for metformin during 2009–2011 were screened for study eligibility. Inclusion criteria were all patients in the diabetes registry who have been receiving metformin monotherapy for at least 90 continuous days prior to an available HbA1c result of >7%. The date of the HbA1c measurement was defined as the index date. Patients which were not continuously enrolled in MHS for at least 12 months prior to and 12 months following the index date were excluded (see Appendix 1 for patient selection process). Cardiovascular disease (CVD) was defined as occurrence of myocardial infarction or performance of cardiac revascularizations by percutaneous coronary intervention or coronary artery bypass grafting as reported from hospital charge records, as indicated in the MHS' registry of cardiovascular patients [13].

Renal impairment at baseline was defined as at least one eGFR test <45 mmol/l in the year prior to index date.

Diabetic ophthalmic disease or disorder was defined as any diagnosis of retinopathy, retinal edema or diabetic glaucoma before index date [14].

Socioeconomic status (SES) was defined by the 2008 national census [15] according to the poverty index of the member's enumeration area, ranging between 1 (lowest) and 10 (highest). The poverty index was based on several parameters including household income, education, crowding, material conditions and car ownership. For analyses, the continuous covariate was categorized as low (<5), moderate (5–6) and high (>7) socioeconomic status.

Data extracted for this study included sociodemographic characteristics, diabetes duration, diabetes medications, co-morbidities and HbA1c laboratory values.

We classified treatment change groups based on the first treatment change when it occurred during the follow up period.

• Statistical analysis

Chi-square test for categorical variables and ANOVA test for continuous variables were performed to determine significant differences in baseline characteristics between treatment groups. The baseline period was defined as 12 months prior to index date.

Multivariable logistic regression with first order interactions was used to describe the association between patients characteristic and treatment change within one year of the index date. For the analysis of associations between treatment change and T2DM patient characteristics we excluded patients who discontinued therapy (n = 677). No co-linearity was observed by variance Inflation Factors test (all factors <5). The outcome is a composite indicator of treatment intensification (defined as metformin titration or add-on) versus switch or continuation of the same dose of metformin without any DM medication adds on.

Odds ratios (ORs) and their 95% confidence intervals (CIs) were computed, controlled for potential confounders associated with increased probability of treatment change.

Variance Inflation Factors test was performed to detect co-linearity between covariates in the multivariable logistic regression model.

Model selection was performed using likelihood ratio forward selection, to assess appropriateness of each covariate to be included in the model.

Classification and regression (CART, also known as recursive partitioning) decision tree was used to account for higher order interactions (thus improving the possible predictive accuracy). CART was implemented using R software [16]. Complexity parameter (cp) for the tree was selected by the minimum cross validation error, to avoid over-fitting and thus increase external validity.

Results

Of 120,813 patients with T2DM included in the registry during this time period, a total of 7705 patients were eligible for analysis, with a mean follow-up time of 3 years (SD = 9 months) (see appendix for patient selection process). **Table 1** lists baseline characteristics in the year before index date. Mean age was 61.87 years (SD 11.37); 56% were males. Mean HbA1c was 7.68% (SD 0.88). A total of 69.3% of patients had hypertension, 90% had dyslipidemia, 53% were obese and 25% had CVD co-morbidity **(Table 1)**.

Figure 1 describes the distribution of treatment patterns among the study population. A total of 4336 (56%) patients changed their treatment within 1 year, either by increasing metformin dose (n = 1550 [36%]), by adding

Table 1. Baseline patients characteristics and characteristics by treatment group.

Characteristic	Total	Continued metformin monotherapy† with same dose	Discontinued metformin‡	Add-on§ therapy	Metformin titration¶	Switch# to other agent	p-value
Patients (n)	7705	2692	677	2591	1550	195	–
Age, years (mean, SD)	61.87 (11.37)	64.47 (11.28)	61.05 (11.97)	59.43 (10.55)	61.59 (11.03)	64.76 (12.64)	<0.001
HbA1c (mean, SD), %	7.68 (0.88)	7.48 (0.58)	7.63 (0.8)	8.02 (1.14)	7.59 (0.72)	7.77 (0.92)	<0.001
BMI kg/m^2 (mean, SD)	31.07 (5.48)	30.67 (5.35)	30.62 (5.42)	31.59 (5.58)	31.43 (5.57)	30.97 (5.19)	<0.001
SES (mean, SD)	5.88 (2.18)	5.74 (2.18)	5.75 (2.23)	6.11 (2.17)	5.82 (2.16)	5.84 (2.08)	<0.001
Male sex (%)	4311 (56)	53.4%	56.2%	58.8%	54.7%	57.9%	0.003
CVD (%)	1903 (25)	26.7%	23.1%	22.5%	24.3%	38.5%	<0.001
Hypertension (%)	5339 (69)	72.5%	63.6%	68.5%	68.5%	76.9%	<0.001
Ophthalmic disorders (%)	570 (7)	7.3%	6.6%	7.9%	6.7%	10.8%	0.002
Dyslipidemia (%)	6915 (90)	90.8%	87.1%	89.7%	90.5%	89.2%	0.010
Renal impairment (%)	277 (4)	3.0%	3.3%	2.1%	1.7%	24.0%	<0.001

Baseline characteristics of the total study populations and the different observed treatment groups. Differences between groups were assessed by analysis of variance.
†Metformin monotherapy: patients who remained on same dose of metformin monotherapy until end of follow-up
‡Discontinued metformin: patients who during the follow-up period discontinued metformin and did not receive alternative antidiabetic medications.
§Add-on: patients who during the follow-up received additional antidiabetic medications.
¶Metformin titration: patients in whom during the follow-up the metformin dose was increased.
#Switch: patients in whom during the follow-up metformin was stopped and other antidiabetic medications were prescribed.
CVD: Cardiovascular disease; SD: Standard deviation; SES: Socioeconomic status (1–10 scale).

a drug to metformin therapy (n = 2591 [60%]) or by discontinuing metformin treatment and switching to different antidiabetic medications (n = 195 [4%]). Most common drugs added to metformin treatment were dipeptidyl peptidase 4 (DPP-4) inhibitors (n = 1470 [57%[) and sulfonylurea (SU; n = 839 [32%]).

Time to treatment change in patients with add-on therapy, metformin titration, and patients who switched treatment was 4.08 (SD 3.78), 3.88 (SD 3.56) and 5.90 (SD 4.35) months, respectively. There was no significant difference in time to treatment add-on between the various drugs added.

In a multivariate analysis of associations between treatment intensifiers (patients who had treatment add-on or an increase in metformin dose) and all examined covariates, after controlling for sex and co-morbidities, we found that the strongest predictors of treatment change were higher HbA1c, younger age, higher socioeconomic status (SES) and patients with risk factors for CVD (hypertension or obesity and dyslipidemia) (CI to be added). Patients with HbA1c of ≥8.5% had an odds ratio (OR) of 3.42 (95% CI: 2.88–4.07) for treatment change compared with HbA1c 7–7.5%. Patients aged ≥75 years had an OR of 0.46 (95% CI: 0.38–0.55) for change compared with patients <55 years and patients with high vs. low SES had an OR of 1.33 (95% CI: 1.17–1.50) **(Table 2)**.

The association between treatment change and baseline covariates analyzed by CART. There was a high similarity between the logistic regression and the CART results, i.e., the most important variables in classification were HbA1c and age. Cut point of the decision tree for treatment intensification by CART analysis was identifies at HbA1c of 7.75% and in patients younger than 63.5 years of age. A small portion of the population (3%) suffered from renal impairment at baseline and thus this partitioning did not add enough value and was pruned in the final version of the tree with the minimum cross-validation error.

Discussion

In this real-world study, we demonstrated that in 56% of T2DM patients treated with metformin only, who have suboptimal glucose control as demonstrated by an HbA1c >7%, treatment was changed within 1 year. In 36% of these patients metformin dose was increased, in 60% another antihyperglycemic drug was added, and 4% of patients switch to a different medication. Median time to treatment change was 3 months.

Only a few studies have addressed the issue of time to change of diabetes medications in patients with suboptimal glucose control. In a study assessing glycemic control in seven European countries, of 2023 patients treated with metformin and either SU or thiazolidinedione only

23% had adequate glycemic control, defined as HbA1c <6.5% a mean of 2.6 years after treatment change [8]. These results imply that most patients fail to reach the target HbA1c, yet physicians are slow to respond and intensify their treatment. In another study [9], among 8068 T2DM patients receiving oral antidiabetic monotherapy only 21.4% reached the goal of HbA1c <7%. Median time to treatment change in patients with an HbA1c in the range of 7–10% was 372 days, and for patients with an HbA1c >10% median time to treatment change was 166 days. Mean follow-up was 2.5 years (SD: 1.3 years). Fu *et al.* [10] demonstrated that among 12,566 patients with HbA1c >7% receiving metformin monotherapy for at least 6 months, median time to treatment intensification was 14 months. The median follow-up time was 2.2 years (mean: 2.9 years).

Our results show that in this cohort, physicians were inclined to perform treatment change sooner compared with other reports and that in about 25% of patients treatment change was performed very early, within 3 months. In MHS diabetes treatment guidelines and protocols widely distributed through patients medical records, physicians receive reminders regarding in case patients do not reach HbA1c goals, and are reminded to perform regular follow-up procedures. This probably contributed to less inertia in treating these patients.

The strongest predictors of treatment change were higher HbA1c, younger age and a higher

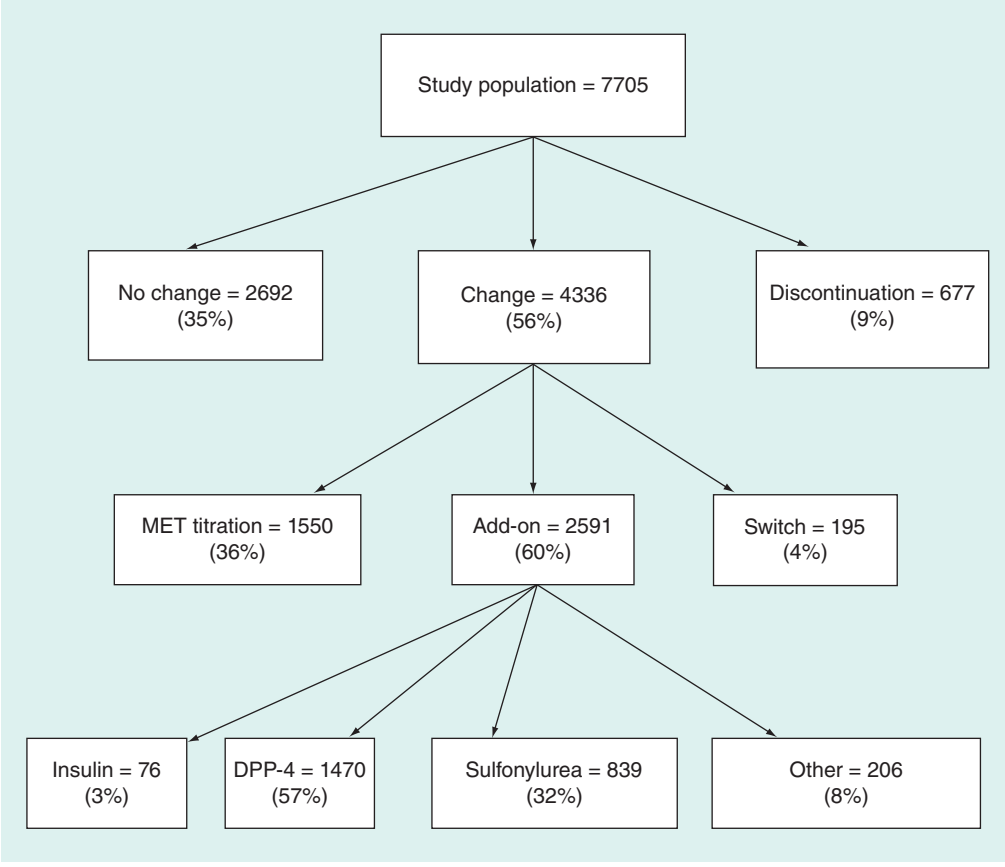

Figure 1. Distribution of treatment patterns among the study populations. No change signifies patients who remained on MET monotherapy without a dose change until the end of follow-up. Change signifies patients who had additional antidiabetic drugs added to their regimen or patients that had their MET therapy titrated. MET titration signifies patients in whom during the follow-up the MET dose was increased (calculated average dose based on pharmacy claims). Add-on signifies patients who during the follow-up received additional antidiabetic medications. Switch signifies patients in whom during the follow-up MET was stopped and other antidiabetic medications were prescribed. DPP-4 signifies DPP-4 inhibitors. Other signifies other antidiabetic drugs.
DPP-4: Dipeptidyl peptidase 4; MET: Metformin.

Table 2. Association between patient characteristics and treatment intensification (logistic regression results).

Covariate	p-value	OR	95% CI
Age group (<55 years as reference):	<0.001	–	–
– 55–64 years	0.059	0.88	0.77–1.00
– 65–74 years	<0.001	0.66	0.57–0.76
– ≥75 years	<0.001	0.46	0.38–0.55
HbA1c (7–7.5% as reference):	<0.001	–	–
– 7.5–8%	<0.001	1.55	1.38–1.75
– 8–8.5%	<0.001	2.33	1.93–2.81
– >8.5%	<0.001	3.42	2.88–4.07
Renal impairment	0.714	1.40	0.23–8.62
Dyslipidemia	0.022	1.22	1.03–1.44
Socioeconomic status (low as reference)	<0.001	0.00	0.00–0.00
Moderate socioeconomic status	0.113	1.11	0.98–1.26
High socioeconomic status	<0.001	1.33	1.17–1.50
Obesity	<0.001	1.25	1.13–1.39
Age group (<55 years as reference) × renal impairment	0.026	–	–
Age group (55–64 years) × renal impairment	0.891	1.15	0.16–8.45
Age group (65–74 years) × renal impairment	0.161	0.25	0.04–1.74
Age group (≥75 years) × renal impairment	0.651	0.65	0.10–4.21
Constant	<0.001	–	–

OR: Odds ratio.

socioeconomic status based on the multivariate model. The relationship between increased HbA1c and morbidity and mortality is well documented in T2DM [17,18]. Therefore, it is not surprising that higher levels of HbA1c are perceived by physicians as related to increased patients risk and are therefore a driver for treatment intensification [9,10,18]. Our results support these findings.

Age was a major factor affecting treatment change. Patients aged ≥75 years were less likely to have a treatment change compared with patients <55 years. Results from other studies regarding the impact of age on treatment intensity are conflicting. Fu *et al.* [10] demonstrated a significant association between younger age and treatment change in response to suboptimal HbA1c levels in patients failing metformin monotherapy. Gomez *et al.* [19] demonstrated that in newly diagnosed elderly patients (mean age was 73 years) treated with metformin only, median time to treatment change was 5.1 years in 1997, and increased to 6.1 years in 2003. In contrast, Mata-Cases *et al.* [19] demonstrated that age was not related to clinical inertia. Mean age was similar (67 years) in patients with clinical inertia and in patients with clinical intensification.

Others have demonstrated that cardiovascular disease was related to a more aggressive clinical approach [20]. This was in accordance with our findings that hypertension or obesity and dyslipidemia were significantly related to a more proactive clinical approach.

Among patients who added a second anti hyperglycemic agent DPP-4 inhibitors were the leading choice (57%) followed by Sulfonylurea (32%). This choice represents the acceptance that DPP-4 inhibitors provide noninferior glycemic control compared with sulfonylureas, but result in a reduction of body weight and a significantly lower risk of hypoglycemia in patients with Type 2 diabetes, as shown in both clinical trials and real life settings [21]. The higher co-payment required for DPP-4 inhibitors may explain the observation that of their users belonged to a higher SES and had a lower BMI.

Our study has limitations which should be recognized. This was a noninterventional observational study. Therefore, all information relied on the completeness of the medical records of routine clinical visits. Since data were obtained from an observational registry, clinical events may not have been captured in full and patient follow-up may have been less stringent compared with randomized controlled trials. It is possible that some co-morbidities were not recorded in full and laboratory data were missing at times in the relevant time frame prespecified in this study. It is also important to note that failing to achieve HbA1c target depends not only on the physician's

activism but also on the patient's personal preferences as well as difficulties with adherence both to medications and to regular clinical follow-up. Although we did not directly measure patients preferences, our results support the notion that physicians incorporated personal tailoring to their clinical approach, thus promoting a more aggressive clinical approach to younger patients with higher HbA1c levels and less co-morbidity.

To conclude, this real world study indicates that some clinical inertia in T2DM patients treated with metformin and suboptimal compliance with treatment guidelines was evident in the study population some clinical inertia in T2DM patients treated with metformin monotherapy and suboptimal compliance with treatment guidelines was evident in the study population. The extent of the problems in Israel appears to be less severe than that reported in previous studies, particularly among younger patients and those with cardiovascular risk factors. In addition, our data suggest there also appears to be some adherence to the approach of personally adjusted treatment goals as suggested by the ADA/EASD guidelines. Nonetheless, given that some T2DM patients are still not optimally managed, disease management programs aimed at improving guideline adherence and reducing inertia are warranted.

Conclusion & future perspective

In this study, we used a large real life medical database to evaluate the implementation of treatment guidelines in initial therapy of patients with Type 2 diabetes. Future analysis will include evaluation of the value of adherence to guidelines and the effect of each drug choice on long-term glucose control, time to insulin use and development of diabetes complications. The comprehensive background information in these databases can be used to better characterize patients who benefit from each medication, setting the basis for a more personalized treatment approach.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Appendix 1

Patients' selection process

N = 120,813 Type 2 diabetes in the database.

- Exclude n = 39,237 (32%) no metformin purchases between 2009 and 2012.

N = 81,576

- Exclude n = 26,851 (33%) patients who received nonmetformin antidiabetic medications during 12 months before the first metformin purchase.

N = 54,725

- Exclude n = 16,929 (31%) with less than 90 days continuous metformin coverage.

N = 37,796

- Exclude n = 7,990 (21%) patients without any HbA1c measurement in the relevant time window, namely: after at least 90 days of metformin continuous monotherapy, within 60 days since discontinuation of continuous monotherapy (if any), and before any other antidiabetic medication purchase.

N = 29,806

- Exclude n = 19,213 (51% of 37,796) where all such measurements were <=7.

N = 10,593

- Exclude n = 810 (8%) ages <18 or >89.

N = 9,783

- Exclude n = 356 (3%) patients who left the HMO after less than 12 months since index or continuously enrolled less than 12 months before index and n = 1722 (18%) with less than 12-months follow-up.

N = 7705