Metformin treatment does not affect the risk of ruptured abdominal aortic aneurysms

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ABSTRACT

Objective: Diabetes counteracts formation and rupture of abdominal aortic aneurysms, possibly through arterial matrix accumulation. Use of metformin, on the other hand, reduces arterial accumulation of matrix molecules. Consequently, we hypothesized that metformin treatment may reverse the protective role of diabetes on the development and course of aneurysms, that is, that metformin would be associated with aneurysm rupture among individuals with diabetes.

Methods: Using nationwide Danish registry data, we performed a nested case-control study on the association between long-term use of metformin and ruptured abdominal aortic aneurysm (RAAA). The source population was defined as all individuals in Denmark with diabetes. Cases were all individuals within the source population who were hospitalized with a primary diagnosis of RAAA. For each case, 10 controls matched by age and sex were randomly selected from the source population by risk set sampling. The main exposure measure was a cumulative dispensing of 1000 g of metformin between January 1995 and the index date.

Results: We identified 362 cases of RAAA during 1998 to 2013, of which 83.7% occurred in men with a median age of 74 years. In total, 22.4% of the case population were long-term metformin users compared with 28.8% of the controls. We found a statistically nonsignificant protective effect of long-term metformin use toward RAAA with crude odds ratio (OR) of 0.74 (confidence interval, 0.54-1.00). When adjusted for covariates, OR increased to 0.84 (confidence interval, 0.61-1.17). None of the subgroups had ORs deviating substantially from the main result.

Conclusions: Metformin use does not increase the risk of RAAA among individuals with diabetes. (J Vasc Surg 2017;■:1-7.)

Abdominal aortic aneurysm (AAA) is a common, asymptomatic condition with a prevalence of 1.2% to 4% in people older than 50 years.[1-4] If left untreated, AAAs may progress to rupture, which has a short-term mortality rate of up to 76%.[5,6] The risk of rupture is closely related to aneurysmal size.[7,8] Roughly, it is estimated that 40% of ruptured AAAs (RAAAs) never reach the hospital.[5,9,10] The progression of AAAs is characterized by degradation and remodeling of the arterial extracellular matrix. AAAs have traditionally been seen as a manifestation of atherosclerosis in the abdominal aorta, and the usual risk factors for atherosclerosis, including diabetes, were assumed to apply.[3,11-13] However, studies have consistently found that diabetes markedly reduces the prevalence of AAA.[14-17] The mechanism underlying this paradoxical association is unknown but may relate to hyperglycemia,[18] the effects of antidiabetics,[19] or other factors in the diabetic environment.

The commonly prescribed antidiabetic drug metformin has documented beneficial cardiovascular effects in patients with type 2 diabetes.[20] The mechanisms underlying metformin's cardiovascular effects are unknown, but it is noteworthy that metformin users have reduced accumulation of vascular basement membrane proteins, which was recently found as a distinct feature of the arterial disease in type 2 diabetes.[21] In line with this observation, it is of interest that genetically engineered mice lacking basement membrane collagens display arterial fragility including aneurysms.[22,23] The observed effect of metformin use on arterial basement membranes is moreover in line with metformin's capacity to reduce the amount of the basement membrane protein fibulin-1 in plasma, an effect that was independent of its glucose-lowering effects as shown in a randomized study including treatment with both metformin and glitazones.[24] In relation to putative effects of metformin in the vasculature, it is also noteworthy that experimental stimulation of the metformin-sensitive adenosine monophosphate-activated kinase leads to acceleration of AAA formation in mice caused by dysfunctional

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arterial matrix turnover.[25] Thus, there is a theoretical rationale that metformin use could reverse the protective effect of diabetes on AAA formation through effects on the arterial matrix metabolism. Of note, other studies' hypotheses have been opposite; for example, Fujimura et al[26] suggested that use of metformin reduces the risk of AAA formation, in continuation of the findings that diabetes reduces the prevalence of AAA.

The aim of this study was to investigate whether the risk of RAAA among individuals with diabetes is reversed in relation to intake of metformin. If this were the case, it would be manifested as a positive association between metformin use and risk of RAAA among individuals with diabetes.

ARTICLE HIGHLIGHTS

- **Type of Research:** Nested case-control study of a nationwide Danish registry
- **Take Home Message:** In 362 cases of ruptured abdominal aortic aneurysm, metformin did not increase the risk of rupture among individuals with diabetes.
- **Recommendation:** Metformin does not appear to increase the rate of aneurysm rupture among individuals with diabetes, despite antagonizing some effects of diabetes that are thought to protect against rupture.

METHODS

Using nationwide Danish data sources, we performed a population-based case-control study analyzing the association between long-term use of metformin and RAAA. In keeping with the underlying rationale explained before, the study was nested within a cohort of individuals with diabetes.

Data sources. Three nationwide Danish data sources were used for this study: the Danish National Patient Register, the Danish National Prescription Register, and the Danish Civil Registration System.

The National Patient Register contains data regarding all hospitalizations in Denmark since 1977 and outpatient visits since 1995. The hospitals report admissions, surgical procedures, and diagnoses, the last using the *International Classification of Diseases* (ICD-8 from 1978 to 1993 and ICD-10 thereafter).[27] Surgical procedures are recorded by the Nordic Classification of Surgical Procedures.

The National Prescription Register contains data on all redeemed prescriptions at an individual user level since 1995.[28] The information includes the prescription holder, the substance, the date, and the prescriber among 46 variables in total. The dosing information and the indication for prescribing are not recorded. Drugs are grouped according to the Anatomical Therapeutic Chemical classification system developed by the World Health Organization, and the quantity is expressed by the defined daily dose also developed by the World Health Organization.[29]

The Civil Registration System contains daily updated information on marital status, addresses, emigration, vital status, date of death, and causes of death, if any.[30,31]

The Danish national health care system is tax supported and provides the entire Danish population (approximately 5.6 million in 2014) with free, unrestricted access to public health services, including hospital care, and partial reimbursement for most prescribed drugs. All Danish residents are assigned a unique 10-digit civil registration number, and this number enables unambiguous linkage across all health care registers at an individual level. Statistics Denmark, a governmental institution, performed anonymous linkage of the data.[32]

Source population. The source population (ie, the cohort that gave rise to the cases and the controls) was defined as all individuals in Denmark with diabetes mellitus of any type. Individuals entered the cohort of eligible cases and controls on the first date of fulfilling either of two criteria: (1) any hospital diagnosis (inpatient or outpatient) of diabetes (ICD-10 code E10-11) or (2) having redeemed at least two prescriptions of an antidiabetic (Anatomical Therapeutic Chemical code A10) other than metformin.

The study period was 1998 to 2013. Individuals were required to be at least 50 years of age for cohort entry and left the cohort on the earliest of the following events: RAAA, death, first emigration, or end of study period. Exclusion criteria were any history of Marfan syndrome, Ehlers-Danlos syndrome, or other known aortic disease (dissection or thoracoabdominal aortic aneurysm) before cohort entry.

Cases and controls. Cases were all individuals within the source population who were hospitalized with a main diagnosis of RAAA (ICD-10 code I713) between 1998 and 2013. We excluded individuals who survived >30 days after the diagnosis of RAAA without undergoing any surgery within the first 7 days as we assumed those to be erroneously coded as RAAA. We did not differentiate severity of RAAA. Cases were assigned an index date identical to their first contact with this diagnosis.

Controls were selected from the source cohort by use of a risk set sampling strategy. For each case, we randomly selected 10 controls alive at the index date matched by birth year and sex from our source population. The controls were assigned an index date identical to the diagnosis date of the corresponding case, and on that date they were analyzed regarding potential use of drugs and baseline confounders. Individuals were eligible for sampling as controls before they became cases. Thereby, the calculated odds ratios (ORs) are unbiased estimates of the incidence rate ratios that would have emerged from a cohort study in the source population.[33]

Exposure definition. The main exposure measure (long-term exposure) was a cumulative amount of metformin of 1000 g dispensed between January 1995 and the index date. For pharmaceutical products consisting of a combination of metformin and other antidiabetics, we included the amount of the metformin component in our exposure measure. The limit of 1000 g of metformin was subjected to sensitivity analyses as described later. As data from the Prescription Registry are available only from 1995 onward,[28] we studied cases and controls only from 1998 to allow subjects to be able to collect a cumulative dose of 1000 g of metformin and to be able to better ascertain the duration of exposure.

Confounders. The potential confounding effects of age, sex, and calendar year were controlled for by using the matched design and conditional analysis. Other covariates included in the analysis were any previous diagnosis or treatment of chronic obstructive pulmonary disease, atherosclerotic disease (any of the following: coronary heart disease, cerebrovascular disease, peripheral atherosclerotic disease), renal failure, and cancer. In addition, we included any history of use of lipid-lowering drugs, oral corticosteroids, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and platelet inhibitors. Individuals whose hypertension is treated exclusively in general practice do not have their hypertension diagnosis reported to the National Patient Register. Unfortunately, we cannot identify hypertensive individuals from the prescription data because the indication for treatment is rarely recorded and because all drugs for hypertension can be used for other indications as well. Last, we adjusted for additional use of antidiabetics other than metformin.

The distribution of these covariates was described for cases, controls, exposed controls, and unexposed controls separately (Table I) in keeping with the "quasi-cohort" rationale described by Suissa.[34] The codes used to identify these conditions or drug-related covariates are listed in Supplementary Tables I and II (online only).

Analysis. The analysis conformed to a conventional matched case-control study. We used conditional logistic regression to compute the OR associating long-term metformin exposure with RAAA while including the potential confounders as covariates in the model. Both crude and the adjusted ORs are presented. The reference for all analyses was individuals with no past prescriptions for metformin, unless otherwise specified.

We included several prespecified sensitivity and subgroup analyses: the definition of long-term metformin exposure was set to 200, 400, 2000, and 4000 g instead of the 1000 g as in the main analysis; the main result was analyzed separately for men, women, and individuals older or younger than 70 years; and analyses of the cases were performed regarding fatal or nonfatal outcome within 30 days and whether the individuals had a prior diagnosis of AAA.

All analyses were performed using Stata Release 13.0 (StataCorp LP, College Station, Tex).

Ethics. This project was approved by the Danish Data Protection Agency (14/40202). Approval from an ethics review board is not required in Denmark for register-based studies.[35] Analyses were done on anonymized data, and therefore no patient informed consent was required according to Danish law.[27]

RESULTS

During 1998 to 2013, 502 eligible individuals with diabetes and RAAA were identified from the National Patient Register. We excluded 140 individuals who did not undergo surgery and were still alive after 7 days, thus leaving 362 cases. The baseline characteristics of the RAAA cases and corresponding controls are shown in Table I. The median age was 74 years, and 84% were men. In all, 22.4% of the case population were long-term metformin users compared with 28.8% of the controls.

Comparing cases and controls in relation to long-term metformin use, we found an OR of 0.74 (confidence interval, 0.54-1.00). When adjusted for covariates, the OR increased to 0.84 (confidence interval, 0.61-1.17).

When changing the cumulated use of metformin from 1000 g used in our main analysis, we found lower ORs with increasing metformin use, whereas the OR for doses <1000 g was above unity (Table II).

In subgroup analyses, ORs were above 1 for individuals older than 80 years and with longer duration of diabetes (Table III). No other subgroup differed markedly.

DISCUSSION

In this nationwide case-control study investigating the association between RAAA and use of metformin among individuals with diabetes, metformin use did not increase the risk of RAAA.

This could seem in contrast to other studies. Fujimura et al[26] studied 58 individuals with diabetes and AAAs and found an inverse association with metformin and AAA enlargement. However, this is a modest sample size for using growth rate as an outcome variable as it is known to be associated with large variability of measurement, leaving the study insufficiently powered. In contrast, Hsu et al[36] recently studied 4468 cases with AAAs and 4468 matched controls. They found that metformin, sulfonylureas, and thiazolidinedione were associated with a lower risk for development of AAAs in a dose-response pattern. Although this dose-response pattern could be interpreted as an argument for a protective effect, the prescription of higher dose may also relate to the presence of worse glycemic status. The interpretation is therefore not simple, and the higher

Table I. Characteristics of cases of ruptured abdominal aortic aneurysm (*RAAA*) and corresponding controls

Characteristics	Cases of RAAA (n = 362)	Controls (n = 3620)	*	Exposed controls (n = 1044)	Unexposed controls (n = 2576)
Sex					
Men	303 (83.7)	3030 (83.7)		888 (85.1)	2142 (83.2)
Women	59 (16.3)	590 (16.3)		156 (14.9)	434 (16.8)
Age, years, median (IQR)	74 (68-79)	74 (68-79)		72 (68-77)	74 (69-80)
Year of inclusion					
1998-2002	90 (24.9)	900 (24.9)		115 (11.0)	785 (30.5)
2003-2007	106 (29.3)	1060 (29.3)		238 (22.8)	822 (31.9)
2008-2013	166 (45.9)	1660 (45.9)		691 (66.2)	969 (37.6)
Use of antidiabetics					
Metformin, never use	184 (50.8)	1691 (46.7)		(n < 5)	1691 (65.6)
Metformin, ever use	178 (49.2)	1929 (53.3)		1044 (100.0)	885 (34.4)
Metformin, long-term use	81 (22.4)	1044 (28.8)	*	1044 (100.0)	(n < 5)
Insulins	49 (13.5)	1010 (27.9)	*	350 (33.5)	660 (25.6)
Sulfonylureas[a]	185 (51.1)	2261 (62.5)	*	756 (72.4)	1505 (58.4)
Other antidiabetics[b]	31 (8.6)	353 (9.8)		217 (20.8)	136 (5.3)
Preadmission hospital-diagnosed comorbidity					
Atherosclerotic disease[c]	167 (46.1)	1211 (33.5)	*	330 (31.6)	881 (34.2)
COPD[d]	65 (18.0)	403 (11.1)	*	103 (9.9)	300 (11.6)
Renal disease	36 (9.9)	247 (6.8)	*	69 (6.6)	178 (6.9)
Cancer[e]	34 (9.4)	517 (14.3)	*	138 (13.2)	379 (14.7)
Preadmission medicines					
NSAIDs	278 (76.8)	2593 (71.6)	*	811 (77.7)	1782 (69.2)
Statins	220 (60.8)	1815 (50.1)	*	738 (70.7)	1077 (41.8)
Angiotensin-converting enzyme inhibitors	229 (63.3)	2047 (56.5)	*	721 (69.1)	1326 (51.5)
Antiplatelet therapy[f]	259 (71.5)	2172 (60.0)	*	696 (66.7)	1476 (57.3)
Oral corticosteroids	123 (34.0)	989 (27.3)	*	308 (29.5)	681 (26.4)

COPD, Chronic obstructive pulmonary disease; *IQR,* interquartile range; *NSAIDs,* nonsteroidal anti-inflammatory drugs.
Exposure was defined by a cumulative dispensing of 1000 g of metformin before the index date.
Values in parentheses are percentage unless otherwise indicated.
*$P \leq .05$, statistical significance between cases and controls.
[a]Gliclazide, glipizide, glimepiride, and glibenclamide.
[b]Acarbose, liraglutide, repaglinide, rosiglitazone, and sitagliptine.
[c]Myocardial infarction, congestive heart failure, peripheral arterial disease, or cerebrovascular disease.
[d]Either diagnosis or anti-COPD therapy: leukotriene antagonists, cromoglicic acid, theophylline, anticholinergics, inhaled adrenergics, mucolytics, or inhaled glucocorticoids.
[e]All cancers except from skin cancer.
[f]Acetylsalicylic acid, clopidogrel, or dipyridamole.

protection may also simply relate to different glycemic status among groups taking different doses. Hsu et al[36] focused on individuals with diabetes diagnosed with an AAA, whereas we analyzed individuals with RAAA because this is the main purpose for treating AAA, and RAAAs are a more precise although indirect measure of AAA size and progression. Furthermore, Hsu et al[36] reported a low prevalence of AAA in Asian populations and implied that the results of their study are not necessarily applicable to white populations. This is in agreement with many other studies[11,12] as the prevalence of AAA in Asians is 10-fold lower compared with whites, even when they live in the Western world.[37] Furthermore, the risk of diabetes is reported to be three to four times higher in Asian populations than in white populations,[38] and pathophysiologic differences are also reported.[39,40] These marked differences regarding diabetes and AAAs call for considering whether generalization of observations from Asian populations to a white population is possible.

Our study has several strengths. The main strength was the use of nationwide registers with complete coverage and continuously updated data on all Danish citizens, which eliminated recall bias, minimized selection bias, and provided a large sample compared with single-center studies. The proportion of individuals with diabetes not included in our study is likely to be small. The Danish National Patient Register comprises hospitalizations and outpatient visits, but we identified individuals with diabetes who only had been in contact with the primary

Table II. Dose-response and duration-response association between metformin and ruptured abdominal aortic aneurysm (RAAA) stratified by subgroups

	Cases (n = 362)	Controls (n = 3620)	Crude OR (CI)	Adjusted OR (CI)
Use of metformin				
Never	184	1691	1.00 (ref)	1.00 (ref)
Ever	178	1929	0.83 (0.66-1.04)	0.87 (0.69-1.11)
Long term	81	1044	0.74 (0.54-1.00)	0.84 (0.61-1.17)
Cumulative dose, g				
<500	59	547	0.98 (0.71-1.36)	0.99 (0.71-1.39)
500-999	37	317	1.13 (0.76-1.69)	1.14 (0.75-1.73)
1000-1999	40	377	0.95 (0.64-1.42)	0.98 (0.64-1.49)
2000-2999	18	223	0.82 (0.47-1.42)	0.92 (0.51-1.65)
≥3000	24	465	0.53 (0.32-0.87)	0.68 (0.40-1.15)

CI, Confidence interval; *OR*, odds ratio.
We adjusted for any previous diagnosis or treatment of chronic obstructive pulmonary disease, atherosclerotic disease (any of the following: coronary heart disease, cerebrovascular disease, peripheral atherosclerotic disease), renal failure, and cancer. In addition, we included any history of use of lipid-lowering drugs, oral corticosteroids, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, platelet inhibitors, and additional use of antidiabetics other than metformin.

Table III. Subgroup analysis of the association between long-term metformin use and ruptured abdominal aortic aneurysm (RAAA)

	Cases, long-term/never use	Controls, long-term/never use	Crude OR	Adjusted OR
Total	81/184	1044/1691	0.74 (0.54-1.00)	0.84 (0.61-1.17)
Sex				
Men	68/148	888/1407	0.76 (0.54-1.06)	0.85 (0.60-1.22)
Women	13/36	156/284	0.64 (0.31-1.32)	0.69 (0.29-1.64)
Age				
50-59 years	6/13	63/104	0.95 (0.33-2.77)	0.58 (0.10-3.32)
60-69 years	21/38	266/335	0.72 (0.38-1.35)	0.73 (0.36-1.50)
70-79 years	37/89	531/780	0.57 (0.37-0.89)	0.75 (0.46-1.22)
80+ years	17/44	184/472	1.23 (0.65-2.35)	1.36 (0.69-2.66)
Time since first antidiabetic				
1-4 years	26/54	243/502	0.87 (0.38-1.99)	1.10 (0.43-2.80)
>5 years	55/36	801/726	1.42 (0.86-2.35)	1.43 (0.84-2.43)
No. of oral antidiabetics other than metformin				
0	40/88	375/728	1.02 (0.63-1.66)	0.99 (0.56-1.76)
1 or more	41/96	669/963	0.62 (0.38-1.02)	0.65 (0.38-1.11)
Other subgroups				
No atherosclerotic disease[a]	43/98	714/1090	0.66 (0.43-1.02)	0.70 (0.44-1.11)
No previous AAA diagnosis	64/130	1027/1666	0.86 (0.61-1.23)	0.93 (0.64-1.34)
No COPD[b]	71/143	941/1492	0.78 (0.55-1.10)	0.83 (0.58-1.21)

AAA, Abdominal aortic aneurysm; *COPD*, chronic obstructive pulmonary disease; *OR*, odds ratio.
Long-term metformin use: cumulative use of 1000 g.
We adjusted for any previous diagnosis or treatment of chronic obstructive pulmonary disease, atherosclerotic disease (any of the following: coronary heart disease, cerebrovascular disease, peripheral atherosclerotic disease), renal failure, and cancer. In addition, we included any history of use of lipid-lowering drugs, oral corticosteroids, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, platelet inhibitors, and additional use of antidiabetics other than metformin.
[a]Myocardial infarction, congestive heart failure, peripheral arterial disease, or cerebrovascular disease.
[b]Either diagnosis or anti-COPD therapy: leukotriene antagonists, cromoglicic acid, theophylline, anticholinergics, inhaled adrenergics, mucolytics, or inhaled glucocorticoids.

health care system by including them on the basis of prescriptions of antidiabetics. Because all of our exposure measures were based on large cumulative amounts (ie, requiring multiple repeated prescriptions), they were likely to reflect the individuals' true intake. To our knowledge, the Danish National Patient Register has been validated by two studies regarding the diagnoses of aortic aneurysms, RAAA, and AAA.[41,42] The positive predictive value

for an "aortic aneurysms" diagnosis was ≥90%,[41] whereas it was 86% for RAAAs and 96% for AAAs.[42]

Our study also has potential limitations. The left truncation of medicine use from the Prescription Register may cause individuals who stopped using metformin before 1995 to be misclassified as metformin never users in our study, resulting in a potential conservative bias. Furthermore, we did not have data on lifestyle factors that could be potential confounders and had to rely on proxies (eg, chronic obstructive pulmonary disease for heavy smoking).

Several studies have analyzed drug modulation on aneurysmal growth,[19,26,36,43-45] and to the best of our knowledge, only three studies have previously analyzed the effect of antidiabetics in relation to AAAs in humans.[19,26,36] Thompson et al[19] studied drug-related modification on AAA growth and found that antidiabetics were associated with a reduced growth rate, independently of confounding factors such as use of other drugs. Although their number of individuals with antidiabetic use was limited compared with ours, they found that no single subclass of antidiabetics had a greater effect than the others.[19] This observation combined with ours suggests that it is diabetes, not its treatment, that has the protective effect on AAAs. Our results are in agreement with that.

CONCLUSIONS

We reject our hypothesis that metformin reverses the protective effect of diabetes on AAAs. This has both clinical and research implications. For the clinician, metformin can be safely prescribed to individuals with diabetes without fear of increasing their risk of RAAA. For the researcher, functional consequences of metformin's apparent effect on the arterial matrix composition should be re-evaluated.

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AUTHOR CONTRIBUTIONS

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Additional material for this article may be found online at www.jvascsurg.org.

Supplementary Table I (online only). *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes used to identify individuals with ruptured abdominal aortic aneurysm (*RAAA*), to exclude individuals without aneurysm, and to identify comorbidities

	ICD-8	ICD-10
Diabetes mellitus	249, 250	E10-11
RAAA	441.21	I713, DI718
AAA	441.20, 441.29	I714
Aortic dissection	441.09	I710
Thoracic or thoracoabdominal aortic aneurysm	441.10, 441.11, 441.19	I711-712, I715-716
Any dilation of the aorta	441.99	I719
Marfan syndrome	759.80	Q874
Ehlers-Danlos syndrome	757.24	Q796
Polycystic ovarian syndrome	256.90	E282
Comorbidities		
Myocardial infarction	410	I21-23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I110, I130, I132
Peripheral vascular disease	440, 441, 442, 443, 444, 445 Not 441.20, 441.21, 441.29	I70-74, I77 Not I713, I714, I718, I719
Cerebrovascular disease	430-438	I60-I69, G45-46
Hypertension	401, 403	I109, I15
Chronic pulmonary disease	490-493, 515-518	J40-47, J60-67, J684, J701, J703, J841, DJ920, J961, J982-3
Moderate to severe renal disease	403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12-13, N00-05, N07, N11, N14, N17-19, Q61
Any cancer	140-207 Not 173-174 (skin cancer except from malignant melanoma)	C00-96 Except from C44, skin cancer other than malignant melanoma

AAA, Abdominal aortic aneurysm; *ICD-8*, International Classification of Diseases, Eighth Revision.

Supplementary Table II (online only). Anatomical Therapeutic Chemical prescription codes used to identify preadmission medicine

A10BA02	Metformin
A10BD02	Metformin + sulfonamides
A10BD03	Metformin + rosiglitazone
A10BD05	Metformin + pioglitazone
A10BD07	Metformin + sitagliptin
A10BD08	Metformin + vildagliptin
A10BD10	Metformin + saxagliptin
A10BD11	Metformin + linagliptin
A10BD13	Metformin + alogliptin
A10BD15	Metformin + dapagliflozin
A10BD16	Metformin + canagliflozin
A10A	Insulins (change in subgroups in 1997)
A10BB01	Glibenclamide
A10BB03	Tolbutamide
A10BB07	Glipizide
A10BB09	Gliclazide
A10BB12	Glimepiride
A10BF01	Acarbose
A10BG02	Rosiglitazone
A10BH01	Sitagliptin
A10BX02	Repaglinide
A10BX07	Liraglutide
C10AA	Statins
C09AA/C09BA	Angiotensin-converting enzyme inhibitors plain + combinations (C02EA/C02LM before 1996)
C09C+D	Angiotensin II antagonists plain + combinations (losartan changed in 1996 from C02EX01)
C08	Calcium channel blockers (combination with diuretics changed in 1996 from C02LI)
C07	Beta-blocking agents
B01AC04	Clopidogrel
B01AC06	Acetylsalicylic acid
B01AC07	Dipyridamole
M01A	Nonsteroidal anti-inflammatory products
H02	Corticosteroids for systemic use
R03A	Inhaled adrenergics
R03BA	Inhaled glucocorticoids
R03BB	Inhaled anticholinergics
R03BC01	Cromoglicic acid, inhalant
R03DA	Xanthines
R03DC	Leukotriene receptor antagonists
R05CB	Mucolytics