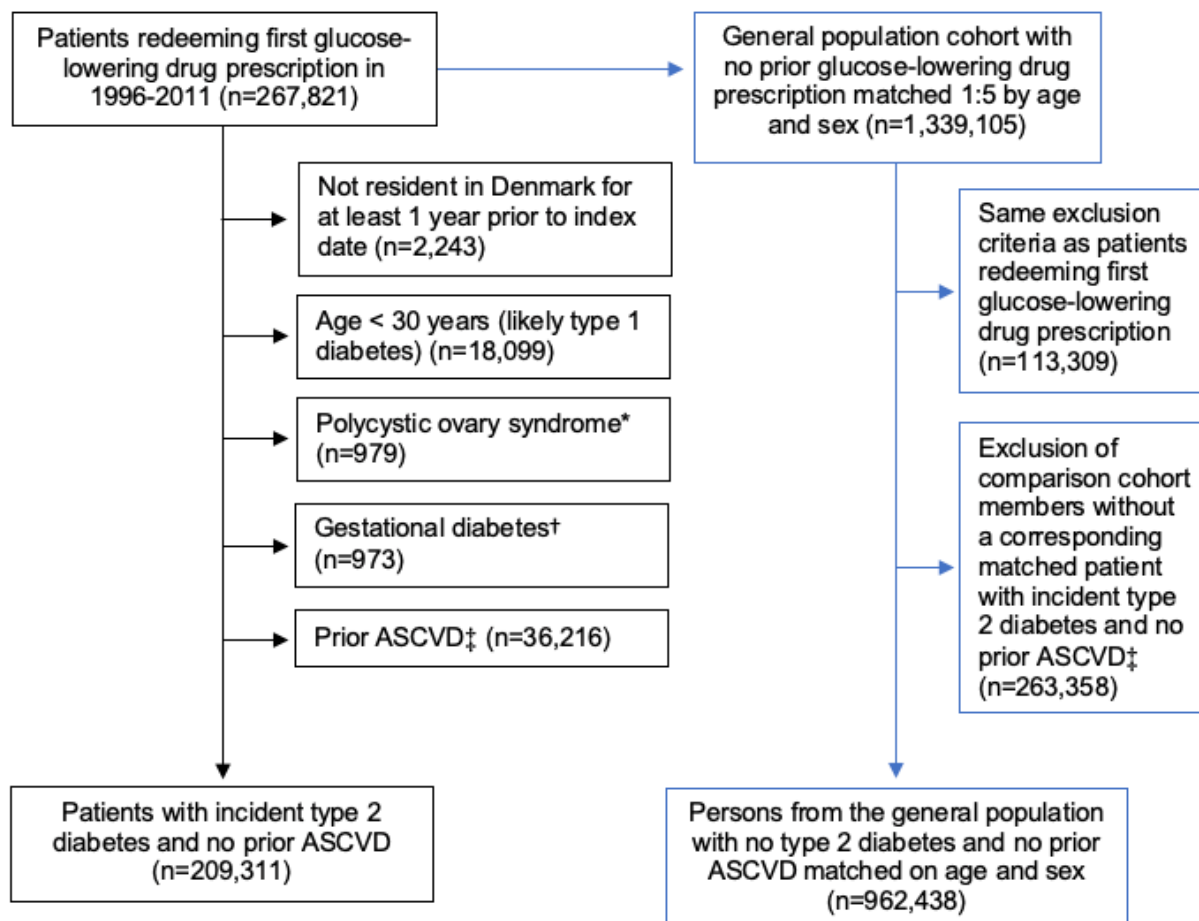


Supplemental Material

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Supplemental Figure S1. Flowchart of the study population

Flowchart of the study population selection with incident type 2 diabetes and matched persons from the general population, all without prior atherosclerotic cardiovascular disease.



* Polycystic ovary syndrome was defined as pre-existing hospital diagnosed polycystic ovary syndrome (ICD-10 code E28.2) or redemption of any metformin prescription (ATC code A10BA02) in combination with clomifen (ATC code G03GB02) within 12 months following inclusion.

† Gestational diabetes was defined as women giving birth (ICD-10 code O80-O84) within 9 months after inclusion.

‡ Prior atherosclerotic cardiovascular disease (ASCVD) was defined as previous diagnoses of ischemic stroke, myocardial infarction, coronary revascularization, peripheral artery disease, peripheral revascularization, and lower-limb amputation.

Supplemental Table S1. Anatomical therapeutic chemical codes used

Redemption of drug prescriptions identified in the Danish Prescription Registry using anatomical therapeutic chemical codes.

Medication	Anatomical Therapeutic Chemical Code
Insulin	A10A ^a
Metformin	A10BA ^a , A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD15, A10BD16, A10BD20, A10BD23
Sulfonylurea	A10BB ^a
DPP-4 inhibitor	A10BH, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD19, A10BD21, A10BD24
Glitazone	A10BG ^a
Statin	C10AA ^a , C10BA ^a
Beta-blocker	C07 ^a
Angiotensin-converting enzyme inhibitor	C09A ^a , C09B ^a
Angiotensin II receptor blocker	C09C ^a , C09D ^a
Calcium channel blocker	C08 ^a , C09BB, C09DB
Thiazide	C03AA ^a , C03AB ^a , C07B ^a
Aspirin	B01AC06, N02BA01
Adenosine diphosphate receptor inhibitor	B01AC04, B01AC22, B01AC24, B01AC25
Vitamin K antagonist (Warfarin, Phenprocoumon)	B01AA03, B01AA04
Clomifen	G03GB02
Markers of smoking	R03, N07BA
Alcohol-related disorders	N07BB

^aIncluding underlying codes

Supplemental Table S2. ICD-8 and ICD-10 codes used

Diagnoses identified in the Danish Register of Causes of Death and the Danish National Patient Registry using the International Classification of Diseases (ICD) codes, 8th and 10th revision.

Diagnosis	ICD-8 codes	ICD-10 codes	Comment
Women giving birth		E28.2	From the Danish National Patient Registry
Polycystic ovarian syndrome		O80-O84	From the Danish National Patient Registry
Cardiac death	410 ^a -414 ^a , 427.2, 427.6, 427.9, 427.0, 427.1, 795 ^a , 796 ^a	I20 ^a -I25 ^a , I46 ^a , I47.2, I49 ^a , I50 ^a , R96 ^a , R98.9, R99.9	From the Cause of Death Registry
Myocardial infarction	410	DI21 ^a	From the Danish National Patient Registry
Ischemic stroke	433, 434	DI63 ^a , DI64 ^a	From the Danish National Patient Registry
Heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	DI11.0, DI13.0, DI13.2, DI42.0, DI50 ^a	From the Danish National Patient Registry
Peripheral artery disease	440, 443, 444	DI70.1-DI70.9, DI73.9	From the Danish National Patient Registry
Moderate to severe renal disease	403, 404, 580-584, 590.09, 593.19, 753.10-753.19, 792	DI12 ^a , DI13 ^a , DN00 ^a -DN05 ^a , DN07 ^a , DN11 ^a , DN14 ^a , DN17 ^a -DN19 ^a , DQ61 ^a , BJFD2	From the Danish National Patient Registry
Atrial fibrillation	4274 ^a	I48 ^a	From the Danish National Patient Registry
Connective tissue disease	712 ^a , 716 ^a , 734 ^a , 446 ^a , 135.99	M05 ^a , M06 ^a , M08 ^a , M09 ^a , M30-M36 ^a , D86 ^a	From the Danish National Patient Registry
Any malignancy (excluding skin cancer)	140-194 ^a , 204-207 ^a , 200-203 ^a , 275.59	C00-C43 ^a , C45-C96 ^a	From the Danish National Patient Registry
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85	From the Danish National Patient Registry
Markers of smoking	491, 492	F17, J40-J44, Z72.0, Z71.6	From the Danish National Patient Registry
Obesity	277.99	E65-E68	From the Danish National Patient Registry
Alcohol-related disorders	291, 303.09-303.99, 456.00-456.09, 577.10, 571.10, 571.09, 979	E244, F10, G312, G721, I426, K70, K292, K852, K860, Z714, Z721, DQ860, DZ502	From the Danish National Patient Registry

^aIncluding underlying diagnosis codes

Procedures identified using surgical codes the Danish National Patient Registry and from the NOMESCO Classification of Surgical Procedures.

^aIncluding underlying procedure codes

Supplemental Table S4. Baseline patient characteristics of persons in the general population comparison cohort

	Comparison cohort for all analyses (no. = 962,438)	Comparison cohort: 1996-1999 (no. = 187,046)	Comparison cohort: 2000-2003 (no. = 205,228)	Comparison cohort: 2004-2007 (no. = 247,323)	Comparison cohort: 2008-2011 (no. = 322,841)
Male sex	517,916 (54)	103,634 (55)	113,223 (55)	130,020 (53)	171,039 (53)
Median age – yr (QL-QU)	60.5 (50.9, 69.9)	62.2 (52.3, 72.8)	60.4 (51.5, 70.7)	59.7 (49.7, 68.8)	60.5 (50.6, 68.6)
Hypertension	261,949 (27)	46,454 (25)	51,458 (25)	66,406 (27)	97,631 (30)
Heart failure	11,468 (1)	2,054 (1)	2,721 (1)	3,139 (1)	3,554 (1)
Moderate to severe renal disease	6,056 (1)	934 (0)	1,076 (1)	1,631 (1)	2,415 (1)
Atrial fibrillation	5,752 (1)	661 (0)	1,009 (0)	1,590 (1)	2,492 (1)
Connective tissue disease	21,881 (2)	3,548 (2)	4,255 (2)	5,579 (2)	8,499 (3)
Any malignancy (excluding skin cancer)	60,851 (6)	10,559 (6)	11,950 (6)	15,204 (6)	23,138 (7)
Moderate to severe liver disease	5,752 (1)	661 (0)	1,009 (0)	1,590 (1)	2,492 (1)
Obesity (ICD registered)	11,108 (1)	484 (0)	1,062 (1)	2,806 (1)	6,756 (2)
Markers of smoking	89,742 (9)	17,096 (14)	18,102 (14)	22,313 (14)	32,231 (10)
<i>Medical treatment</i>					
Statins	64,476 (7)	2,177 (1)	5,239 (3)	16,593 (7)	40,467 (13)
Beta-blocker	77,740 (8)	11,862 (6)	15,355 (7)	21,753 (9)	28,770 (9)
ACE inhibitor	72,070 (7)	8,125 (4)	10,009 (5)	18,137 (7)	35,799 (11)
ARB	47,474 (5)	2,691 (1)	7,597 (4)	13,711 (6)	23,475 (7)
Calcium channel blocker	80,016 (8)	13,410 (7)	14,679 (7)	18,806 (8)	33,121 (10)
Thiazide	93,086 (10)	16,013 (9)	18,735 (9)	25,626 (10)	32,712 (10)
Aspirin	81,206 (8)	15,255 (8)	16,471 (8)	21,286 (9)	28,194 (9)
ADP receptor inhibitor	1,115 (0)	<5 (0)	99 (0)	248 (0)	766 (0)
VKA	17,267 (2)	2,246 (1)	3,020 (1)	4,683 (2)	7,318 (2)

Numbers are counts (%) unless otherwise indicated. ARB, angiotensin II receptor blocker; QL, lower quartile; QU, upper quartile; VKA, vitamin K antagonist.

Supplemental Table S5. Risk of cardiac outcomes and all-cause death in patients with incident type 2 diabetes versus matched cohort

	Matched cohort				Diabetes vs. matched cohort			
	Matched cohort (no.)	Events (no.)	Event rate per 100 person-years (95% CI)	7-year CIP* (95% CI)	7-year risk difference †	Crude 7-year hazard ratio† (95% CI)	Sex- and age-adjusted 7-year hazard ratio† (95% CI)	Adjusted 7-year hazard ratio†, ‡ (95% CI)
Myocardial infarction								
1996-1999	187,046	13,850	0.5 (0.5 - 0.5)	3.6 (3.5 - 3.7)	3.3	1.90 (1.84 - 1.96)	2.00 (1.94-2.07)	1.92 (1.86 - 1.99)
2000-2003	205,228	11,564	0.4 (0.4 - 0.4)	3.0 (2.9 - 3.1)	2.2	1.71 (1.64 - 1.77)	1.73 (1.67-1.80)	1.60 (1.54 - 1.67)
2004-2007	247,323	9,335	0.3 (0.3 - 0.3)	2.3 (2.3 - 2.4)	1.1	1.48 (1.41 - 1.54)	1.46 (1.40-1.53)	1.36 (1.30 - 1.42)
2008-2011	322,841	7,617	0.3 (0.3 - 0.3)	2.0 (2.0 - 2.1)	0.8	1.38 (1.32 - 1.45)	1.34 (1.28-1.41)	1.29 (1.22 - 1.35)
Cardiac death								
1996-1999	187,046	15,729	0.6 (0.5 - 0.6)	4.4 (4.3 - 4.5)	2.7	1.59 (1.54 - 1.65)	1.77 (1.71-1.83)	1.62 (1.56 - 1.67)
2000-2003	205,228	10,016	0.4 (0.4 - 0.4)	2.8 (2.7 - 2.8)	1.4	1.53 (1.47 - 1.60)	1.59 (1.53-1.66)	1.41 (1.35 - 1.47)
2004-2007	247,323	6,171	0.2 (0.2 - 0.2)	1.6 (1.6 - 1.7)	0.9	1.51 (1.43 - 1.59)	1.50 (1.43-1.58)	1.31 (1.24 - 1.38)
2008-2011	322,841	3,730	0.1 (0.1 - 0.1)	1.1 (1.0 - 1.1)	0.5	1.53 (1.44 - 1.64)	1.45 (1.36-1.55)	1.35 (1.26 - 1.44)
All-cause death								
1996-1999	187,046	96,862	3.4 (3.4 - 3.4)	18.4 (18.2 - 18.6)	10.6	1.56 (1.54 - 1.58)	1.73 (1.70-1.75)	1.63 (1.61 - 1.65)
2000-2003	205,228	76,554	2.7 (2.7 - 2.7)	15.2 (15.0 - 15.3)	9.2	1.58 (1.56 - 1.61)	1.65 (1.63-1.68)	1.54 (1.52 - 1.57)
2004-2007	247,323	59,150	2.1 (2.1 - 2.1)	12.3 (12.2 - 12.5)	7.6	1.58 (1.56 - 1.61)	1.59 (1.56-1.61)	1.53 (1.50 - 1.56)
2008-2011	322,841	45,941	1.7 (1.7 - 1.7)	10.9 (10.7 - 10.9)	6.0	1.57 (1.54 - 1.60)	1.50 (1.48-1.53)	1.51 (1.48 - 1.54)

*7-year CIP for myocardial infarction and cardiac death was adjusted for the competing risk of death.

†Matched cohort from same calendar period were used as reference.

‡Adjusted for age, sex, heart failure, renal disease, hypertension, markers of smoking, obesity, hypercholesterolemia, and alcohol-related disorders.
CIP, cumulated incidence proportion.

Supplemental Table S6. Proportion of patients with incident type 2 diabetes redeeming prescriptions for prophylactic cardiovascular medications

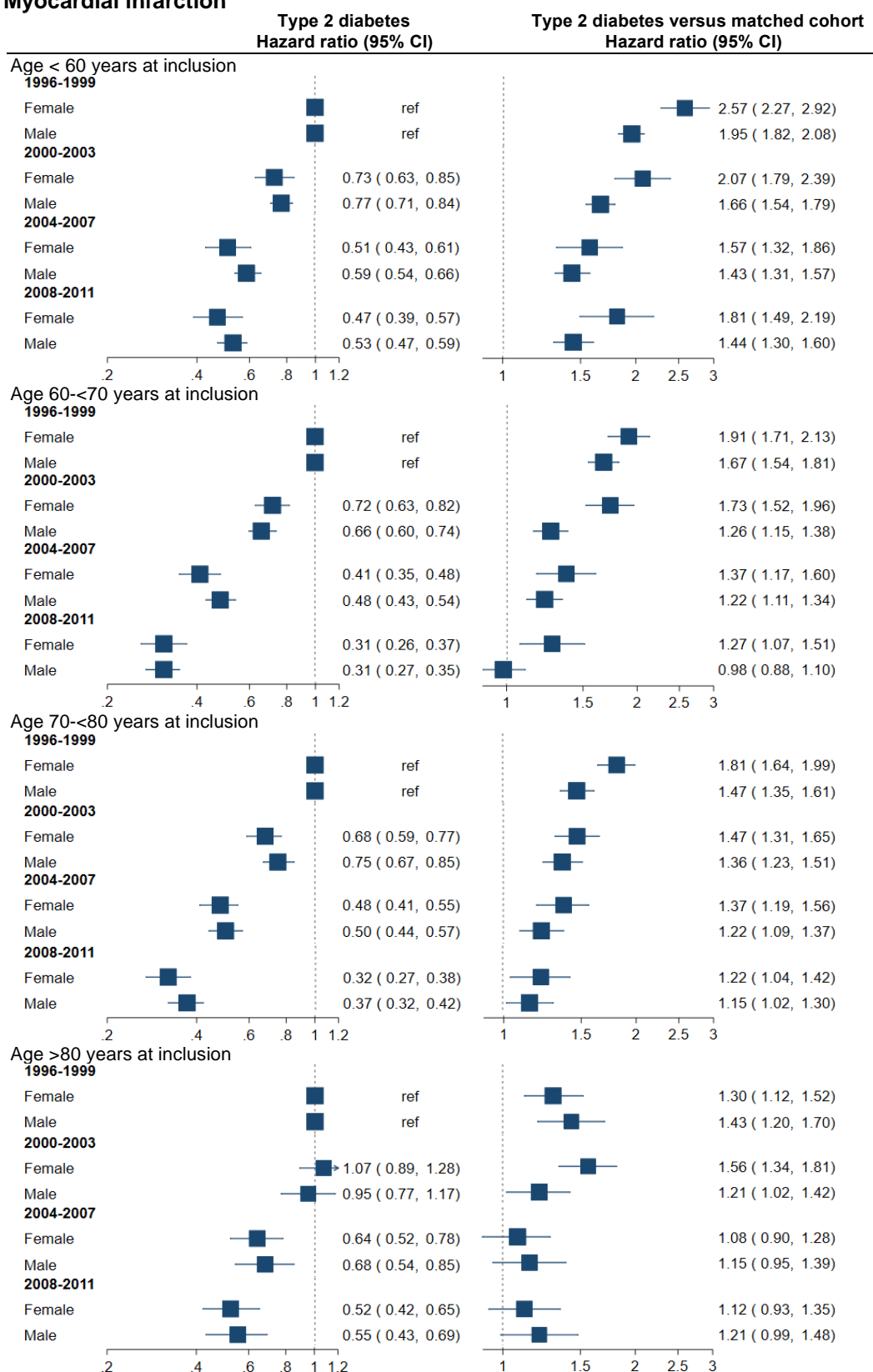
	1996-1999 (no. = 39,546)	2000-2003 (no. = 44,364)	2004-2007 (no. = 54,122)	2008-2011 (no. = 71,279)
Statins				
Within ± 1 year of inclusion	1,905 (5)	9,393 (21)	25,916 (48)	42,581 (60)
Initiated after inclusion	941 (2)	5,035 (11)	9,359 (17)	10,821 (15)
Beta-blockers				
Within ± 1 year of inclusion	4,883 (12)	7,653 (17)	10,503 (19)	15,004 (21)
Initiated after inclusion	1,013 (3)	1,656 (4)	1,708 (3)	2,154 (3)
ACE inhibitor				
Within ± 1 year of inclusion	7,380 (19)	11,008 (25)	16,501 (30)	25,857 (36)
Initiated after inclusion	2,504 (6)	4,069 (9)	5,133 (9)	6,638 (9)
ARB				
Within ± 1 year of inclusion	2,047 (5)	5,766 (13)	10,206 (19)	14,993 (21)
Initiated after inclusion	887 (2)	2,079 (5)	2,879 (5)	3,501 (5)
Calcium channel blockers				
Within ± 1 year of inclusion	6,470 (16)	7,227 (16)	10,421 (19)	17,875 (25)
Initiated after inclusion	1,258 (3)	1,532 (3)	2,599 (5)	3,883 (5)
Thiazides				
Within ± 1 year of inclusion	5,815 (15)	7,987 (18)	10,937 (20)	13,653 (19)
Initiated after inclusion	1,307 (3)	1,906 (4)	2,222 (4)	2,350 (3)
Aspirin				
Within ± 1 year of inclusion	7,162 (18)	10,637 (24)	15,444 (29)	19,169 (27)
Initiated after inclusion	2,048 (5)	3,849 (9)	4,496 (8)	4,119 (6)
ADP receptor inhibitors				
Within ± 1 year of inclusion	32 (0)	318 (1)	499 (1)	923 (1)
Initiated after inclusion	28 (0)	295 (1)	410 (1)	692 (1)
Vitamin K antagonist				
Within ± 1 year of inclusion	1,418 (4)	1,971 (4)	2,767 (5)	3,962 (6)
Initiated after inclusion	404 (1)	480 (1)	505 (1)	640 (1)

Numbers are counts (%). Treatment ± 1 year of inclusion was defined as redemption of ≥ 1 prescription within 12 months before and/or 12 months after the inclusion date. Treatment initiated after inclusion was defined as redemption of ≥ 1 prescription within 12 months after the inclusion date.

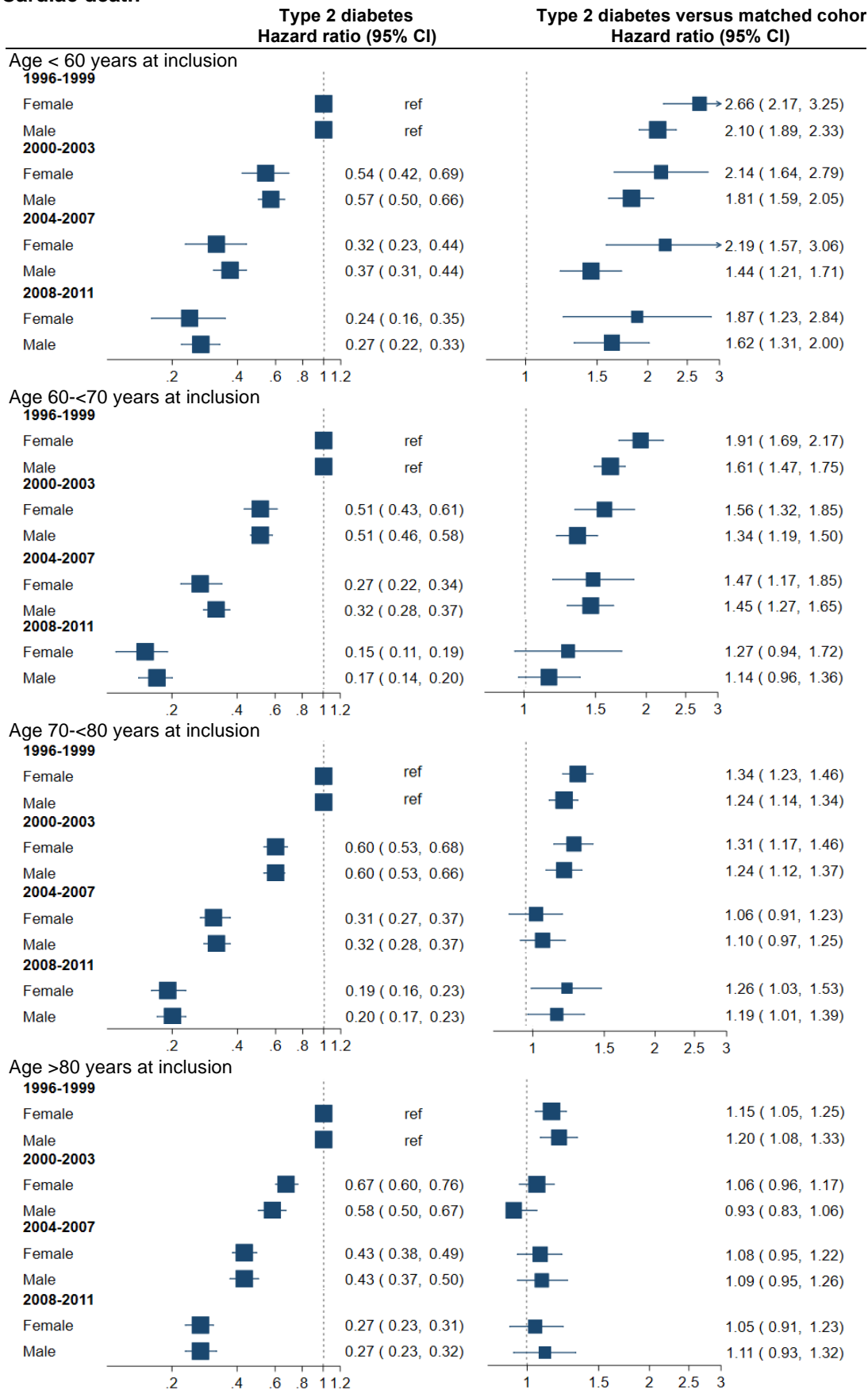
ARB, angiotensin II receptor blocker.

Supplemental Figure S2. Risk of cardiac outcomes and all-cause death in patients with diabetes vs. matched cohort, stratified by sex and age-group at study inclusion

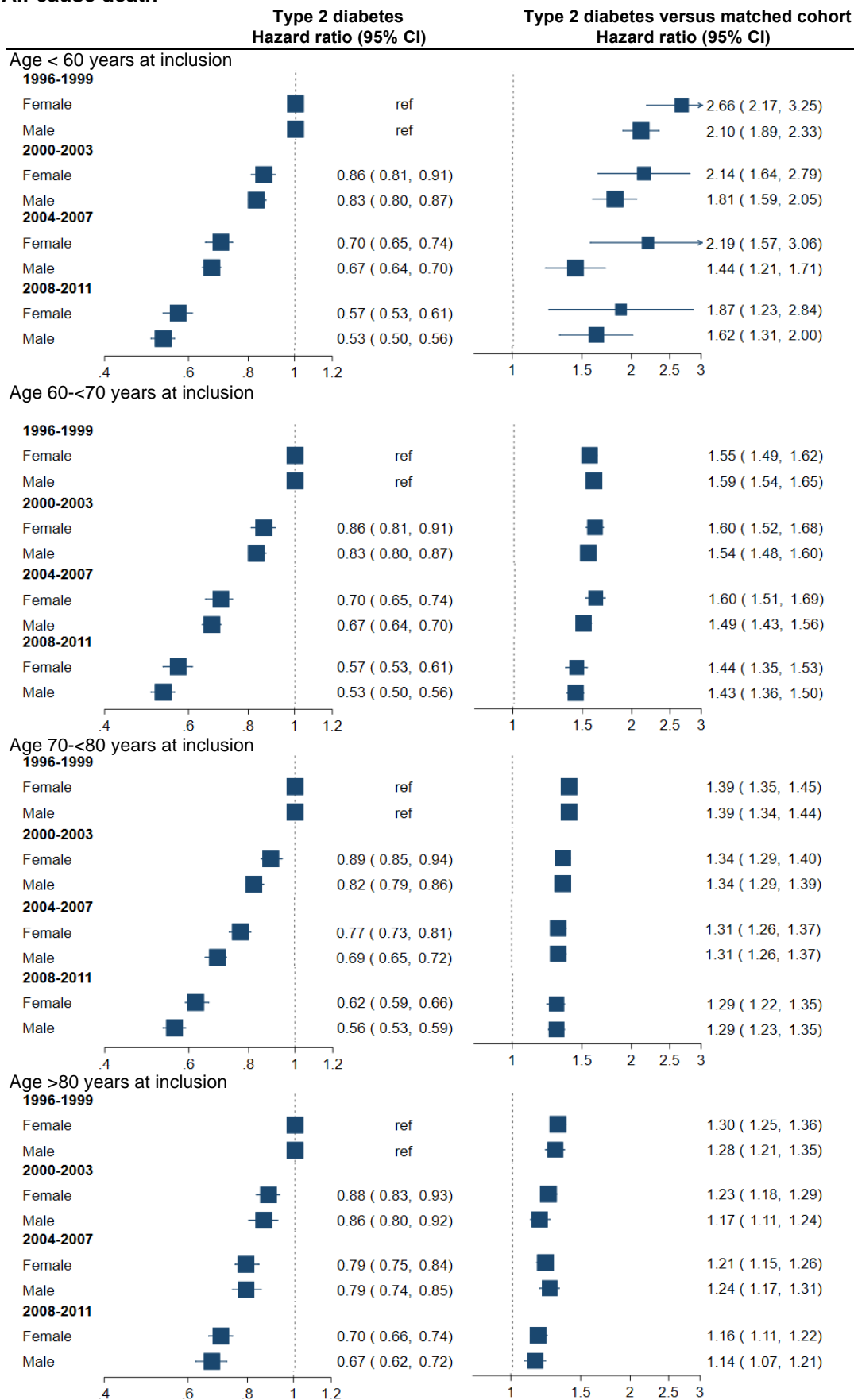
Myocardial infarction



Cardiac death



All-cause death



Supplemental Table S7. Association of cardiac outcomes and all-cause death with early statin use in patients with incident type 2 diabetes*

	Number at risk	Events	Crude hazard ratio (95% CI)	Adjusted hazard ratio† (95% CI)
Myocardial infarction	53,532	1,556	0.88 (0.79-0.98)	0.80 (0.71-0.90)
Cardiac death	53,532	694	0.79 (0.68-0.92)	0.82 (0.70-0.97)
All-cause death	53,532	8,976	0.71 (0.68-0.74)	0.68 (0.65-0.71)

*For patients with incident type 2 diabetes included in 2008-2011, we compared patients initiating statin therapy before the inclusion date or within 12 months after the inclusion date vs. those who did not initiate statin therapy within 12 months after the inclusion date (either late-users or non-users).

†Adjusted for age, sex, heart failure, renal disease, hypertension, chronic obstructive pulmonary disease, use of antiplatelet drugs, use of any prophylactic cardiovascular medications, and early statin use (i.e. redemption of ≥ 1 prescription within 12 months after the inclusion date).