Cardiovascular risk in patients with and without diabetes presenting with chronic coronary syndrome in 2004–2016

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Abstract

Background: It was recently shown that new-onset diabetes patients without previous cardiovascular disease have experienced a markedly reduced risk of adverse cardiovascular events from 1996 to 2011. However, it remains unknown if similar improvements are present following the diagnosis of chronic coronary syndrome. The purpose of this study was to examine the change in cardiovascular risk among diabetes patients with chronic coronary syndrome from 2004 to 2016.

Methods: We included patients with documentation of coronary artery disease by coronary angiography between 2004 and 2016 in Western Denmark. Patients were stratified by year of index coronary angiography (2004–2006, 2007–2009, 2010–2012, and 2013–2016) and followed for two years. The main outcome was major adverse cardiovascular events (MACE) defined as myocardial infarction, ischemic stroke, or death. Analyses were performed separately in patients with and without diabetes. We estimated two-year risk of each outcome and adjusted incidence rate ratios (aIRR) using patients examined in 2004-2006 as reference.

Results: Among 5931 patients with diabetes, two-year MACE risks were 8.4% in 2004–2006, 8.5% in 2007–2009, and then decreased to 6.2% in 2010–2012 and 6.7% in 2013–2016 (2013–2016 vs 2004–2006: aIRR 0.70, 95% CI 0.53–0.93). In comparison, 23,540 patients without diabetes had event rates of 6.3%, 5.2%, 4.2%, and 3.9% for the study intervals (2013–2016 vs 2004–2006: aIRR 0.57, 95% CI 0.48–0.68).

Conclusions: Between 2004 and 2016, the two-year relative risk of MACE decreased by 30% in patients with diabetes and chronic coronary syndrome, but slightly larger absolute and relative reductions were observed in patients without diabetes.

Keywords: Diabetes, Coronary artery disease, Major adverse cardiovascular event, Trend

Background

Among patients with diabetes, randomized clinical studies have shown that multifactorial medical intervention with tight regulation of blood glucose, blood pressure, and lipid-levels reduces the risk of myocardial infarction (MI) and premature death [1]. This subsequently led to changes of the diabetes guidelines with focus on prophylactic multifactorial intervention [2–6]. We recently...
found substantial reduction in the risk of MI among new-onset type 2 diabetes patients in Denmark without previous cardiovascular disease, simultaneous with the implementation of multifactorial intervention [7]. Further, following documentation of coronary artery disease (CAD) in patients with diabetes, the management and treatment of CAD have also improved in the last decades with the documentation of coronary artery bypass grafting (CABG) being superior to percutaneous coronary intervention (PCI) when multivessel disease is present, the implementation of fractional flow reserve (FFR) measurement as an important diagnostic tool, and the development of newer-generation drug-eluting stents (DES) with lower risk of stent thrombosis being the most important improvements [8–10]. However, whether cardiovascular risk for diabetes patients with chronic coronary syndrome has changed over the last decades has not been examined in the setting of daily clinical practice on a nationwide level. Therefore, we investigated changes in cardiovascular risk among diabetes patients with chronic coronary syndrome from 2004 to 2016 and used patients without diabetes as a comparison cohort.

We hypothesized that substantial improvements in cardiovascular risk had taken place.

Methods
Data sources
The Western Denmark Heart Registry is a clinical database that provides prospective registration of all patients in Western Denmark undergoing cardiac intervention such as coronary angiography (CAG), PCI, and CABG since 1999. The registry has previously been described in detail [11]. Using each patient’s unique 10-digit identifier, patients can be linked with other national health care registries, including the Danish National Prescription Registry, the Civil Registration System, the Danish Register of Causes of Death, and the Danish National Patient Registry [12–15].

Patient selection
Patients undergoing CAG were identified using first-time procedures registered in the Western Denmark Heart Registry from 2004 through 2016 (n = 146,191) (Fig. 1). If a patient had multiple CAGs registered during this time,
the first was considered the index examination. Four patients < 18 years and 51,181 patients with no CAD were excluded from this analysis. Since we aimed to assess risk following the first-time diagnosis of chronic coronary syndrome by CAG, we excluded 8159 patients with previous MI, PCI, or CABG. Patients referred for CAG due to a different indication than chronic coronary syndrome were also excluded (n = 57,375).

CAD

Presence and extent of CAD were entered into the database by the interventional cardiologist immediately following examination. CAD was classified as either obstructive disease in 1, 2, or 3 vessels (with obstructive disease defined as > 50% diameter stenosis and FFR ≤ 0.80 if measured) or as diffuse CAD defined as non-significant CAD involving > 1 vessel. Patients with only a single stenosis < 50% or FFR > 0.80 if measured were classified as no CAD and excluded from the study.

Diabetes

Diabetes was defined as either (1) diet treatment only, non-insulin anti-diabetic treatment, or insulin (± non-insulin anti-diabetic treatment) as registered in the Western Denmark Heart Registry, (2) diabetes diagnosis prior to CAG in the Danish National Patient Registry, or (3) collecting one or more prescriptions of insulin or non-insulin anti-diabetic treatment less than six months prior to CAG according to the Danish National Prescription Registry [12].

Comorbidity

Comorbidities were ascertained through the Danish National Patient Registry relying on diagnoses prior to CAG with full look-back (from 1977 and onwards). Information regarding smoking status, body mass index (BMI), and hypertension was ascertained through the Western Danish Heart Registry. We estimated burden of comorbidity using a modified Charlson’s Comorbidity Index score, in which ‘Diabetes, type I and II’ and ‘Diabetes with end-organ failure’ were excluded in the final score [16].

Medication

Records of treatment with aspirin, adenosine diphosphate (ADP) receptor inhibitor, angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB), beta-blocker, and statin were collected from the Danish National Prescription Database. Medical treatment prior to CAG was defined as one or more redeemed prescriptions six months or less before CAG. Changes in medical treatment because of the CAG or peri-procedural diagnosis were investigated by looking at redeemed prescriptions six months or less after CAG in patients who completed six months of follow-up (n = 29,071) (Additional file 1: Tables S1 and S2).

Outcomes

The primary outcome was major adverse cardiovascular event (MACE); a composite of MI, ischemic stroke, and all-cause death. Secondary outcomes were the individual components of MACE, cardiac death, PCI, and CABG.

MI and ischemic stroke were identified in the Danish National Patient Registry [17, 18]. Vital status (alive, death, or emigration) was obtained through the Danish Civil Registration System [15]. Cardiac death included deaths resulting from ischemic heart disease, sudden cardiac death, heart failure, or sudden death, unspecified, according to death certificates from the Danish Register of Causes of Death [14].

Anatomical Therapeutic Chemical (ATC) codes used in the Danish Prescription Registry and International Classification of Diseases 10 (ICD-10) codes used in the Danish National Health Registry and the Danish Register of Causes of Death are listed in supplemental material of previous work [19].

Statistical analysis

Patients with chronic coronary syndrome were stratified by diabetes status at the time of examination and year of index CAG (2004–2006, 2007–2009, 2010–2012, and 2013–2016). We estimated two-year risks (cumulative incidence proportions) of MACE, MI, ischemic stroke, all-cause death, cardiac death, PCI, and CABG. Follow-up continued until an outcome event, death, emigration, or 24 months after CAG. Cumulative incidence proportion curves were constructed. We estimated the incidence rate ratio (IRR) using a modified Poisson regression with a robust variance–covariance estimator using the natural log of person-years as the offset [20]. IRRs were adjusted for sex, age, hypertension, previous ischemic stroke, peripheral artery disease, smoking, statin treatment, antiplatelet treatment, and oral anticoagulant treatment. Analyses of MACE, ischemic stroke, cardiac death, and all-cause death were additionally adjusted for atrial fibrillation and heart failure [21]. Patients examined between 2004 and 2006 were used as reference group throughout analyses.

We performed a number of sensitivity analyses. First, two-year MACE risks were compared between patients with and without diabetes (Additional file 1: Table S3). Secondly, we conducted a subgroup analysis of patients diagnosed with obstructive CAD at index CAG (n = 23,858) (Additional file 1: Tables S4 and S5). Other analyses included stratifying by sex and age above or below 70 years (Additional file 1: Tables S6, S7, S8, and
S9). Lastly, we performed an analysis of revascularization patterns as a consequence of the angiographic findings defined as PCI or CABG within three months after index CAG (Additional file 1: Table S10). Stata/MP 16.0 (StataCorp LLC, College Station, TX, USA) was used for all analyses.

**Results**

A total of 29,471 patients with chronic coronary syndrome, of whom 5931 (20%) had diabetes, were included and eligible for analyses.

**Baseline characteristics**

Patient characteristics are outlined in Table 1 (diabetes) and Table 2 (non-diabetes). In general, similar changes in baseline characteristics were observed for diabetes and non-diabetes patients. The median age increased from 67 to 69 years for patients with diabetes and from 66 to 68 years for patients without diabetes from 2004–2006 to 2013–2016. We observed a reduction in the proportion of active smokers. Median BMI was 29 for patients with diabetes and 27 for patients without diabetes throughout the study period. Comorbidities increased in both groups with increasing Charlson’s Comorbidity Index scores. The extent of CAD changed over time with a decrease in obstructive multivessel disease and increased presence of diffuse non-significant CAD.

Statin treatment after CAG was around 90% for all groups. The primary choice of statin changed from simvastatin to the more potent atorvastatin (Additional file 1: Tables S1 and S2) during the study period. For example, simvastatin and atorvastatin were used in 74% and 12% of patients with diabetes in 2004–2006, but these percentages had changed to 34% and 47% in 2013–2016. The use of antihypertensive drugs also changed over time but in a more heterogeneous way. The use of beta-blockers, ACE inhibitors, and thiazides decreased, the use of ARBs increased, and the use of calcium channel blockers remained stable. Finally, in the diabetes group, insulin treatment decreased from the first to the last study interval while use of non-insulin anti-diabetic medication increased.

**Clinical outcomes**

Tables 3 (diabetes) and 4 (non-diabetes) report the two-year absolute and relative risks for the four study intervals and is graphically illustrated in Fig. 2. The risk of MACE decreased among patients with diabetes (8.4–6.7%, adjusted incidence rate ratios (aIRR) 0.70, 95% CI 0.53–0.93) and patients without diabetes (6.3–3.9%, aIRR 0.57, 95% CI 0.48–0.68). The two-year risk of MACE remained around 2.5% higher among patients with diabetes in comparison to patients without diabetes through all study intervals (Additional file 1: Table S3). The results were consistent in both patients below and above 70 years (Additional file 1: Tables S8 and S9). Men had 1–2% higher absolute risk of MACE compared to women in patients without diabetes, whereas sex differences was less pronounced among patients with diabetes (Additional file 1: Tables S6 and S7). Both men and women had reductions in MACE through the study period in accordance with our main analysis. In the diabetes group, the MACE reduction was primarily caused by halving the risk of ischemic stroke while relatively smaller, and statistically insignificant, reductions of MI and all-cause death were found. Similar results were found for patients without diabetes. These results were robust when we restricted the analyses to patients with obstructive CAD (i.e., excluding those with diffuse CAD) (Additional file 1: Tables S4 and S5).

**Revascularization**

The revascularization rates decreased within the first three months after index CAG for both PCI and CABG from the first to the last study interval (Table 5). This was found for both diabetes and non-diabetes patients. Similar results were found when analysing revascularization for the entire two-year study period (Additional file 1: Table S10). However, when restricting the analysis to patients with obstructive CAD, we found a change in the revascularization pattern with more patients being treated with PCI and fewer patients with CABG over time, a finding that was consistent among diabetes and non-diabetes patients (Additional file 1: Table S10).

**Discussion**

**Statement of principal findings**

Our main finding is that the two-year relative MACE risk decreased by 30% in patients with diabetes who presented with chronic coronary syndrome in Denmark from 2004 to 2016. This result was primarily caused by a reduction in ischemic stroke. However, since even larger relative and absolute risk reductions were observed among patients without diabetes, the gap between patients with and without diabetes did not change.

**Diabetes**

In the diabetes group, the absolute two-year risk of MACE decreased by 1.7% from 2004–2006 to 2013–2016. This is likely the result of several guideline-directed initiatives implemented in Denmark within the inclusion period. First, the focus on cardiovascular prevention has increased in diabetes patients where an intensified multifactorial intervention with tight regulation of blood glucose, blood pressure, and lipid-levels has proven to lower cardiovascular risk in diabetes.
|                                | 2004–2006 n = 1066 | 2007–2009 n = 1507 | 2010–2012 n = 1523 | 2013–2016 n = 1835 |
|--------------------------------|---------------------|-------------------|--------------------|-------------------|
| **Baseline characteristics in patients with diabetes** |                     |                   |                    |                   |
| **Median age, years (IQR)**    | 67 (59–73)          | 67 (60–74)        | 68 (61–75)         | 69 (61–75)        |
| **Male sex**                   | 780                 | 73.2              | 1061               | 70.4              |
| **Family history of ischemic heart disease** | 486                 | 45.6              | 671                | 44.5              |
| **Active smoker**              | 239                 | 22.4              | 313                | 20.8              |
| **Comorbidity**                |                     |                   |                    |                   |
| **Hypertension**               | 834                 | 78.2              | 1272               | 84.4              |
| **Previous ischemic stroke**   | 37                  | 3.5               | 52                 | 3.5               |
| **Atrial fibrillation**        | 86                  | 8.1               | 141                | 9.4               |
| **Peripheral artery disease**  | 101                 | 9.5               | 162                | 10.7              |
| **Heart failure**              | 116                 | 10.9              | 186                | 12.3              |
| **Mean eGFR, mL/min (IQR)**    | 84 (65–101)         | 88 (68–107)       | 91 (71–108)        | 90 (71–108)       |
| **Median BMI, kg/m² (IQR)**    | 29 (26–32)          | 29 (26–33)        | 29 (26–33)         | 29 (26–33)        |
| **Modified Charlson Comorbidity Index score** |                     |                   |                    |                   |
| 0 points                       | 853                 | 80.0              | 1111               | 73.7              |
| 1 point                        | 152                 | 14.3              | 275                | 18.2              |
| 2 point                        | 58                  | 5.4               | 105                | 7.0               |
| ≥ 3 points                     | 3                   | 0.3               | 16                 | 1.1               |
| **CAD extent**                 |                     |                   |                    |                   |
| 1 VD                           | 307                 | 28.8              | 450                | 29.9              |
| 2 VD                           | 269                 | 25.2              | 336                | 22.3              |
| 3 VD                           | 438                 | 41.1              | 456                | 30.3              |
| Diffuse VD                     | 52                  | 4.9               | 265                | 17.6              |
| **Medication**                 |                     |                   |                    |                   |
| **Statin**                     | Before              | 868               | 1244               | 82.5              |
| **Aspirin**                    | After               | 972               | 1349               | 91.4              |
| **ADP-inhibitor**              | Before              | 876               | 1200               | 79.6              |
| **Vitamin K antagonists**      | After               | 941               | 1284               | 87.0              |
| **Non-vitamin K antagonists**  | Before              | 519               | 655                | 44.4              |
| **Beta-blocker**               | Before              | 732               | 894                | 59.3              |
| **ACE inhibitor**              | After               | 820               | 1050               | 71.1              |
| **ARB**                        | Before              | 500               | 758                | 50.3              |
| **Thiazides**                  | After               | 540               | 791                | 53.6              |
patients [1]. Although approximately 90% of diabetes patients received statin treatment after the CAG, we observed a change in the primary choice of statin from simvastatin to the more potent atorvastatin during the study period, i.e., suggesting intensified lipid-lowering treatment [22]. Second, CABG is superior to PCI in patients with diabetes plus obstructive multivessel disease [10, 23]. In the diabetes cohort, the use of PCI was reduced by an absolute 8% while CABG decreased from 23% in 2004–2006 and remained stable around 18% throughout the last three study intervals. This suggests adherence to clinical guidelines in a time where FFR often led to downgrading of multivessel disease and where PCI in general tended to be preferred over CABG. Third, newer-generation DES have replaced bare-metal stents and first-generation DES during the study period. Newer-generation DES reduce MACE rates up to five years after PCI compared with first-generation DES [9, 24] and the two-year follow-up period may be too short to capture the benefit of newer-generation DES. Newer-generation DES also displayed higher safety in patients with diabetes [25, 26]. However, the main reduction among diabetes patients was caused by reduced risk of ischemic stroke while patients without diabetes had reduced risk of all cardiovascular events.

Obstructive CAD
Fewer patients were classified as having obstructive multivessel CAD while more were classified as diffuse non-obstructive CAD. Theoretically, this can be explained by earlier detection of CAD (lead time bias), delayed progression of CAD, or changed perception of CAD significance. Since the median age increased from 66 years in 2004–2006 to 68 years in 2013–2016, we find it unlikely that lead time bias and delayed progression of CAD are the main explanations for the observed reduced rates of multi-vessel disease. In contrast, the gradual implementation of intracoronary physiology measurements, such as FFR, to assist visual assessment of intermediate stenoses has undoubtedly led to downgrading of CAD severity since visual assessment alone tend to overestimate disease significance [27]. Importantly, MACE also decreased when we restricted our analyses to only include patients with obstructive CAD, i.e., the reduction of events was not explained by inclusion of more patients with diffuse CAD due to a changed registration pattern of non-obstructive CAD. Furthermore, the reduced cardiovascular risk among patients with obstructive CAD is presumably an underestimation of the actual reduced risk as we expect that some of the patients with “obstructive” CAD in the earlier study periods would have been classified as non-obstructive in the later periods when FFR became a standard tool in our daily clinical practice. Finally, in our sensitivity analysis of patients with obstructive CAD, it is noteworthy that the “downgrading” of CAD severity led to more use of PCI and less use of CABG among both diabetes and non-diabetes patients.

Comparison with other work
We have not been able to identify previous studies looking at changes in cardiovascular outcomes among patients with diabetes and chronic coronary syndrome. Our results, however, are in accordance with our previous study looking at improvements in 7-years outcomes among Danish patients with new-onset diabetes from

Table 1 (continued)

| Year        | 2004–2006 | 2007–2009 | 2010–2012 | 2013–2016 |
|-------------|-----------|-----------|-----------|-----------|
|             | n = 1066  | n = 1507  | n = 1523  | n = 1835  |
| Before      | Before    | Before    | Before    | Before    |
|             | 231       | 21.7      | 317       | 21.0      | 331       | 21.7      | 298       | 16.2      | 247       | 23.5      | 309       | 20.9      | 317       | 21.1      | 281       | 15.6      |
| After       | Calcium channel blocker | Before    | 423       | 39.7      | 621       | 41.2      | 662       | 43.5      | 705       | 38.4      |
|             | After     | Calcium channel blocker | 446       | 42.5      | 695       | 47.1      | 733       | 48.8      | 811       | 45.0      |
| Before      | Insulin   | Before    | 349       | 32.7      | 495       | 32.8      | 503       | 33.0      | 547       | 29.8      |
|             | After     | Insulin   | 377       | 35.9      | 538       | 36.4      | 524       | 34.9      | 572       | 31.7      |
| Before      | Non-insulin | Before  | 644       | 60.4      | 936       | 62.1      | 1042      | 68.4      | 1346      | 73.4      |
|             | Non-insulin | After  | 630       | 60.1      | 934       | 63.3      | 1035      | 68.9      | 1306      | 72.4      |

Values are numbers and percentages unless otherwise stated

ACE angiotensin converting enzyme, ADP adenosine diphosphate, ARB angiotensin-II receptor blocker, BMI body mass index, CAD coronary artery disease, eGFR estimated glomerular filtration rate, IQR inter-quartile range, VD vessel disease
Table 2 Baseline characteristics in patients without diabetes

|                         | 2004–2006 n = 4847 | 2007–2009 n = 6104 | 2010–2012 n = 5547 | 2013–2016 n = 7042 |
|-------------------------|---------------------|--------------------|--------------------|--------------------|
| **Mean age, years (IQR)** | 66 (58–74)          | 67 (59–74)         | 67 (59–75)         | 68 (59–75)         |
| **Male sex**            | 3554 73.3           | 4279 70.1          | 3732 67.3          | 4843 68.8          |
| **Family history**      | 2290 47.2           | 2892 47.4          | 2687 48.4          | 3218 45.7          |
| **Active smoker**       | 1293 26.7           | 1401 23.0          | 1275 23.0          | 1467 20.8          |
| **Comorbidity**         |                     |                    |                    |                    |
| Hypertension            | 2875 59.3           | 3949 64.7          | 3736 67.4          | 4488 63.7          |
| Previous ischemic stroke| 42 0.9              | 88 1.4             | 113 2.0            | 158 2.2            |
| Atrial fibrillation     | 391 8.1             | 499 8.2            | 474 8.5            | 643 9.1            |
| Peripheral artery disease | 260 5.4          | 361 5.9            | 363 6.5            | 427 6.1            |
| Heart failure           | 390 8.0             | 434 7.1            | 357 6.4            | 358 5.1            |
| Renal disease           | 61 1.3              | 93 1.5             | 91 1.6             | 171 2.4            |
| **Mean eGFR, mL/min (IQR)** | 81 (66–96)       | 86 (70–102)        | 89 (74–104)        | 89 (74–104)        |
| **Median BMI, kg/m² (IQR)** | 27 (24–29)      | 27 (24–30)         | 27 (24–29)         | 27 (24–29)         |
| **Modified Charlson Comorbidity Index score** | | | | |
| 0 points                | 3931 81.1           | 4568 74.8          | 3917 70.6          | 4799 68.1          |
| 1 point                 | 607 12.5            | 929 15.2           | 893 16.1           | 1162 16.5          |
| 2 point                 | 222 4.6             | 411 6.7            | 488 8.8            | 696 9.9            |
| ≥ 3 points              | 87 1.8              | 196 3.2            | 249 4.5            | 385 5.5            |
| **CAD extent**          |                     |                    |                    |                    |
| 1 VD                    | 1764 36.4           | 2321 38.0          | 2049 36.9          | 2661 37.8          |
| 2 VD                    | 1236 25.5           | 1437 23.3          | 1141 20.6          | 1391 19.8          |
| 3 VD                    | 1530 31.6           | 1386 22.2          | 1029 18.6          | 1132 16.1          |
| Diffuse VD              | 317 6.5             | 960 15.7           | 1328 23.9          | 1858 26.4          |
| **Medication**          |                     |                    |                    |                    |
| **Statin**              |                     |                    |                    |                    |
| Before                  | 3141 64.8           | 4136 67.8          | 3667 66.1          | 4490 63.8          |
| After                   | 4347 91.4           | 5453 90.9          | 4879 89.1          | 6195 89.0          |
| **Aspirin**             |                     |                    |                    |                    |
| Before                  | 3795 78.3           | 4621 75.7          | 4009 72.3          | 4717 67.0          |
| After                   | 4105 86.3           | 5067 84.5          | 4555 83.2          | 5500 79.0          |
| **ADP-inhibitor**       |                     |                    |                    |                    |
| Before                  | 148 3.1             | 145 2.4            | 215 3.9            | 487 6.9            |
| After                   | 2540 53.4           | 2962 49.4          | 2535 46.3          | 3240 46.5          |
| **Vitamin K antagonists** |                     |                    |                    |                    |
| Before                  | 354 7.3             | 427 7.0            | 360 6.5            | 376 5.3            |
| After                   | 519 10.7            | 535 8.9            | 471 8.6            | 484 7.0            |
| **Non-vitamin K antagonists** |                     |                    |                    |                    |
| Before                  | 0 0.0               | < 5 0.0            | 38 0.7             | 268 3.8            |
| After                   | 0 0.0               | < 5 0.0            | 61 1.1             | 347 5.0            |
| **Beta-blocker**        |                     |                    |                    |                    |
| Before                  | 3348 69.1           | 3674 60.2          | 2868 51.7          | 2756 39.1          |
| After                   | 3582 75.3           | 4219 70.3          | 3498 63.9          | 3707 53.2          |
| **ACE inhibitor**       |                     |                    |                    |                    |
| Before                  | 1260 26.0           | 1643 26.9          | 1587 28.6          | 1590 22.6          |
| After                   | 1534 32.3           | 1947 32.5          | 1749 31.9          | 1694 24.3          |
| **ARB**                 |                     |                    |                    |                    |
| Before                  | 667 13.8            | 976 16.0           | 978 17.6           | 1479 21.0          |
| After                   | 731 15.4            | 1041 17.4          | 1057 19.3          | 1564 22.5          |
Table 2 (continued)

|                        | 2004–2006 n = 4847 | 2007–2009 n = 6104 | 2010–2012 n = 5547 | 2013–2016 n = 7042 |
|------------------------|--------------------|--------------------|--------------------|--------------------|
| **Thiazides**           |                    |                    |                    |                    |
| Before                 | 891 18.4           | 1077 17.6          | 954 17.2           | 917 13.0           |
| After                  | 964 20.3           | 1111 18.5          | 930 17.0           | 914 13.1           |
| **Calcium channel blocker** |                |                    |                    |                    |
| Before                 | 1601 33.0          | 1958 32.1          | 1741 31.4          | 1982 28.1          |
| After                  | 1777 37.4          | 2408 40.1          | 2211 40.4          | 2550 36.6          |

Values are numbers and percentages unless otherwise stated. To preserve patient anonymity following Danish data regulations, cells with < 5 observations are presented as such

ACE angiotensin converting enzyme, ADP adenosine diphosphate, ARB angiotensin-II receptor blocker, BMI body mass index, CAD coronary artery disease, eGFR estimated glomerular filtration rate, IQR inter-quartile range, VD vessel disease

Table 3 Two-year risk of adverse cardiovascular outcomes after coronary angiography in elective diabetes patients with chronic coronary syndrome

|                              | Patients | Events | Two-year cumulative incidence proportion (95% CI) | Unadjusted IRR (95% CI) | Adjusted IRR* (95% CI) |
|------------------------------|----------|--------|--------------------------------------------------|-------------------------|------------------------|
| **MACE**                     |          |        |                                                  |                         |                        |
| 2004–2006                    | 1066     | 89     | 8.4% (6.9–10.3)                                  | Reference               | Reference              |
| 2007–2009                    | 1507     | 126    | 8.5% (7.2–10.0)                                  | 1.01 (0.77–1.33)        | 0.96 (0.73–1.27)       |
| 2010–2012                    | 1523     | 94     | 6.2% (5.2–7.6)                                   | 0.73 (0.55–1.98)        | 0.67 (0.50–0.91)       |
| 2013–2016                    | 1835     | 121    | 6.7% (5.6–7.9)                                   | 0.78 (0.59–1.03)        | 0.70 (0.53–0.93)       |
| **Myocardial infarction**    |          |        |                                                  |                         |                        |
| 2004–2006                    | 1066     | 42     | 4.0% (3.0–5.4)                                   | Reference               | Reference              |
| 2007–2009                    | 1507     | 57     | 3.9% (3.0–5.0)                                   | 0.97 (0.65–1.45)        | 0.96 (0.64–1.43)       |
| 2010–2012                    | 1523     | 61     | 4.1% (3.2–5.2)                                   | 1.02 (0.69–1.51)        | 0.97 (0.65–1.44)       |
| 2013–2016                    | 1835     | 66     | 3.7% (2.9–4.7)                                   | 0.91 (0.61–1.34)        | 0.85 (0.57–1.25)       |
| **Ischemic stroke**          |          |        |                                                  |                         |                        |
| 2004–2006                    | 1066     | 36     | 3.4% (2.5–4.7)                                   | Reference               | Reference              |
| 2007–2009                    | 1507     | 40     | 2.7% (2.0–3.7)                                   | 0.79 (0.50–1.24)        | 0.76 (0.48–1.21)       |
| 2010–2012                    | 1523     | 24     | 1.6% (1.1–2.4)                                   | 0.46 (0.27–0.78)        | 0.40 (0.24–0.69)       |
| 2013–2016                    | 1835     | 35     | 2.0% (1.4–2.7)                                   | 0.56 (0.35–0.89)        | 0.47 (0.29–0.76)       |
| **Cardiac death**            |          |        |                                                  |                         |                        |
| 2004–2006                    | 1066     | 24     | 2.3% (1.5–3.4)                                   | Reference               | Reference              |
| 2007–2009                    | 1507     | 41     | 2.8% (2.1–3.8)                                   | 1.22 (0.74–2.20)        | 1.12 (0.67–1.87)       |
| 2010–2012                    | 1523     | 17     | 1.1% (0.7–1.8)                                   | 0.50 (0.27–0.92)        | 0.45 (0.24–0.85)       |
| 2013–2016                    | 1835     | 30     | 1.7% (1.2–2.4)                                   | 0.73 (0.42–1.24)        | 0.65 (0.38–1.14)       |
| **Death**                    |          |        |                                                  |                         |                        |
| 2004–2006                    | 1066     | 64     | 6.0% (4.7–7.6)                                   | Reference               | Reference              |
| 2007–2009                    | 1507     | 115    | 7.6% (6.4–9.1)                                   | 1.28 (0.95–1.74)        | 1.21 (0.89–1.64)       |
| 2010–2012                    | 1523     | 85     | 5.6% (4.5–6.9)                                   | 0.93 (0.67–1.28)        | 0.84 (0.61–1.17)       |
| 2013–2016                    | 1835     | 97     | 5.3% (4.4–6.4)                                   | 0.88 (0.64–1.21)        | 0.78 (0.56–1.06)       |

*Adjusted for sex, age, smoking, hypertension, previous ischemic stroke, peripheral artery disease, statin treatment, antiplatelet treatment, and oral anti-coagulant treatment. Ischemic stroke and death were additionally adjusted for atrial fibrillation and heart failure.

1996 to 2011 [28] as well as a Swedish study examining outcomes among patients with prevalent diabetes from 1998 to 2014 [29]. Moreover, two Swedish studies compared outcomes for all patients with acute coronary syndrome from 1995 to 2014 [30, 31] but differed concerning inclusion criteria (chronic vs acute coronary syndrome), study period, and lack of stratification based on presence of diabetes. Still, the studies share
similarities by including a Scandinavian cohort treated in a national, tax-payer funded, public health care system, and the overall trends with reduced cardiovascular risk over the study period.

Clinical implications
It was recently shown that the risk of adverse cardiovascular events among patients with new-onset diabetes without previous cardiovascular disease decreased markedly from 1996 to 2011, drawing close to the cardiovascular risk of patients without diabetes [28]. In our study, we found that the relative risk of MACE decreased by 30% in patients with diabetes from 2004–2016, although their risk remained substantially increased compared to patients without diabetes. Therefore, an early and aggressive treatment strategy (i.e. cholesterol lowering drugs, blood pressure management, exercise, diet counseling, and smoking cessation) before the development of cardiovascular disease seems essential in order to minimize cardiovascular risk among diabetes patients, and such a multifactorial strategy, as documented by fewer active smokers and more use of high-intensity statins, likely played a role for the 30% risk reduction observed among the diabetes patients.

Limitations
Our study has some limitations to consider. The definition of MI was revised in 2007 and again in 2012 following the introduction of new high-sensitive cardiac troponin assays [32, 33]. Lowering of the 99th percentile upper normal reference limit due to improved biomarker sensitivity enabled smaller increases in troponin levels to meet the MI criteria. The lower MI diagnosis threshold in the later examination year intervals may underestimate the true reduction in MI during the study period [34].

Due to lack of biochemical data on our study group, we were unable to differentiate between prediabetic patients and normoglycemic patients in the non-diabetes group.

Table 4 Two-year risk of adverse cardiovascular outcomes after coronary angiography in elective non-diabetes patients with chronic coronary syndrome

| Patients | Events | Two-year cumulative incidence proportion (95% CI) | Unadjusted IRR (95% CI) | Adjusted IRR* (95% CI) |
|----------|--------|-------------------------------------------------|------------------------|------------------------|
| **MACE** |        |                                                 |                        |                        |
| 2004–2006 | 4847   | 302                                             | 6.3% (5.6–7.0)         | Reference              |
| 2007–2009 | 6104   | 312                                             | 5.2% (4.6–5.7)         | 0.81 (0.69–0.96)       | 0.81 (0.69–0.95) |
| 2010–2012 | 5547   | 243                                             | 4.2% (3.9–5.0)         | 0.69 (0.59–0.82)       | 0.65 (0.55–0.78) |
| 2013–2016 | 7042   | 272                                             | 3.9% (3.5–4.4)         | 0.61 (0.52–0.72)       | 0.57 (0.48–0.68) |
| **Myocardial infarction** |        |                                                 |                        |                        |
| 2004–2006 | 4847   | 154                                             | 3.2% (2.8–3.8)         | Reference              |
| 2007–2009 | 6104   | 173                                             | 2.9% (2.5–3.3)         | 0.89 (0.71–1.10)       | 0.89 (0.72–1.11) |
| 2010–2012 | 5547   | 125                                             | 2.3% (1.0–2.7)         | 0.70 (0.55–0.89)       | 0.68 (0.54–0.87) |
| 2013–2016 | 7042   | 175                                             | 2.5% (2.2–2.9)         | 0.77 (0.62–0.96)       | 0.75 (0.60–0.93) |
| **Ischemic stroke** |        |                                                 |                        |                        |
| 2004–2006 | 4847   | 72                                              | 1.5% (1.2–1.9)         | Reference              |
| 2007–2009 | 6104   | 69                                              | 1.2% (0.9–1.5)         | 0.76 (0.54–1.05)       | 0.71 (0.51–0.99) |
| 2010–2012 | 5547   | 64                                              | 1.2% (0.9–1.5)         | 0.77 (0.55–1.07)       | 0.65 (0.46–0.92) |
| 2013–2016 | 7042   | 62                                              | 0.9% (0.7–1.1)         | 0.58 (0.42–0.82)       | 0.48 (0.34–0.68) |
| **Cardiac death** |        |                                                 |                        |                        |
| 2004–2006 | 4847   | 102                                             | 2.1% (1.8–2.6)         | Reference              |
| 2007–2009 | 6104   | 99                                              | 1.6% (1.4–2.0)         | 0.77 (0.58–1.01)       | 0.77 (0.58–1.87) |
| 2010–2012 | 5547   | 65                                              | 1.2% (0.9–1.5)         | 0.55 (0.40–0.76)       | 0.52 (0.38–0.71) |
| 2013–2016 | 7042   | 50                                              | 0.7% (0.5–0.9)         | 0.33 (0.24–0.47)       | 0.31 (0.22–0.44) |
| **Death** |        |                                                 |                        |                        |
| 2004–2006 | 4847   | 229                                             | 4.7% (4.2–5.4)         | Reference              |
| 2007–2009 | 6104   | 270                                             | 4.4% (3.9–5.0)         | 0.93 (0.78–1.11)       | 0.95 (0.79–1.13) |
| 2010–2012 | 5547   | 219                                             | 4.0% (3.5–4.5)         | 0.83 (0.69–1.00)       | 0.80 (0.66–0.97) |
| 2013–2016 | 7042   | 216                                             | 3.1% (2.7–3.5)         | 0.64 (0.53–0.77)       | 0.61 (0.51–0.74) |

*Adjusted for sex, age, smoking, hypertension, previous ischemic stroke, peripheral artery disease, statin treatment, antiplatelet treatment, and oral anti-coagulant treatment. Ischemic stroke and death were additionally adjusted for atrial fibrillation and heart failure.
and investigate potential differences in cardiovascular outcomes [35, 36].

It is difficult to distinguish between type 1 and 2 diabetes based on registries alone. However, type 2 diabetes is by far the most common diabetes type in this age group and our results are thus mainly representative of patients with type 2 diabetes. As such, our results may not be representative for type 1 diabetes patients.

All studies assessing changes over time are limited by the fact that multiple changes have taken place during a long study period. While the main finding is that a large relative risk reduction was observed, which thereby shows that cardiovascular risk reduction is possible even in a 12-year period, it is difficult to define a specific cause.

Finally, our results were obtained in a tax-payer funded, public health care system with equal access for all citizens, and the external validity to societies with greater socioeconomic disparities needs confirmation.

**Conclusion**

In Denmark from 2004 to 2016, we found a reduced two-year risk of MACE among both diabetes and non-diabetes patients with chronic coronary syndrome. However, despite improvements in cardiovascular risk and changed

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**Fig. 2** Two-year risks of MACE with 95% confidence intervals (a) and adjusted IRR in non-diabetes (b) and in diabetes (c) patients from 2004 to 2016.
treatment patterns, diabetes patients with chronic coronary syndrome remain at higher risk of MACE than patients without diabetes. An intensive, multifactorial treatment strategy before the development of cardiovascular disease is essential in order to minimize cardiovascular risk among diabetes patients.

Abbreviations
MI: Myocardial infarction; CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; FFR: Fractional flow reserve; CAG: Coronary angiography; CABG: Coronary artery bypass grafting; BMI: Body mass index; ADP: Adenosine diphosphate; ACE: Angiotensin-converting enzyme; ARB: Angiotensin II receptor blocker; MACE: Major adverse cardiovascular event; ATC: Anatomic Therapeutic Chemical; ICD-10: International Classification of Diseases 10; IRR: Incidence rate ratio; aIRR: Adjusted incidence rate ratio; DES: Drug-eluting stent.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12872-021-02312-y.

Additional file 1: Table S1 and Table S2 show changes in statin and ADP inhibitor treatment in diabetes and non-diabetes patients from 2004 to 2016. Table S3 compares two-year risks of major adverse cardiovascular events between diabetes and non-diabetes patients from 2004 to 2016. Table S4 and S5 show two-year risks of major adverse cardiovascular events in diabetes and non-diabetes patients with chronic coronary disease and obstructive coronary disease. Table S6 and S7 show two-year risks of major adverse cardiovascular events in diabetes and non-diabetes patients stratified by sex. Table S8 and S9 show two-year risks of major adverse cardiovascular events in diabetes and non-diabetes patients stratified by age above or below 70 years. Table S10 shows two-year risks of coronary revascularization after coronary angiography in diabetes and non-diabetes patients with any coronary artery disease and in diabetes and non-diabetes patients with obstructive coronary artery disease.

Table S4 and S5 show two-year risks of major adverse cardiovascular events in diabetes and non-diabetes patients with chronic coronary disease and obstructive coronary disease. Table S6 and S7 show two-year risks of major adverse cardiovascular events in diabetes and non-diabetes patients stratified by sex. Table S8 and S9 show two-year risks of major adverse cardiovascular events in diabetes and non-diabetes patients stratified by age above or below 70 years. Table S10 shows two-year risks of coronary revascularization after coronary angiography in diabetes and non-diabetes patients with any coronary artery disease and in diabetes and non-diabetes patients with obstructive coronary artery disease.

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Authors’ contributions
ESJ, KKWO, CG, PGT, LOJ, BR, PLP, RWT, and MM conceptualized the study. ESJ, KKWO, and MM designed the study. KKWO was responsible for data acquisition, data management and analysis. ESJ, KKWO, and MM contributed to data interpretation. ESJ wrote the first draft of the manuscript. ESJ, KKWO, CG, PGT, LOJ, BR, PLP, RWT, and MM provided significant revision of the manuscript and gave final approval for publication. All authors read and approved the final manuscript.

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Availability of data and materials
According to Danish data protection regulations, data cannot be made publicly available.
Declarations

Ethics approval and consent to participate
This study was approved by the Danish Data Protection Agency (record no. 1-16-02-193-18). According to Danish regulations, observational non-interventional registry-based studies do not require approval from ethics committees or informed consent from participants.

Consent for publication
Informed consent is not required from participants in registry-based, non-interventional cohort studies according to Danish regulation.

Competing interests
The authors declare that they have no competing interests. Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to and administered by Aarhus University.

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