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Concomitant use of clopidogrel and statins and risk of major adverse cardiovascular events following coronary stent implantation

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The CYP3A4 inhibition by lipophilic statins may attenuate the effectiveness of clopidogrel.
- No studies have measured drug exposure in a time-varying manner that detects discontinuation and restart of clopidogrel and statin therapy, allowing clinical quantification of the interaction effect.

WHAT THIS STUDY ADDS

- Clopidogrel and CYP3A4-metabolizing statin use were each associated with a substantially reduced rate of major adverse cardiovascular events within 12 months after coronary stent implantation.
- Although we observed an interaction between use of clopidogrel and statins, statin use *vs.* non-use was not associated with an increased rate of major adverse cardiovascular events in patients using clopidogrel after coronary stent implantation.

AIMS

To examine whether CYP3A4-metabolizing statin use modified the association between clopidogrel use and major adverse cardiovascular events (MACE) after coronary stent implantation, using time-varying drug exposure ascertainment.

METHODS

We conducted this population-based cohort study in Western Denmark (population: 3 million) using medical databases. We identified all 13 001 patients with coronary stent implantation between 2002 and 2005 and their comorbidities. During 12 months of follow-up, we tracked the use of clopidogrel and CYP3A4-metabolizing statins and the rate of MACE. We used Cox regression to compute hazard ratios (HRs) controlling for potential confounders.

RESULTS

The rate of MACE per 1000 person years was 104 for concomitant clopidogrel and statin use, 130 for clopidogrel without statin use, 108 for statin without clopidogrel use and 446 for no use of either drug. The adjusted HR comparing clopidogrel use with non-use was 0.68 (95% confidence interval (CI) 0.58, 0.79) among statin users and 0.34 (95% CI 0.29, 0.40) among statin non-users, yielding an interaction effect (i.e. relative rate increase) of 1.97 (95% CI 1.59, 2.44). The adjusted HR for MACE comparing statin use with non-use was 0.97 (95% CI 0.83, 1.13) among clopidogrel users and 0.49 (95% CI 0.42, 0.57) among clopidogrel non-users.

CONCLUSIONS

Clopidogrel and CYP3A4-metabolizing statin use were each associated with a substantially reduced rate of MACE within 12 months after coronary stent implantation. Although we observed an interaction between use of clopidogrel and statins, statin use *vs.* non-use was not associated with an increased rate of MACE in patients using clopidogrel after coronary stent implantation.

Introduction

Currently the thienopyridine clopidogrel is a mainstay in the treatment of vascular events in patients with coronary artery disease or ischaemic stroke [1]. Clopidogrel is a prodrug metabolized by hepatic cytochrome P450 (CYP) enzymes (primarily the 2C19 and 3A4 isoforms) to an active thiol metabolite, which irreversibly inhibits adenosine-5-diphosphate (ADP) binding to the platelet $P2Y_{12}$-receptor. Debate is ongoing about possible interactions between clopidogrel and other commonly used drugs [2], including 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) that are widely used to lower cholesterol concentrations [2]. In several *ex vivo* studies, two CYP3A4-metabolizing statins, atorvastatin [3–5] and simvastatin [6], have been reported to diminish the antiplatelet effect of clopidogrel, but these findings have not convincingly been confirmed in clinical settings [7–15]. None of the previous studies have measured drug exposure in a time-varying manner that detects discontinuation and restart of clopidogrel and statin therapy, allowing clinical quantification of the interaction effect [16].

The clinical importance of a possible clopidogrel–statin interaction arises from the large number of percutaneous coronary interventions (PCIs) performed annually, the increasing use of drug-eluting stents that necessitate long term treatment with clopidogrel [1], and the fact that any adverse interaction may be prevented by avoiding co-administration of clopidogrel and a statin. We therefore conducted a population-based cohort study with complete 12 month follow-up, taking into consideration comorbidity, time-varying medication use and multiple outcomes. We examined whether statin use modified the association between clopidogrel use and major adverse cardiovascular events (MACE) after coronary stent implantation, and whether clopidogrel users were at increased risk of MACE when co-administered a statin.

Methods

Setting

We conducted this population-based cohort study using medical databases in Western Denmark, which has three million inhabitants (55% of the Danish population) [17]. The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals, and partial reimbursement for prescribed medications, including clopidogrel and statins [18]. Accurate and unambiguous linkage of all registries at the individual level is possible in Denmark using the unique central personal registry number assigned to each Danish citizen at birth and to residents upon immigration [19].

As this study did not involve any contact with patients or any intervention, it was not necessary to procure permission from the Danish Scientific Ethical Committee.

Patients and procedures

We used the Western Denmark Heart Registry (WDHR) to identify all PCIs performed between 1 January 2002 and 30 June 2005 in the study region [17]. Since 1999 this registry has collected patient and procedure data from all cardiac intervention centres in Western Denmark [17]. We defined the first PCI during the inclusion period as the 'index PCI' and the date of the procedure as the 'index date'. We did not include patients treated with balloon angioplasty without stenting.

The participating centres were high volume facilities, each performing more than 1000 PCIs per year. The interventions were performed according to current standards, with the interventional strategy (including balloon angioplasty, pre- or post-dilatation, choice of stent, direct stenting, administration of periprocedural glycoprotein IIb/IIIa inhibitor) left to the operator's discretion [17].

Medication use

We used the Danish Nationwide Prescription Database (DNPD) [20] to identify prospectively all filled prescriptions for clopidogrel and statins [21]. Thienopyridines and statins are available by prescription only. As no prescriptions were filled for ticlopidine, no alternative ADP receptor inhibitor was included in the study. Associated Anatomical Therapeutic Chemical (ATC) codes are provided in the Appendix.

The recommended daily maintenance dose of clopidogrel for secondary prevention of ischaemic vascular events in Denmark is 75 mg (one tablet) daily for up to 12 months [21]. Thus, for study purposes the number of days supplied from a dispensed clopidogrel prescription corresponded to the number of tablets per package. Available packages on the Danish market contain 28 or 84 tablets [21]. We computed the number of days exposed by adding 7 days to the number of days supplied. This buffer allowed for a 7 day gap to occur between prescription fillings before a patient was considered to have discontinued the medication.

We grouped the CYP3A4-metabolizing statins (simvastatin, lovastatin and atorvastatin) into one main exposure group [22]. As in the case of clopidogrel, we computed the number of days exposed for statins. For clopidogrel and statins individually, we defined current users at a given point in time as patients exposed by the most recent filled prescription. In a time-varying manner, patients thus contributed time-at-risk as a current or as a non-user of each drug.

Major adverse cardiovascular events

In line with the recommended duration of clopidogrel treatment [21], we identified MACE occurrences within 12

months after the index date. We defined MACE as a first occurrence of myocardial infarction (MI), ischaemic stroke, stent thrombosis, target lesion revascularization or cardiac death. A committee of cardiac specialists, blinded to the history of medication use, reviewed relevant records to determine the occurrence of stent thrombosis and cardiac death, which originally were not included in the medical registries [17].

Myocardial infarction and ischaemic stroke

We used the Danish National Registry of Patients (DNRP) [23], covering all non-psychiatric hospitals since 1977, and emergency room and outpatient clinic visits since 1995, to identify admissions for MI and ischaemic stroke [24]. Associated International Classification of Diseases (ICD) codes are provided in the Appendix.

Stent thrombosis and target lesion revascularization

Based on review of original medical records and catheterization angiograms, the cardiac specialist committee adjudicated the occurrence of definite stent thrombosis as defined by the Academic Research Consortium [17]. We defined target lesion revascularization (TLR) as a repeat PCI or coronary artery bypass grafting of the index lesion, identified from the WDHR [17].

Cardiac death

We obtained data on all cause mortality from the Danish Civil Registration System [19]. This registry has recorded vital statistics, including date of birth, change of address, date of emigration and exact date of death, for the Danish population since 1968 [19]. The cardiac specialist committee then retrieved original paper death certificates from the National Registry of Causes of Deaths, which has collected data on dates and causes of death in Denmark since 1943 [25]. As recorded on the paper death certificate, deaths were classified as either cardiac or non-cardiac, based on underlying cause [17]. Cardiac death was defined as an evident cardiac death, unwitnessed death or death from unknown causes.

Patient characteristics

We obtained information on potential confounders (diabetes, hypertension and obesity) from diagnoses recorded in the DNRP [23] between 1977 and the index date. To ensure complete identification of patients with diabetes, we also searched the DNPD for any previous use of antidiabetic drugs since 1995. From the WDHR [17], we retrieved procedure-specific data, including the year of index PCI, PCI indication (ST-segment elevation MI (STEMI), non-STEMI or unstable angina pectoris (AP), or stable AP, number of treated arteries (1, 2 or 3 or more), number of implanted stents (1, 2 or 3 or more), lesion type (A, B or C) [26], and stent type (drug-eluting or bare-metal stent). We used the DNPD to obtain information on use of the following medications: aspirin, calcium channel blockers, proton pump inhibitors, vitamin K antagonists, non-selective non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2 selective inhibitors and systemic glucocorticoids. Associated ICD and ATC codes are provided in the Appendix.

Statistical analysis

We characterized the patients using medical, procedural, and demographic variables. We followed all patients from the index date until the date of MACE, non-cardiac death, emigration, or 12 months of follow-up, whichever came first. We examined the proportions of clopidogrel and statin users that were covered at end of follow-up by the last redeemed prescription. We stratified the analyses according to whether patients had initiated therapy before index PCI or not.

The time-varying exposure assessment allowed a patient to be considered exposed to different medications over time: clopidogrel plus a statin, clopidogrel without a statin, a statin without clopidogrel or no use of clopidogrel or a statin. This approach permitted comparison of the MACE frequency per cumulative time-at-risk associated with each of the four exposure categories.

We examined whether CYP3A4-metabolizing statins modified the association between clopidogrel and MACE, by comparing current use of clopidogrel with non-use, in subgroups of patients with or without concomitant statin use. We used Cox proportional hazards regression to compute hazard ratios (HRs) with 95% confidence intervals (CIs). The 'interaction effect' is the exponentiated coefficient for the interaction term in the model, that is, the ratio of the stratum-specific HRs [16]. The interaction effect estimates the relative hazard rate increase in patients with concomitant use of clopidogrel and a statin, beyond that expected from the independent effects of each drug alone [16]. An interaction effect different from 1.0 suggests that concomitant statin use modifies any protective effect of clopidogrel. We used the Wald χ^2 test to assess the null hypothesis of no interaction.

In regression analyses, we adjusted for the following potential confounders: age, gender, diabetes, hypertension, obesity, and time-varying use (calculated from the number of days exposed) of aspirin and the potential clopidogrel-interacting drugs of calcium channel blockers and proton pump inhibitors [2]. To examine the confounding impact of our measures of diabetes, hypertension, and obesity, we fitted a minimally adjusted model without these variables. The results from the minimally adjusted model were similar to those from the fully adjusted model and are therefore not further reported. We repeated the analyses stratifying by age, gender, PCI indication, stent type and presence/absence of diabetes. We repeated the analyses for the most commonly used statins in the database (simvastatin and atorvastatin) and the individual outcomes separately. Due to few events of stent thrombosis

and ischaemic stroke, we do not report further on these outcomes.

Finally, we also examined whether clopidogrel modified the association between statin use and MACE, by comparing current statin use with non-use, in subgroups of patients with or without concomitant clopidogrel use. To examine the impact of new use and longer term statin use starting before the PCI date [27], we repeated the analysis in subgroups of patients with or without one or more filled statin prescriptions before index PCI. The results were similar to the overall results and therefore not further reported.

Results

Patient characteristics

We identified 13 001 patients who had undergone coronary stent implantation (Table 1). The median age on the index date was 64 years and 27.7% were female. The indications for PCI were STEMI for 3790 (29.2%) patients, non-STEMI or unstable AP for 3987 (30.7%) patients and stable AP for 4876 (37.5%) patients. During follow-up, 11 859 (91%) patients filled at least one prescription for clopidogrel and 9685 (74%) filled at least one prescription for a CYP3A4-metabolizing statin. Among patients using clopidogrel after PCI, only 45% continued treatment until end of follow-up. This proportion was 84% among statin users (Table 2).

Clinical outcomes

Overall 1890 (14.5%) patients experienced a MACE during follow-up. Among these patients, those who did not use one drug at time of outcome tended also not to use the other (Table 3). The rates of MACE per 1000 person years were 104 for clopidogrel plus CYP3A4-metabolizing statin use, 130 for clopidogrel without statin use, 108 for statin without clopidogrel use and 446 for no use of either drug (Table 3). The adjusted HR for MACE comparing clopidogrel use with non-use was 0.68 (95% CI 0.58, 0.79) among statin users and 0.34 (95% CI 0.29, 0.40) among statin non-users, yielding an interaction effect of 1.97 (95% CI 1.59, 2.44, $P < 0.0001$). The results were consistent for MI, TLR or cardiac death as separate outcomes (Table 4).

We observed no substantial difference from the overall results when stratifying by age, gender, stent type, presence/absence of diabetes (data not shown). Stratifying on PCI indication, the adjusted HR for MACE comparing clopidogrel use with non-use among STEMI patients was 0.68 (95% CI 0.58, 0.79) among CYP3A4-metabolizing statin users and 0.34 (95% CI 0.29, 0.40) among statin non-users (interaction effect = 2.24, 95% CI 1.49, 3.36). Among patients with non-STEMI or unstable AP, these were 0.66 (95% CI 0.48, 0.91) and 0.30 (95% CI 0.22, 0.40), respectively (interaction effect = 0.99, 95% CI 0.68, 1.43), and among those with stable AP, 0.89 (95% CI 0.69, 1.16) and 0.51 (95% CI 0.37, 0.71), respectively (interaction effect = 1.75, 95% CI 1.17, 2.62).

The adjusted HR for MACE comparing statin use with non-use, was 0.97 (95% CI 0.83, 1.13) among clopidogrel users and 0.49 (95% CI 0.42, 0.57) among clopidogrel non-users (Table 5). Results for simvastatin and atorvastatin use were similar to those associated with statin use overall (Tables 3–5).

Discussion

In this population-based cohort study of 13 001 patients undergoing PCI, clopidogrel and CYP3A4-metabolizing statin use were each associated with a markedly reduced rate of MACE within 12 months after coronary stent implantation. When used concomitantly, each drug modified modestly the magnitude of the protective effect of the other. Of major clinical importance, however, statin use was not associated with any increased cardiovascular risk in patients using clopidogrel after coronary stent implantation.

Our study adds important information about the clinical implications of the clopidogrel–statin interaction. In several *ex vivo* studies, atorvastatin [3–5] and simvastatin [6] were reported to diminish the antiplatelet effect of clopidogrel. Furthermore, the inhibitory effect by atorvastatin appeared dose-dependent [4, 5]. However, other studies did not support these findings [28–39], in particular when measurements of clopidogrel's antiplatelet effect were made several weeks after onset of statin co-administration [31–34] or when the statin examined was atorvastatin [35, 36]. High loading doses of clopidogrel (600 mg) could in some of the *ex vivo* studies, however, have masked any statin-mediated reduction in the antiplatelet effect of clopidogrel [37–39]. The conflicting results and methodological limitations due to small sample sizes and different drug doses, measurement techniques and protocols make the *ex vivo* data inconclusive [2].

Several studies have sought to address whether the potential pharmacokinetic interaction between clopidogrel and statins is of clinical importance. A Canadian study of 2927 patients found concomitant use of atorvastatin and clopidogrel associated with a 1.65-fold (95% CI 1.07, 2.54) increased risk for MACE within 30 days after PCI, compared with use of clopidogrel alone [40]. Other CYP3A4-metabolizing drugs were associated with similar risks [40]. In a subsequent analysis of 10 491 patients with a 90 days follow-up, the HR for adverse outcomes associated with concomitant use of CYP3A4-metabolized statins was reduced to 1.16 (95% CI 0.91, 1.47) when the reference group was non-CYP3A4 metabolized statins [15]. Also, a study of 211 patients treated with clopidogrel before PCI reported a lower rate of periprocedural MI for patients treated with pravastatin

Table 1

Characteristics of the entire stent cohort and the subgroup experiencing major adverse cardiovascular events (MACE)

	All patients (n = 13 001) n (%)	MACE patients* (n = 1 890) (%)
Female	3 599 (27.7)	533 (28.2)
Age group		
<60 years	4 763 (36.6)	585 (31.0)
60–69 years	3 949 (30.4)	825 (27.9)
≥70 years	4 289 (33.0)	777 (41.1)
Medication use†		
Clopidogrel	11 859 (91.2)	1 097 (58.0)
Statins	9 685 (74.5)	759 (40.2)
Simvastatin	8810 (67.8)	673 (35.6)
Lovastatin	42 (0.3)	3 (0.2)
Atorvastatin	1243 (9.6)	96 (5.1)
Aspirin	11 231 (86.4)	906 (47.9)
Vitamin K antagonists	889 (6.8)	93 (4.9)
Non-selective NSAIDs	1 409 (10.8)	75 (4.0)
COX-2 inhibitors	1 322 (10.2)	78 (4.1)
Oral glucocorticoids	943 (7.3)	70 (3.7)
Calcium channel blockers	3 016 (23.2)	244 (12.9)
Proton pump inhibitors	2 742 (21.1)	271 (14.3)
Comorbidities‡		
Diabetes	1 390 (10.7)	267 (14.1)
Hypertension	389 (3.0)	76 (4.0)
Obesity	82 (0.6)	12 (0.6)
Procedure data		
Year of study entry		
2002	3 112 (23.9)	496 (26.2)
2003	3 722 (28.6)	561 (29.7)
2004	3 986 (30.7)	542 (28.7)
2005	2 181 (16.8)	291 (15.4)
PCI indication		
STEMI	3 790 (29.2)	862 (45.6)
Non-STEMI or unstable AP	3 987 (30.7)	508 (26.9)
Stable AP	4 876 (37.5)	461 (24.4)
Other	348 (2.7)	59 (3.1)
Number of treated arteries§		
1	10 184 (78.3)	1 472 (77.9)
2	2 366 (18.2)	356 (18.8)
≥3	339 (2.6)	47 (2.5)
Number of stents§		
1	10 761 (82.8)	1 483 (78.5)
2	1 720 (13.2)	308 (16.3)
≥3	458 (3.5)	93 (4.9)
Lesion type§¶		
A	2 684 (20.6)	310 (16.4)
B	7 884 (60.6)	1 200 (63.5)
C	2 427 (18.7)	380 (20.1)
Stent type		
BMS	8 847 (68.0)	1 428 (75.6)
DES	3 548 (27.3)	378 (20.0)
BMS and DES	606 (4.7)	84 (4.4)

*Patients with myocardial infarction, ischaemic stroke, stent thrombosis, target lesion revascularization or cardiac death during the 12 month follow-up period. †Any prescription filling during follow-up. ‡Registered between 1977 and the index PCI. §Data were not available on the number of treated arteries for 112 patients, on the number of stents for 62 patients, and on the lesion type for 6 patients. ¶Lesion classification (simplified): A = non-complicated, length <10 mm, B = irregular, length 10–20 mm, C = irregular, sidebranch, 90 degrees, chronic occlusion, length >20 mm [26]. AP angina pectoris, BMS bare-metal stent, COX cyclo-oxygenase, DES drug-eluting stent, NSAIDs non-steroidal anti-inflammatory drugs, PCI percutaneous coronary intervention, STEMI ST-segment elevation myocardial infarction.

or fluvastatin compared with atorvastatin or simvastatin**.** Contrasting these findings, a randomized controlled trial [7], *post hoc* analyses of the CREDO, CHARISMA and PROVE IT–TIMI trials [8–10] and registry-based studies [11–15] did not support any substantial adverse outcome associated with co-administration of lipophilic statins and clopidogrel. Whereas some of these studies reported no increased risk [11–13], others reported only non-significant increased risks (comparing atorvastatin with pravastatin or no statin use [8, 9, 14] or comparing CYP-metabolized statins with non-CYP metabolized statins [8, 9, 15].

Table 2

The proportion of clopidogrel and statin users who continued therapy until the end of follow-up*

	No	Drug use at end of follow-up* No (%)	Yes (%)
Ever use of clopidogrel after PCI†	11 859	6 557 (55.3)	5 302 (44.7)
Ever use of clopidogrel before PCI‡	1 698	811 (47.8)	887 (52.2)
No clopidogrel prescription before PCI	10 161	5 746 (56.5)	4 415 (43.5)
No clopidogrel prescription after PCI	1 142	1 102 (96.5)	40 (3.5)§
Ever use of clopidogrel before PCI‡	169	129 (76.3)	40 (23.7)§
No clopidogrel prescription before PCI	973	973 (100)	–
Ever use of a CYP3A4-metabolizing statin after PCI†	9 685	1 519 (15.7)	8 166 (84.3)
Ever use of a statin before PCI‡	4 387	662 (15.1)	3 725 (84.9)
No statin prescription before PCI	5 298	857 (16.2)	4 441 (83.8)
No CYP3A4-metabolizing statin prescription after PCI	3 316	3 171 (95.6)	145 (4.4)
Ever use of a statin before PCI‡	461	316 (68.5)	145 (31.5)
No statin prescription before PCI	2 855	2 855 (100)	–

*End of follow-up was defined by a major adverse cardiovascular event, non-cardiac death, emigration or 12 months of follow-up, whichever came first. Patients were considered drug users at end of follow-up if they were covered by the number of days exposed from their last prescription redemption. †At least one prescription redemption within follow-up. ‡At least one prescription redemption within 5 years before PCI. §Patients who at time of death were covered by the number of days exposed from their last prescription redemption before PCI and who did not live to fill a new prescription after PCI. PCI percutaneous coronary intervention.

One major limitation of all previous clinical outcome studies [7–15] was an inability to quantify the isolated interaction effect [16]. Initiating clopidogrel therapy may not be a valid proxy for exposure status throughout follow-up, because patients may stop and restart treatment or may discontinue completely before the end of the recommended treatment period, for example due to intolerable side effects, as it was seen for a large proportion of the clopidogrel-using patients. To quantify the actual interaction effect [16], it is therefore necessary to examine and compare the rate of MACE associated with use of clopidogrel alone, clopidogrel plus a statin, a statin alone or neither. Through our time-varying exposure ascertainment, we thus avoided the assumption that once a patient initiated a medication it was continued for the remainder of its recommended treatment period.

Our study supports both *ex vivo* studies [3–6] reporting an attenuated antiplatelet effect of clopidogrel due to concomitant statin use and clinical outcome studies reporting no increased risk of co-administering statins to clopidogrel-treated patients [2, 41]. This fact is likely explained by the protective effects of statins themselves. Independent of their beneficial lipid lowering effects, statins are reported also to reduce morbidity and mortality after coronary stent implantation through anti-oxidative, anti-inflammatory and anti-thrombotic properties [42]. These so called 'pleiotropic' effects thus may improve endothelial function, stabilize atherosclerotic plaques, decrease oxidative stress and minimize the thrombogenic response [42]. While stents deal effectively with the mechanical aspects of atherosclerosis, statins play an important role in reducing the progression of the atherosclerotic process itself. In our study, the rate of MACE among statin users was similar to that among patients using both clopidogrel and a statin. Our results thus support that statins should not be withheld from patients with appropriate indications due to concerns for a potential interaction with clopidogrel.

Strength and limitations

A number of issues should be considered when interpreting our results. The population-based design within the setting of a tax-supported universal healthcare system largely eliminated selection biases. Data in the prescription database are virtually complete [20]. Although we had to use prescription data as a proxy for actual drug use, we based drug exposure information on actual dispensing at pharmacies [20]. Copayment requirements increased the likelihood of compliance. We were able to calculate the number of days exposed from the number of days of medication supplied, increasing the accuracy of exposure information [43]. Although relying on assumptions regarding the use of dispensed medications, these advanced methods of defining exposure reduced the likelihood of non-differential misclassification [44]. A limitation was that the prescribed daily dose of statins was not available. Also, individuals who continue to use drugs such as statins for prolonged periods are likely to be particularly healthy [45]. This can distort findings regarding the effects of the drugs, but we were able to confirm that this potential bias did not affect our findings by studying statin 'new users' [27]. On the other hand, discontinuation of statins might be associated with poor health [45], but the low rate of statin discontinuation we observed implies that our findings are unlikely to be biased in this way.

Use of the WDHR and DNRP data to ascertain study outcomes has previously been validated [17, 24] and the DNPD has been shown to be accurate and complete [20]. Information on drug use and hospitalizations were collected independently from medical databases, avoiding

Table 3

Hazard ratio for major adverse cardiovascular events* comparing clopidogrel use with non-use, with and without concomitant use of statins

		Clopidogrel use Number†		Rates†		Unadjusted hazard ratio (95% CI)	Interaction effect‡ (95% CI)	*P*§	Adjusted hazard ratio¶ (95% CI)	Interaction effect‡ (95% CI)	*P*§
		–	+	–	+						
Overall††	–	838	231	446	130	0.32 (0.28,0.38)			0.34 (0.29, 0.40)		
	+	237	584	108	104	0.66 (0.56,0.77)	2.03 (1.64, 2.51)	<0.0001	0.68 (0.58, 0.79)	1.97 (1.59, 2.44)	<0.0001
Simvastatin	–	881	292	395	130	0.35 (0.30,0.40)			0.34 (0.30, 0.39)		
	+	194	523	105	101	0.65 (0.55,0.78)	1.87 (1.51, 2.32)	<0.0001	0.66 (0.56, 0.79)	1.95 (1.57, 2.41)	<0.0001
Atorvastatin	–	1031	755	277	109	0.38 (0.34,0.42)			0.38 (0.34, 0.43)		
	+	44	60	124	126	0.64 (0.43,0.95)	1.68 (1.13, 2.51)	0.0110	0.63 (0.43, 0.93)	1.65 (1.10, 2.46)	0.01

*Composite of myocardial infarction, ischaemic stroke, stent thrombosis, target lesion revascularization and cardiac death. †Numbers reflect exposure status at time of outcome. Rates are number of events per 1000 person years. ‡The ratio of the stratum-specific hazard ratios, which estimates the relative hazard rate increase associated with concomitant use of clopidogrel and statins, beyond that expected from the independent effects of these drugs alone. §Wald χ^2 test for no interaction in the model. ¶Adjusted for age, gender, diabetes, hypertension, obesity and time-varying use of aspirin, calcium channel blockers and proton pump inhibitors. ††Current use of simvastatin, lovastatin or atorvastatin.

Table 4

Adjusted hazard ratio for individual outcomes comparing clopidogrel use with non-use, with and without concomitant use of statins

		Myocardial infarction Hazard ratio* (95% CI)	Interaction effect† (95% CI)	*P*‡	Target lesion revascularization Hazard ratio* (95% CI)	Interaction effect† (95% CI)	*P*‡	Cardiac death Hazard ratio* (95% CI)	Interaction effect† (95% CI)	*P*‡
Overall§	–	0.24 (0.18, 0.31)	2.44 (1.68, 3.56)	<0.0001	0.45 (0.35, 0.57)	1.84 (1.34, 2.52)	<0.001	0.14 (0.10, 0.22)	3.30 (1.77, 6.12)	<0.001
	+	0.58 (0.43, 0.78)			0.82 (0.66, 1.02)			0.47 (0.29, 0.78)		
Simvastatin	–	0.20 (0.16, 0.25)	2.75 (1.88, 4.03)	<0.0001	0.44 (0.35, 0.54)	1.89 (1.38, 2.59)	<0.0001	0.11 (0.08, 0.16)	3.97 (2.13, 7.41)	<0.0001
	+	0.54 (0.39, 0.74)			0.82 (0.65, 1.05)			0.44 (0.26, 0.73)		
Atorvastatin	–	0.22 (0.19, 0.26)	2.09 (0.96, 4.53)	0.06	0.49 (0.42, 0.57)	1.58 (0.92, 2.71)	0.10	0.12 (0.09, 0.16)	2.78 (0.55, 14.0)	0.22
	+	0.47 (0.22, 1.00)			0.77 (0.46, 1.30)			0.34 (0.07, 1.71)		

*Adjusted for age, gender, diabetes, hypertension, obesity and time-varying use of aspirin, calcium channel blockers and proton pump inhibitors. †The ratio of the stratum specific hazard ratios, which estimates the increase in hazard ratio associated with concomitant use of clopidogrel and calcium channel blockers, beyond that expected from the independent effects of these drugs alone. ‡Wald χ^2 test for no interaction in the adjusted model. §Current use of simvastatin, lovastatin or atorvastatin.

Table 5

Hazard ratio for major adverse cardiovascular events* comparing use of statins with non-use, with and without concomitant use of clopidogrel

	Unadjusted hazard ratio (95% CI)	Interaction effect† (95% CI)	*P*‡	Adjusted hazard ratio§ (95% CI)	Interaction effect† (95% CI)	*P*‡
Overall¶						
–Clopidogrel	0.45 (0.38, 0.52)	2.03 (1.64, 2.51)	<0.0001	0.49 (0.42, 0.57)	1.97 (1.59, 2.44)	<0.0001
+Clopidogrel	0.90 (0.78, 1.05)			0.97 (0.83, 1.13)		
Simvastatin						
–Clopidogrel	0.47 (0.40, 0.55)	1.87 (1.51, 2.32)	<0.0001	0.47 (0.40, 0.55)	1.95 (1.57, 2.41)	<0.0001
+Clopidogrel	0.87 (0.76, 1.01)			0.91 (0.79, 1.05)		
Atorvastatin						
–Clopidogrel	0.67 (0.49, 0.91)	1.68 (1.13, 2.51)	0.01	0.68 (0.50, 0.92)	1.65 (1.10, 2.46)	0.01
+Clopidogrel	1.13 (0.87, 1.46)			1.12 (0.86, 1.46)		

*Composite of myocardial infarction, ischaemic stroke, stent thrombosis, target lesion revascularization and cardiac death. †The ratio of the stratum specific hazard ratios, which estimates the relative hazard rate increase associated with concomitant use of clopidogrel and statins, beyond that expected from the independent effects of these drugs alone. ‡Wald χ^2 test for no interaction in the adjusted model. §Adjusted for age, gender, diabetes, hypertension, obesity and time-varying use of aspirin, proton pump inhibitors and calcium channel blockers. ¶Current use of simvastatin, lovastatin and atorvastatin.

reliance upon self-reporting and thus reducing the potential for differential misclassification. We note that we observed higher protective effects of clopidogrel and statins than reported in clinical trials [46, 47]. However, population-based effects may differ from those seen in selected trial participants. Moreover, intention to treat analysis in randomized controlled trials is generally conservative. Nonetheless, we cannot rule out confounding from unmeasured variables such as tobacco and alcohol use or residual confounding from unregistered diabetes, hypertension or obesity.

In conclusion, we found that clopidogrel and statin use was individually associated with a markedly reduced rate of MACE within 12 months after coronary stent implantation. Although we observed an interaction between use of clopidogrel and CYP3A4-metabolizing statins, use of statins in addition to clopidogrel was not associated with an increased rate of MACE, implying that statins should remain a recommended lipid-lowering therapy for these patients.

Competing Interests

None of the authors received any fees, honoraria, grants or consultancies that would constitute a conflict of interest with the current study, except for JAB who is a consultant to Bayer. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies has any relation to the present study.

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Contributions

MS, JAB and HTS conceived the study idea and designed the study. MBJ, MM, AK, LOJ, HHT, HEB and HTS collected the data. MS, JAB and HTS reviewed the literature. MJB analyzed the data and MS, JAB and HTS participated in the discussion of the analyses. All authors participated in the interpretation of the findings. MS organized the writing and wrote the initial draft. All authors edited the manuscript and approved the final version. HTS is the guarantor.

Appendix

ATC codes defining drug use

Clopidogrel: B01AC04

Statins: simvastatin: C10AA01; lovastatin: C10AA02; atorvastatin: C10AA05.

Aspirin: B01AC06, N02BA01, N02BA51, B01AC30

Vitamin K antagonists: B01AA03, B01AA04

Non-selective non-steroidal anti-inflammatory drugs: M01AB01, M01AC01, M01AE01, M01AE51, M01AE02, M01AE03, M01AE53, M01AE14, M01AG02

Cyclo-oxygenase-2 selective inhibitors: M01AH, M01AB05, M01AB55, M01AB08, M01AC06, M01AX01

Systemic glucocorticoids: H02AB

Proton pump inhibitors: A02BC01-5

Calcium channel blockers: C08CA01, C08CA02, C08CA03, C08CA05, C08CA08, C08CA09, C08CA13, C08CX01, C08DA, C08DB01.

ICD and ATC codes defining diseases

Myocardial infarction: ICD-10 code: I21

Ischaemic stroke: ICD-10 codes: I63-64

Diabetes: ICD-8 codes: 249, 250; ICD-10 codes: E10-14, O24, H36.0; ATC codes: A10A, A10B

Obesity: ICD-8 codes: 277, 279.00, 279.01: ICD-10 codes: E65, E66, E67, E68

Hypertension: ICD-8 codes: 400–404; ICD-10 codes: DI10-DI15

REFERENCES

1 McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004; 364: 1519–21.

2 Bates ER, Lau WC, Angiolillo DJ. Clopidogrel-drug interactions. J Am Coll Cardiol 2011; 57: 1251–63.

3 Clarke TA, Waskell LA. The metabolism of clopidogrel is catalyzed by human cytochrome P450 3A and is inhibited by atorvastatin. Drug Metab Dispos 2003; 31: 53–9.

4 Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, Tait AR, Carville DG, Guyer KE, Bates ER. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction. Circulation 2003; 107: 32–7.

5 Neubauer H, Günesdogan B, Hanefeld C, Spiecker M, Mügge A. Lipophilic statins interfere with the inhibitory effects of clopidogrel on platelet function – a flow cytometry study. Eur Heart J 2003; 24: 1744–9.

6 Mach F, Senouf D, Fontana P, Boehlen F, Reber G, Daali Y, de Moerloose P, Sigwart U. Not all statins interfere with clopidogrel during antiplatelet therapy. Eur J Clin Invest 2005; 35: 476–81.

7 Han YL, Zhang ZL, Li Y, Wang SL, Jing QM, Wang ZL, Wang DM. Comparison on long-term effects of atorvastatin or pravastatin combined with clopidogrel for patients undergoing coronary stenting: a randomized controlled trial. Zhonghua Yi Xue Za Zhi 2009; 89: 2240–4.

8 Saw J, Steinhubl SR, Berger PB, Kereiakes DJ, Serebruany VL, Brennan D, Topol EJ. Clopidogrel for the Reduction of Events During Observation I. Lack of adverse clopidogrel-atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. Circulation 2003; 108: 921–4.

9 Saw J, Brennan DM, Steinhubl SR, Bhatt DL, Mak KH, Fox K, Topol EJ, on behalf of the CHARISMA Investigators. Lack of evidence of a clopidogrel-statin interaction in the CHARISMA trial. J Am Coll Cardiol 2007; 50: 291–5.

10 Lotfi A, Schweiger M, Giugliano G, Murphy S, Cannon C. High-dose atorvastatin does not negatively influence clinical outcomes among clopidogrel treated acute coronary syndrome patients – A Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) analysis. Am Heart J 2008; 155: 954–8.

11 Trenk D, Hochholzer W, Frundi D, Stratz C, Valina CM, Bestehorn H-P, Büttner HJ, Neumann F-J. Impact of cytochrome P450 3A4-metabolized statins on the anti-platelet effect of a 600-mg loading dose clopidogrel and on clinical outcome in patients undergoing elective coronary stent placement. Thromb Haemost 2008; 99: 174–81.

12 Mukherjee DF, Kline-Rogers E, Fang J, Munir K, Eagle KA. Lack of clopidogrel-CYP3A4 statin interaction in patients with acute coronary syndrome. Heart 2005; 91: 23–6.

13 Geisler T, Zurn C, Paterok M, Gohring-Frischholz K, Bigalke B, Stellos K, Seizer P, Kraemer BF, Dippon J, May AE, Herdeg C, Gawaz M. Statins do not adversely affect post-interventional residual platelet aggregation and outcomes in patients undergoing coronary stenting treated by dual antiplatelet therapy. Eur Heart J 2008; 29: 1635–43.

14 Wienbergen H, Gitt AK, Schiele R, Juenger C, Heer T, Meisenzahl C, Limbourg P, Bossaller C, Senges J, Group MPS. Comparison of clinical benefits of clopidogrel therapy in patients with acute coronary syndromes taking atorvastatin versus other statin therapies. Am J Cardiol 2003; 92: 285–8.

15 Blagojevic A, Delaney JAC, Lévesque LE, Dendukuri N, Boivin J-F, Brophy JM. Investigation of an interaction between statins and clopidogrel after percutaneous coronary intervention: a cohort study. Pharmacoepidemiol Drug Saf 2009; 18: 362–9.

16 Greenland S, Lash TL, Rothman KJ. Concepts of Interaction. In: Modern Epidemiology, 3rd edn., eds Rothman KJ, Greenland S, Lash TL. Philadelphia, PA: Lippincott Williams & Wilkins, 2008; 71–86.

17 Schmidt M, Maeng M, Jakobsen CJ, Madsen M, Thuesen L, Nielsen PH, Bøtker H, Sørensen HT. Existing data sources for clinical epidemiology: The Western Denmark Heart Registry. Clinical Epidemiology 2010; 2: 137–44.

18 Danish Medicines Agency. Over-the-counter medicine and reimbursement criteria in Denmark [online]. Available at http://www.dkma.dk (last Accessed 1 February 2012).

19 Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 2006; 53: 441–9.

20 Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. Dan Med Bull 1997; 44: 445–8.

21 Danish Medicines Agency. Available drugs and package sizes on the Danish drug market [online]. Available at http://www.lmk.dk (last Accessed 1 February 2012).

22 Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. Circulation 2004; 109: III50–7.

23 Andersen TF, Madsen M, Jorgensen J, Mellemkjaer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999; 46: 263–8.

24 Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. J Clin Epidemiol 2003; 56: 124–30.

25 Juel K, Helweg-Larsen K. The Danish registers of causes of death. Dan Med Bull 1999; 46: 354–7.

26 Ellis SG, Vandormael MG, Cowley MJ, DiSciascio G, Deligonul U, Topol EJ, Bulle TM. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study Group. Circulation 1990; 82: 1193–202.

27 Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003; 158: 915–20.

28 Piorkowski M, Weikert U, Schwimmbeck PL, Martus P, Schultheiss HP, Rauch U. ADP induced platelet degranulation in healthy individuals is reduced by clopidogrel after pretreatment with atorvastatin. Thromb Haemost 2004; 92: 614–20.

29 Serebruany VL, Midei MG, Malinin AI, Oshrine BR, Lowry DR, Sane DC, Tanguay JF, Steinhubl SR, Berger PB, O'Connor CM, Hennekens CH. Absence of interaction between atorvastatin or other statins and clopidogrel: results from the interaction study. Arch Intern Med 2004; 164: 2051–7.

30 Farid NA, Small DS, Payne CD, Jakubowski JA, Brandt JT, Li YG, Ernest CS, Salazar DE, Konkoy CS, Winters KJ. Effect of atorvastatin on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel in healthy subjects. Pharmacotherapy 2008; 28: 1483–94.

31 Smith SM, Judge HM, Peters G, Storey RF. Multiple antiplatelet effects of clopidogrel are not modulated by statin type in patients undergoing percutaneous coronary intervention. Platelets 2004; 15: 465–74.

32 Malmström RE, Östergren J, Jørgensen L, Hjemdahl P. Influence of statin treatment on platelet inhibition by clopidogrel – a randomized comparison of rosuvastatin, atorvastatin and simvastatin co-treatment. J Intern Med 2009; 266: 457–66.

33 Mitsios JV, Papathanasiou AI, Rodis FI, Elisaf M, Goudevenos JA, Tselepis AD. Atorvastatin does not affect the antiplatelet potency of clopidogrel when it is administered concomitantly for 5 weeks in patients with acute coronary syndromes. Circulation 2004; 109: 1335–8.

34 Mitsios JV, Papathanasiou AI, Elisaf M, Goudevenos JA, Tselepis AD. The inhibitory potency of clopidogrel on ADP-induced platelet activation is not attenuated when it is co-administered with atorvastatin (20 mg/day) for 5 weeks in patients with acute coronary syndromes. Platelets 2005; 16: 287–92.

35 Vinholt P, Poulsen TS, Korsholm L, Kristensen SR, Hallas J, Damkier P, Mickley H. The antiplatelet effect of clopidogrel is not attenuated by statin treatment in stable patients with ischemic heart disease. Thromb Haemost 2005; 94: 438–43.

36 Wenaweser P, Windecker S, Billinger M, Cook S, Togni M, Meier B, Haeberli A, Hess OM. Effect of atorvastatin and pravastatin on platelet inhibition by aspirin and clopidogrel treatment in patients with coronary stent thrombosis. Am J Cardiol 2007; 99: 353–6.

37 Gorchakova O, von Beckerath N, Gawaz M, Mocz A, Joost A, Schömig A, Kastrati A. Antiplatelet effects of a 600 mg loading dose of clopidogrel are not attenuated in patients receiving atorvastatin or simvastatin for at least 4 weeks prior to coronary artery stenting. Eur Heart J 2004; 25: 1898–902.

38 Motovska Z, Widimsky P, Petr R, Bilkova D, Marinov I, Simek S, Kala P; PRAGUE-8 Study Investigators. Factors influencing clopidogrel efficacy in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention: statin's advantage and the smoking 'paradox'. J Cardiovasc Pharmacol 2009; 53: 368–72.

39 Müller I, Besta F, Schulz C, Li Z, Massberg S, Gawaz M. Effects of statins on platelet inhibition by a high loading dose of clopidogrel. Circulation 2003; 108: 2195–7.

40 Brophy J, Babapulle M, Costa V, Rinfret S. A pharmacoepidemiology study of the interaction between atorvastatin and clopidogrel after percutaneous coronary intervention. Am Heart J 2006; 152: 263–9.

41 Bhindi R, Ormerod O, Newton J, Banning AP, Testa L. Interaction between statins and clopidogrel: is there anything clinically relevant? QJM 2008; 101: 915–25.

42 Nair PK, Mulukutla SR, Marroquin OC. Stents and statins: history, clinical outcomes and mechanisms. Expert Rev Cardiovasc Ther 2010; 8: 1283–95.

43 Schneeweiss S, Patrick AR, Stürmer T, Brookhart MA, Avorn J, Maclure M, Rothman KJ, Glynn RJ. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. Med Care 2007; 45: S131–42.

44 Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. Am J Epidemiol 2005; 162: 1016–23.

45 Stürmer T, Jonsson Funk M, Poole C, Brookhart MA. Nonexperimental comparative effectiveness research using linked healthcare databases. Epidemiology 2011; 22: 298–301.

46 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383–9.

47 Steinhubl SR, Berger PB, Mann JT, Fry ET, DeLago A, Wilmer C, Topol EJ, Credo Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002; 288: 2411–20.