BMJ Open

Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction – a Danish nationwide population based cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-010880
Article Type:	Research
Date Submitted by the Author:	28-Dec-2015
Complete List of Authors:	Green, Anders; Institute of Clinical Research, University of Southern Denmark, Odense Patient data Exploratory Network (OPEN) Pottegard, Anton; University of Southern Denmark, Clinical Pharmacology, Institute of Public Health Broe, Anne Diness, Thomas; AstraZeneca Emneus, Martha; Institute of Applied Economics and Health Research Hasvold, Lars Pål; AstraZeneca Nordic, Medical department Gislason, Gunnar; Copenhagen University Hospital Gentofte, Department of Cardiology
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Myocardial infarction < CARDIOLOGY, dual antiplatelet therapy, persistence, health registers, real-life data

Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction – a Danish nationwide population based cohort study

Key words: Myocardial infarction; dual antiplatelet therapy, persistence; Danish nationwide health registries; real-life data

Anders Green, MD, PhD, DMSc [1, 2], Anton Pottegård, MScPharm, PhD [3], Anne Broe, MD [3], Thomas Goldin Diness, MScPharm, PhD [4], Martha Emneus [2], Pål Hasvold, MScPharm [4], Gunnar H. Gislason, MD, PhD, FACC, FAHA, FESC [5]

[1] Institute of Applied Economics and Health Research, Copenhagen, Denmark

[2] OPEN, Odense Patient Data Explorative Network, Odense University Hospital/Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[3] Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, Odense, Denmark

[4] AstraZeneca, Södertälje, SE-151 85 Sweden

[5] Copenhagen University Hospital Gentofte, 2900 Hellerup, Denmark

Total word count: 3687

Address for correspondence:

Prof. Anders Green, MD, PhD, DMSc
Institute of Applied Economics and Health Research
Ewaldsgade 3, DK-2200 Copenhagen N, Denmark
E-mail: anders.green@dadlnet.dk
Phone: +45 4088 7775 (mobile) FAX: Not available

Author emails:
Anders Green: agreen@dadlnet.dk
Anton Pottegård: apottegaard@health.sdu.dk
Anne Broe: annebroe@gmail.com
Thomas Goldin Diness: Thomas.diness@astrazeneca.com
Martha Emneus: martha.emneus@appliedeconomics.dk
Pål Hasvold: Paal.hasvold@astrazeneca.com
Gunnar Gislason: Gunnar.Gislason@regionh.dk

ABSTRACT

Objectives: The study investigated DAPT patterns over time and patient characteristics associated with the various treatments in an MI population.

Design: A registry-based observational cohort study was performed using antecedent data.

Setting: This study linked morbidity, mortality, and medication data from Danish national registries.

Participants: All 28,449 patients admitted to a Danish hospital with a first time MI and alive at discharge from 2009 through 2012 were included.

Primary and secondary outcome measures: Primary outcome was initiation of DAPT and secondary outcomes comprised persistence in DAPT treatment and switches between DAPT treatments.

Results: The overall proportion of patients prescribed DAPT increased from 68% (C.L.95%: 67% - 69%) to 73% (C.L.95%: 67% - 69%) from 2009 to 2012. For patients treated with and without percutaneous coronary intervention (PCI), the corresponding numbers were from 87% (C.L.95%: 86% - 88%) to 91% (C.L.95%: 90% - 92%) and from 49% (C.L.95%: 47% - 50%) to 52% (C.L.95%: 51% - 54%), respectively. Non-PCI patients had higher cardiovascular risk compared with PCI patients. Among PCI patients, age >75 years, atrial fibrillation, diabetes, and peripheral arterial disease were associated with a higher risk of treatment breaks for DAPT. Among patients without PCI, ticagrelor treatment was associated with an increased risk of treatment breaks during the first 12 months compared with clopidogrel treatment.

Conclusions: From 2009 to 2012, there was an increase in the proportion of MI patients receiving DAPT, and a longer duration of DAPT. Still, a large proportion of patients without PCI are discharged either without DAPT or with a short DAPT duration. These findings may indicate the need for more careful attention to DAPT for MI patients not undergoing PCI in Denmark.

Strength and limitations of this study

- Our study describes dual antiplatelet treatment in Danish patients after myocardial infarction during 2009-2012, making use of the nationwide and complete health registers that may be linked at individual level by means of the unique personal identification system covering all Danish citizens.
- The registry data available for our study are collected for administrative purposes, thereby reducing potential sources of bias otherwise introduced by selection of particular hospitals or healthcare insurance systems.
- Even though coding errors cannot be ruled out in the registry data previous studies have demonstrated high levels of sensitivity and specificity for cardiovascular outcomes in the Danish health registers.
- Our study is limited by not including information on unstable angina, STEMI , NSTEMI, blood pressure, smoking habits, lipid profiles and socioeconomic status.

INTRODUCTION

Platelet activation and subsequent aggregation represent the key targets in the management of acute coronary syndromes (ACS) to prevent recurrent events. However, the incidence of ACS has declined over time supporting the notion that contemporary treatment effectively improves outcomes after an MI[1, 2, 3, 4]. European guidelines recommend initiation of dual antiplatelet therapy (DAPT) with low-dose acetyl salicylic acid (ASA) and a $P2Y_{12}$ antagonist to reduce the risk of both acute ischemic complications and recurrent atherothrombotic events[5]. This treatment is recommended for up to 12 months in patients with ACS, irrespective of whether the patient undergoes revascularization with percutaneous coronary intervention (PCI) or not[5, 6].

Previously, a nationwide Danish study described initiation and persistence patterns for DAPT with clopidogrel and ASA after myocardial infarction (MI) in the years 2000-2005[7]. The study showed a high persistence with clopidogrel treatment among PCI treated patients as compared with non-PCI patients, and a lower degree of clopidogrel use among women and patients admitted to local hospitals[7].

New $P2Y_{12}$ antagonists have recently been introduced in the treatment of ACS patients; prasugrel received European Medicines Agency (EMA) approval in 2009 and ticagrelor in 2011. Ticagrelor, co-administered with ASA, is indicated for patients with ACS, including patients managed medically, and those who are managed with PCI or coronary artery by-pass grafting (CABG)[8]. Prasugrel, co-administered with ASA is indicated for patients with ACS undergoing PCI[9].

In 2011, ticagrelor was recommended as first-line treatment in the national Danish ACS guidelines across sub-diagnoses[10]. How these new multiple DAPT options are used in contemporary clinical practice in Denmark and how guideline recommendations are implemented are not known. Also, as the indication for the different $P2Y_{12}$ antagonists differ, it is likely that the populations treated with the respective $P2Y_{12}$ antagonists diverge with respect to their baseline characteristics. To our knowledge, this has not been investigated in a large scale study. Furthermore, it is of clinical relevance to describe treatment persistence and patient characteristics that are associated with reduced persistence.

The aim of this study was to describe the DAPT pattern in Danish patients with MI during 2009-2012, with focus on comparing treatment in 2009 and 2012, ie, before and after the introduction of prasugrel and ticagrelor, by combining data from nationwide registries on hospital admissions, prescription drug use and date of mortality.

METHODS

Data sources

Data were obtained from Danish nationwide compulsory registries on hospital admissions and prescribed drugs. As virtually all medical care in Denmark is provided by the national health authorities, these data sources allow true population-based studies with national coverage and high levels of completeness[11].

The Danish National Prescription Registry[12] contains data on all prescribed drugs dispensed from Danish community pharmacies since 1995. Prescription data include type of drug, date of dispensing and quantity and are categorized according to the Anatomic Therapeutic Chemical (ATC) index[13]. Drug expenses are partially reimbursed by the Danish health-care authorities.

The Danish National Patient Registry contains data on all somatic hospitalizations in Denmark since 1977 and on outpatient visits since 1995[14]. Hospital discharge and outpatient contact diagnoses are coded according to the International Classification of Diseases (ICD-10) from 1994 onward.

All data sources were linked by means of the personal identification number, a unique identifier encoding gender and date of birth, assigned by the Danish Civil Registration System to all Danish residents since 1968[15]. The Civil Registration System contains continuously updated data on address, date of death, and migration to and from Denmark. All record linkage was performed by Statistics Denmark.

Study design and study population

Patients who experienced a first time hospital admission related to acute MI within the observation period 1 January 2009 to 31 December 2012 were included. MI index event was defined as having an admission with a primary or secondary diagnosis ICD-10 code of I21. Patients with a diagnosis of unstable angina pectoris (ICD-10 code I20.0) were not included. Further, sub classification into ST segment elevation MI (STEMI) and non-segment ST elevation MI (NSTEMI) was not performed since ICD-10 coding specification at this level has not been validated.

An MI episode may present as a sequence of admissions to more than one hospital department and was defined as one admission if the interval was not more than one day between discharge from one hospital and admission date at the next hospital. Only the first episode for each individual within the observation period was included. Thus, we excluded those with a history of previous MI prior to the time of their first eligible admission. We furthermore required that individuals were discharged alive. Patients had to be Danish residents with a Danish permanent address at the time of admission.

The study was approved by the Danish Data Protection Agency. According to Danish law, ethical approval is not required for registry-based studies[16].

ANALYSIS

All individuals were classified according to whether they had been dispensed DAPT or not. The use of DAPT was analyzed among individuals experiencing MI in 2009 and 2012, respectively. All analyses were stratified by type of DAPT, study year and whether or not the patient underwent PCI in relation to the index event.

Baseline characteristics of subjects initiating DAPT following MI

Individuals were described regarding age and gender, the type of hospital at index event, procedures during index event, previous diagnoses and dispensed drugs at the time of admission.

(1) Classification according to admission by type of hospital according to degree of cardiological expertise available was: local hospital, hospital without catheterization laboratory (level 1); main regional hospital, hospital with catheterization laboratory (level 2); tertiary cardiac hospital, university hospital with catheterization laboratory (level 3).

(2) Procedures during index event included angiography (UXAC85), PCI (procedure code FNG) and CABG (procedure code FNA-FNE). We included CABG performed up to 30 days after discharge. Throughout the study period, procedures were coded according to the Nordic classification scheme[17].

(3) Previous diagnoses registered in the Patient Registry up to 5 years prior to the admission for index MI were included. For a full list of diagnoses and definitions, see Appendix A.

(4) Drug use were defined as having filled a prescription for the given drug according to the Prescription Registry within 180 days prior to the index admission and up to 30 days following discharge. For a full list of drugs included, see Appendix B.

Persistence to DAPT following treatment initiation

DAPTs were defined as concomitant use of low-dose ASA and a $P2Y_{12}$ antagonist, and were further subcategorized by the specific $P2Y_{12}$ antagonists. The main drugs examined were the three $P2Y_{12}$ antagonists currently available in Denmark, ie, clopidogrel (ATC B01AC04), prasugrel (B01AC22) and ticagrelor (B01AC24), as well as low-dose ASA (B01AC06 or N02BA01). For all four drugs, use was defined as having filled a prescription for the given drug within 90 days prior to the admission to 30 days after the admission. Individuals filling prescriptions for two different $P2Y_{12}$ antagonists within this interval were classified according to the last prescription filled. Individuals failing to fill a prescription for either a $P2Y_{12}$ antagonist or ASA within 30 days after index MI were classified as not using DAPT.

Persistence with treatment was analyzed during a period of 365 days following the index MI using the 'proportion of patients covered' (PPC) method[18]. In brief, all subjects were followed starting 30 days after discharge from the index event. Over time, we estimated the proportion of all subjects still alive and not migrated and using the same $P2Y_{12}$ antagonist as at discharge. A subject was considered a current user of a given $P2Y_{12}$ antagonist from the day of filling a prescription for that drug and for a number of days corresponding to either the number of tablets for clopidogrel and prasugrel (used once daily) or half the number of tablets for ticagrelor (used twice daily). Finally, a 30-day grace period was added to the estimated duration to account for minor non-compliance and irregular prescription refills. A sensitivity analysis with a grace period of 90 days was also performed. An individual could be regarded as dropped out of treatment at one point in time and later be re-classified as a current user upon filling a new prescription. In the Cox regression analysis for having a treatment break larger than the 30-day grace period, the type of DAPT treatment, age and gender, type of treating hospital department and selected comorbidities were chosen as covariates.

Frequency of switch between different DAPT regimens

To estimate switch patterns, we estimated the proportion of all subjects who within the first year following discharge filled a $P2Y_{12}$ antagonist other than the one they first used following discharge. The observation period for this analysis commenced 30 days after discharge with the index admission of MI.

Statistical program

All calculations were performed using STATA Release 13.0 (StataCorp, College Station, TX, USA).

RESULTS

Overall, 97% (28,449 patients) of all patients admitted to the hospital with a first-time MI during 2009–2012 were alive 30 days after discharge and included in this study. The baseline characteristics for the years 2009 and 2012 are shown in Table 1 and Table 2. Baseline characteristics for the toal material as well as for the years 2010 and 2011 are contained Supplementary Tables 1, 2 and 3, respectively.

Patient characteristics 2009

Of the first time MI patients (median age 69 years [interquartile range (IQR) 59-79 years]; 36% women), 73% underwent angiography and 53% PCI, and a majority of patients (67%) were discharged with DAPT (Table 1 and Figure 1). A larger proportion of patients with PCI were discharged with DAPT (87%) compared with the patients without PCI (51%). The PCI patients were younger and more frequently men than the non-PCI patients. A majority of these patients received ASA, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and statins at discharge, which is in line with guideline recommendations. Among the non-PCI patients, a considerably larger proportion underwent CABG, had a diagnosis of atrial fibrillation, and/or had a history of major bleedings compared with the PCI patients. Notably, a larger proportion of non-PCI patients were discharged without beta-blockers, ACE inhibitors and statins.

Patient characteristics 2012

The median age of first time MI patients was 69 years [IQR, 58-78 years], and 36% were women (Table 2). Overall, 79% underwent angiography and 55% PCI, and the majority (73%) were discharged with DAPT (Table 2 and Figure 1). Still, a large proportion (49%) of the non-PCI patients were discharged without DAPT and other guideline recommended drug therapies compared with the PCI patients. In general, marked differences in patient characteristic were observed dependent on the choice of $P2Y_{12}$ antagonist used in the DAPT regimens. Patients treated with prasugrel were 11 years younger (median), more commonly men, and the majority underwent PCI (84%) compared with the total MI patient population. Most of the prasugrel-treated patients were either managed at a main regional hospital or at a university hospital with a catheterization laboratory.

The proportion of patients prescribed DAPT with ticagrelor increased quickly after its introduction in 2011. By the end of 2012, ticagrelor was the most common $P2Y_{12}$ antagonist in both patients with and without PCI (Figure 1). More patients in the ticagrelor group underwent PCI (71%) compared with clopidogrel treated patients (52%). Ticagrelor-treated patients were 7 years younger and more commonly men. Patients treated with clopidogrel had in general a more severe disease burden at baseline, with additional diagnoses of heart failure, stroke, or atrial fibrillation compared with the other DAPT-treated patients (Table 2).

Table 1 Baseline demographic and clinical characteristics for the 2009 first-time MI population

	Patients with PCI (N=3576, 50%)					Patients without PCI (N=3528, 50%)				
	All patients n=3576	**Clopidogrel n=3087**	**Ticagrelor n=0**	**Prasugrel n=13**	**No DAPT n=476**	**All patients n=3528**	**Clopidogrel n=1712**	**Ticagrelor n=0**	**Prasugrel n=1**	**No DAPT n=1815**
Age [median (IQR)]	64 (55 - 73)	64 (55 - 73)	. (. - .)	57 (50 - 64)	68 (59 - 75)	74 (64 - 83)	74 (64 - 83)	. (. - .)	49 (49 - 49)	74 (63 - 84)
Males	2,643 (73.9%)	2,289 (74.1%)	0 (.%)	8 (61.5%)	346 (72.7%)	1,951 (55.3%)	956 (55.8%)	0 (.%)	0 (0.0%)	995 (54.8%)
Type of hospital (at index MI event)										
Local hospital	946 (26.5%)	805 (26.1%)	0 (.%)	5 (38.5%)	136 (28.6%)	1,440 (40.8%)	659 (38.5%)	0 (.%)	(n<=5)	780 (43.0%)
Main regional hospital	1,149 (32.1%)	1,005 (32.6%)	0 (.%)	5 (38.5%)	139 (29.2%)	1,150 (32.6%)	616 (36.0%)	0 (.%)	0 (0.0%)	534 (29.4%)
Tertiary cardiac hospital	1,481 (41.4%)	1,277 (41.4%)	0 (.%)	(n<=5)	201 (42.2%)	938 (26.6%)	437 (25.5%)	0 (.%)	0 (0.0%)	501 (27.6%)
Procedures (at index event)										
CABG	80 (2.2%)	47 (1.5%)	0 (.%)	0 (0.0%)	33 (6.9%)	412 (11.7%)	197 (11.5%)	0 (.%)	0 (0.0%)	215 (11.8%)
Angiography	3,535 (98.9%)	3,055 (99.0%)	0 (.%)	13 (100.0%)	467 (98.1%)	1,761 (49.9%)	932 (54.4%)	0 (.%)	(n<=5)	828 (45.6%)
Previous diagnoses										
Heart failure	100 (2.8%)	71 (2.3%)	0 (.%)	0 (0.0%)	29 (6.1%)	343 (9.7%)	148 (8.6%)	0 (.%)	0 (0.0%)	195 (10.7%)
Ischaemic heart disease	256 (7.2%)	181 (5.9%)	0 (.%)	(n<=5)	74 (15.5%)	488 (13.8%)	199 (11.6%)	0 (.%)	0 (0.0%)	289 (15.9%)
Unstable angina	55 (1.5%)	43 (1.4%)	0 (.%)	0 (0.0%)	12 (2.5%)	107 (3.0%)	50 (2.9%)	0 (.%)	0 (0.0%)	57 (3.1%)
Peripheral arterial disease	94 (2.6%)	67 (2.2%)	0 (.%)	0 (0.0%)	27 (5.7%)	246 (7.0%)	118 (6.9%)	0 (.%)	0 (0.0%)	128 (7.1%)
Stroke total	132 (3.7%)	98 (3.2%)	0 (.%)	(n<=5)	33 (6.9%)	338 (9.6%)	160 (9.3%)	0 (.%)	0 (0.0%)	178 (9.8%)
Non-ischaemic stroke	(n<=5)	(n<=5)	0 (.%)	0 (0.0%)	(n<=5)	19 (0.5%)	7 (0.4%)	0 (.%)	0 (0.0%)	12 (0.7%)
Ischaemic stroke	130 (3.6%)	96 (3.1%)	0 (.%)	(n<=5)	33 (6.9%)	328 (9.3%)	155 (9.1%)	0 (.%)	0 (0.0%)	173 (9.5%)
Atrial fibrillation	125 (3.5%)	93 (3.0%)	0 (.%)	0 (0.0%)	32 (6.7%)	375 (10.6%)	132 (7.7%)	0 (.%)	0 (0.0%)	243 (13.4%)
Chronic renal dysfunction	16 (0.4%)	11 (0.4%)	0 (.%)	0 (0.0%)	5 (1.1%)	43 (1.2%)	18 (1.1%)	0 (.%)	0 (0.0%)	25 (1.4%)
Diabetes mellitus	396 (11.1%)	327 (10.6%)	0 (.%)	(n<=5)	68 (14.3%)	625 (17.7%)	304 (17.8%)	0 (.%)	0 (0.0%)	321 (17.7%)
Major bleeding	93 (2.6%)	75 (2.4%)	0 (.%)	0 (0.0%)	18 (3.8%)	189 (5.4%)	67 (3.9%)	0 (.%)	0 (0.0%)	122 (6.7%)
Liver disease	(n<=5)	(n<=5)	0 (.%)	0 (0.0%)	0 (0.0%)	5 (0.1%)	(n<=5)	0 (.%)	0 (0.0%)	(n<=5)
Coagulation disorders	9 (0.3%)	8 (0.3%)	0 (.%)	0 (0.0%)	(n<=5)	21 (0.6%)	(n<=5)	0 (.%)	0 (0.0%)	17 (0.9%)
Cancer	193 (5.4%)	158 (5.1%)	0 (.%)	(n<=5)	34 (7.1%)	333 (9.4%)	146 (8.5%)	0 (.%)	0 (0.0%)	187 (10.3%)
Drug use at discharge										
Total number of drugs [median (IQR)]	3 (1 - 6)	3 (1 - 6)	. (. - .)	4 (0 - 8)	4 (2 - 8)	6 (3 - 10)	6 (3 - 10)	. (. - .)	13 (13 - 13)	7 (3 - 11)
ACE-inhbitors and ARB	1,948 (54.5%)	1,678 (54.4%)	0 (.%)	7 (53.8%)	263 (55.3%)	1,984 (56.2%)	992 (57.9%)	0 (.%)	0 (0.0%)	992 (54.7%)

Acetyl salicylic acid	3,379 (94.5%)	3,087 (100.0%)	0 (.%)	13 (100.0%)	279 (58.6%)	2,962 (84.0%)	1,712 (100.0%)	0 (.%)	(n<=5)	1,249 (68.8%)
Betablocker	3,170 (88.6%)	2,760 (89.4%)	0 (.%)	12 (92.3%)	398 (83.6%)	2,537 (71.9%)	1,389 (81.1%)	0 (.%)	0 (0.0%)	1,148 (63.3%)
Calcium-channel blocker	749 (20.9%)	621 (20.1%)	0 (.%)	(n<=5)	127 (26.7%)	1,027 (29.1%)	474 (27.7%)	0 (.%)	(n<=5)	552 (30.4%)
Oral antidiabetics and insulin	369 (10.3%)	308 (10.0%)	0 (.%)	(n<=5)	60 (12.6%)	562 (15.9%)	277 (16.2%)	0 (.%)	0 (0.0%)	285 (15.7%)
Proton pump inhibitors	916 (25.6%)	772 (25.0%)	0 (.%)	(n<=5)	140 (29.4%)	1,302 (36.9%)	579 (33.8%)	0 (.%)	(n<=5)	722 (39.8%)
Statins	3,379 (94.5%)	2,954 (95.7%)	0 (.%)	12 (92.3%)	413 (86.8%)	2,523 (71.5%)	1,427 (83.4%)	0 (.%)	(n<=5)	1,095 (60.3%)
Anticoagulant	224 (6.3%)	162 (5.2%)	0 (.%)	(n<=5)	61 (12.8%)	415 (11.8%)	113 (6.6%)	0 (.%)	0 (0.0%)	302 (16.6%)
NSAIDs	613 (17.1%)	531 (17.2%)	0 (.%)	5 (38.5%)	77 (16.2%)	606 (17.2%)	280 (16.4%)	0 (.%)	0 (0.0%)	326 (18.0%)
Time until $P2Y_{12}$ antagonist prescription claimed										
Prior to MI	122 (3.4%)	103 (3.3%)	0 (.%)	(n<=5)	18 (3.8%)	167 (4.7%)	125 (7.3%)	0 (.%)	0 (0.0%)	42 (2.3%)
1-7 days	3,033 (84.8%)	2,825 (91.5%)	0 (.%)	11 (84.6%)	197 (41.4%)	1,600 (45.4%)	1,438 (84.0%)	0 (.%)	(n<=5)	161 (8.9%)
8-14 days	52 (1.5%)	48 (1.6%)	0 (.%)	0 (0.0%)	(n<=5)	69 (2.0%)	65 (3.8%)	0 (.%)	0 (0.0%)	(n<=5)
15-30 days	120 (3.4%)	111 (3.6%)	0 (.%)	(n<=5)	8 (1.7%)	91 (2.6%)	84 (4.9%)	0 (.%)	0 (0.0%)	7 (0.4%)
No prescription	249 (7.0%)	0 (0.0%)	0 (.%)	0 (0.0%)	249 (52.3%)	1,601 (45.4%)	0 (0.0%)	0 (.%)	0 (0.0%)	1,601 (88.2%)

Numbers in parentheses are percentages of total number of patients in the group; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; IQR, interquartile range; Local hospital, hospital without catheterization laboratory; Main regional hospital, hospital with catheterization laboratory; Tertiary cardiac hospital, university hospital with catheterization laboratory; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2 Baseline demographic and clinical characteristics for the 2012 first-time MI population

	Patients with PCI (n=3852, 55%)					Non-PCI patients (n=3164, 45%)				
	All patients n=3852	**Clopidogrel n=724**	**Ticagrelor n=2238**	**Prasugrel n=531**	**No DAPT n=359**	**All patients n=3164**	**Clopidogrel n=679**	**Ticagrelor n=921**	**Prasugrel n=26**	**No DAPT n=1538**
Age [median (IQR)]	65 (55 - 74)	68 (58 - 79)	65 (55 - 74)	58 (51 - 66)	69 (59 - 77)	74 (63 - 83)	77 (67 - 86)	71 (61 - 80)	52.5 (48 - 67)	75 (64 - 84)
Males	2800 (72.7)	490 (67.7)	1615 (72.2)	440 (82.9)	255 (71.0)	1684 (53.2)	337 (49.6)	500 (54.3)	18 (69.2)	829 (53.9)
Type of hospital (at index MI event)										
Local hospital	1037 (26.9)	291 (40.2)	552 (24.7)	68 (12.8)	126 (35.1)	1285 (40.6)	277 (40.8)	318 (34.5)	n<=5	686 (44.6)
Main regional hospital	1579 (41.0)	202 (27.9)	1021 (45.6)	234 (44.1)	122 (34.0)	1144 (36.2)	247 (36.4)	417 (45.3)	8 (30.8)	472 (30.7)
Tertiary cardiac hospital	1236 (32.1)	231 (31.9)	665 (29.7)	229 (43.1)	111 (30.9)	735 (23.2)	155 (22.8)	186 (20.2)	14 (53.8)	380 (24.7)
Procedures (at index MI event)										
CABG	93 (2.4)	40 (5.5)	20 (0.9)	n<=5	30 (8.4)	453 (14.3)	77 (11.3)	130 (14.1)	n<=5	245 (15.9)
Angiography	3790 (98.4)	704 (97.2)	2213 (98.9)	525 (98.9)	348 (96.9)	1740 (55.0)	340 (50.1)	649 (70.5)	16 (61.5)	735 (47.8)
Previous diagnoses										
Heart failure	83 (2.2)	23 (3.2)	34 (1.5)	7 (1.3)	19 (5.3)	234 (7.4)	67 (9.9)	41 (4.5)	0 (0.0)	126 (8.2)
Ischaemic heart disease	210 (5.5)	59 (8.1)	90 (4.0)	16 (3.0)	45 (12.5)	413 (13.1)	108 (15.9)	101 (11.0)	n<=5	200 (13.0)
Unstable angina pectoris	46 (1.2)	14 (1.9)	21 (0.9)	n<=5	9 (2.5)	77 (2.4)	18 (2.7)	14 (1.5)	n<=5	43 (2.8)
Peripheral arterial disease	110 (2.9)	36 (5.0)	44 (2.0)	6 (1.1)	24 (6.7)	224 (7.1)	61 (9.0)	55 (6.0)	0 (0.0)	108 (7.0)
Stroke total	126 (3.3)	36 (5.0)	62 (2.8)	n<=5	25 (7.0)	257 (8.1)	86 (12.7)	40 (4.3)	0 (0.0)	131 (8.5)
Non-ischaemic stroke	12 (0.3)	n<=5	6 (0.3)	0 (0.0)	(n<=5)	22 (0.7)	5 (0.7)	n<=5	0 (0.0)	14 (0.9)
Ischaemic stroke	117 (3.0)	33 (4.6)	58 (2.6)	n<=5	23 (6.4)	243 (7.7)	83 (12.2)	38 (4.1)	0 (0.0)	122 (7.9)
Atrial fibrillation	150 (3.9)	44 (6.1)	56 (2.5)	5 (0.9)	45 (12.5)	335 (10.6)	63 (9.3)	49 (5.3)	0 (0.0)	223 (14.5)
Chronic renal dysfunction	30 (0.8)	8 (1.1)	11 (0.5)	n<=5	10 (2.8)	41 (1.3)	11 (1.6)	n<=5	n<=5	24 (1.6)
Diabetes mellitas	512 (13.3)	114 (15.7)	279 (12.5)	53 (10.0)	66 (18.4)	585 (18.5)	157 (23.1)	140 (15.2)	n<=5	284 (18.5)
Major bleeding	88 (2.3)	26 (3.6)	41 (1.8)	7 (1.3)	14 (3.9)	155 (4.9)	33 (4.9)	33 (3.6)	0 (0.0)	89 (5.8)
Liver disease	9 (0.2)	n<=5	n<=5	n<=5	n<=5	7 (0.2)	n<=5	n<=5	0 (0.0)	n<=5
Coagulation disorders	15 (0.4)	5 (0.7)	n<=5	0 (0.0)	6 (1.7)	17 (0.5)	n<=5	n<=5	0 (0.0)	14 (0.9)
Cancer	278 (7.2)	66 (9.1)	145 (6.5%)	25 (4.7)	42 (11.7)	339 (10.7)	63 (9.3)	86 (9.3)	0 (0.0)	190 (12.4)

Drug use at discharge										
Total number of drugs [median (IQR)]	3 (1 - 6)	4 (1 - 8)	3 (1 - 6)	2 (0 - 4)	5 (2 - 8)	6 (3 - 10)	7 (4 - 11)	5 (2 - 9)	4.5 (1 - 6)	7 (3 - 11)
ACE-inhibitors and ARB	2076 (53.9)	450 (62.2)	1145 (51.2)	268 (50.5)	213 (59.3)	1748 (55.2)	417 (61.4)	495 (53.7)	15 (57.7)	821 (53.4)
Acetyl salicylic acid	3666 (95.2)	724 (100.0)	2238 (100.0)	531 (100.0)	173 (48.2)	2568 (81.2)	679 (100.0)	921 (100.0)	26 (100.0)	942 (61.2)
Beta-blocker	3364 (87.3)	621 (85.8)	1959 (87.5)	503 (94.7)	281 (78.3)	2226 (70.4)	517 (76.1)	754 (81.9)	20 (76.9)	935 (60.8)
Calcium-channel blocker	877 (22.8)	218 (30.1)	463 (20.7)	79 (14.9)	117 (32.6)	1073 (33.9)	247 (36.4)	305 (33.1)	12 (46.2)	509 (33.1)
Oral antidiabetics and insulin	473 (12.3)	98 (13.5)	265 (11.8)	49 (9.2)	61 (17.0)	532 (16.8)	147 (21.6)	133 (14.4)	n<=5	248 (16.1)
Proton pump inhibitors	1195 (31.0)	275 (38.0)	680 (30.4)	108 (20.3)	132 (36.8)	1280 (40.5)	322 (47.4)	323 (35.1)	9 (34.6)	626 (40.7)
Statins	3661 (95.0)	672 (92.8)	2165 (96.7)	524 (98.7)	300 (83.6)	2219 (70.1)	529 (77.9)	802 (87.1)	22 (84.6)	866 (56.3)
Anticoagulant	266 (6.9)	76 (10.5)	94 (4.2)	14 (2.6)	82 (22.8)	445 (14.1)	65 (9.6)	63 (6.8)	0 (0.0)	317 (20.6)
NSAIDs	624 (16.2)	118 (16.3)	367 (16.4)	79 (14.9)	60 (16.7)	539 (17.0)	104 (15.3)	159 (17.3)	8 (30.8)	268 (17.4)
Time until $P2Y_{12}$ antagonist –prescription claimed										
Prior to MI	165 (4.3)	48 (6.6)	80 (3.6)	16 (3.0)	21 (5.8)	228 (7.2)	121 (17.8)	45 (4.9)	n<=5	61 (4.0)
1-7 days	3472 (90.1)	656 (90.6)	2123 (94.9)	508 (95.7)	185 (51.5)	1543 (48.8)	521 (76.7)	833 (90.4)	24 (92.3)	165 (10.7)
8-14 days	32 (0.8)	8 (1.1)	11 (0.5)	7 (1.3)	6 (1.7)	46 (1.5)	21 (3.1)	21 (2.3)	0 (0.0)	n<=5
15-30 days	44 (1.1)	12 (1.7)	24 (1.1)	0 (0.0)	8 (2.2)	49 (1.5)	16 (2.4)	22 (2.4)	n<=5	10 (0.7)
No prescription	139 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	139 (38.7)	1298 (41.0)	0 (0.0)	0 (0.0)	0 (0.0)	1298 (84.4)

Numbers in parentheses are percentages of total number of patients in the group; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; IQR, interquartile range; Local hospital, hospital without catheterization laboratory; Main regional hospital, hospital with catheterization laboratory; Tertiary cardiac hospital, university hospital with catheterization laboratory; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs

In 2012, the proportion of patients discharged with DAPT was 6% higher compared with that in 2009. The non-DAPT-treated patients were older (+9 years, median age difference) and more commonly women (+20% difference) compared with the DAPT treated patients. Among non-DAPT treated patients, invasive treatment within 30 days from admission was received by relatively few patients; 57% underwent angiography and 19% PCI. A larger proportion of non-DAPT treated patients underwent CABG, were diagnosed with atrial fibrillation, and were treated with warfarin or new oral anticoagulants (NOAC) compared with the DAPT-treated patients. More patients had a prior diagnosis of heart failure, cancer and/or a history of major bleeds or coagulation disorders.

A smaller proportion of the non-DAPT treated patients received ACE inhibitors/ angiotensin receptor blockers (ARBs), beta-blockers, and statins at discharge compared with DAPT-treated patients. Of these, 49% received ASA as mono therapy, and 13% and10% of non-DAPT treated patients were treated with clopidogrel or ticagrelor, respectively, as mono therapies.

Medical history-related predictors of DAPT persistence

Overall persistence was very high among patients initiated on DAPT (Figure 2).

Within the first year post- MI in 2012, 6% of the prasugrel treated patients were switched to another $P2Y_{12}$ antagonist; 11% from the ticagrelor group and 3% from clopidogrel group (Table 3).

Patients undergoing PCI had an overall longer DAPT duration compared with patients not undergoing PCI, and age >75 years and diagnosis of atrial fibrillation, diabetes, and peripheral arterial disease were associated with a higher risk of treatment breaks (Table 4). Furthermore, there was a trend toward increased risk for treatment breaks for PCI patients with heart failure and stroke. For patients not undergoing PCI we did not observe any association between any major baseline diseases and risk for treatment breaks.

Among PCI patients, treatment with prasugrel or ticagrelor compared with clopidogrel was associated with an increased risk of a 30-day treatment break within 365 days after MI (Table 4). However, this risk was not present when extending the grace period to 60 days (data not shown).

For non-PCI patients, ticagrelor compared to clopidogrel treatment was associated with an increased risk of having a 30-day treatment break. This finding was also present when expanding the grace period to 60 days, during which 11% of these patients were switched to clopidogrel after a median of 107 days.

Table 3 MI patients discharged in 2012: switch pattern for dual antiplatelet therapy during the first 365 days after MI

	Drug treatment	No discharged of patients	No of patients switching	Median time (days) to switch	No of patients switching to clopidogrel	No of patients switching to ticagrelor	No of patients switching to prasugrel
PCI treated patients	Clopidogrel	719	25	73 (44-119)	0	18	7
	Ticagrelor	2198	214	110 (62-209)	210	0	n<5
	Prasugrel	524	33	147 (90-230)	29	n<5	0
	Clopidogrel without ASA	74	n<5	83 (12-90)	0	n<5	n<5
	Ticagrelor without ASA	110	18	84 (57-210)	18	0	0
	Prasugrel without ASA	29	n<5	200 (149-310)	n<5	0	0
	No $P2Y_{12}$ antagonist only ASA	118	29	49 (15-119)	13	7	9
	No $P2Y_{12}$ antagonist or ASA	24	14	34 (14-136)	8	n<5	n<5
Non-PCI treated patients	Clopidogrel	635	14	148 (73-213)	0	13	n<5
	Ticagrelor	868	102	107 (49-208)	102	0	0
	Prasugrel	25	n<5	52 (52-52)	0	n<5	0
	Clopidogrel without ASA	161	n<5	44 (33-106)	0	n<5	0
	Ticagrelor without ASA	68	11	133 (108-154)	10	0	n<5
	No $P2Y_{12}$ antagonist only ASA	765	83	77 (13-167)	58	22	n<5
	No $P2Y_{12}$ antagonist or ASA	424	21	92 (55-178)	16	5	0

Table 4 MI patients discharged in 2012: Cox regression analysis: hazard ratio for having a break in $P2Y_{12}$ antagonist treatment >30 days with or without PCI

	Patients with PCI			Non-PCI patients		
	No of patients	No patients with breaks	Hazard ratio (95% CI)	No of patients	No patients with breaks	Hazard ratio (95% CI)
All patients	3373	1,513		1399	972	
Clopidogrel	697	317	Reference	579	411	Reference
Ticagrelor	2164	937	1.20 (1.03-1.39)	800	552	1.48 (1.27-1.72)
Prasugrel	512	259	1.48 (1.24-1.78)	20	9	0.86 (0.47-1.58)
Female	911	398	Reference	666	481	Reference
Male	2462	1115	1.00 (0.88-1.13)	733	491	0.91 (0.78-1.05)
<60 years	1216	503	1.01 (0.90-1.14)	277	168	1.18 (0.97-1.43)
60-75 years	1481	648	Reference	554	344	Reference
>75 years	676	362	1.15 (1.00-1.34)	568	460	1.02 (0.86-1.21)
Local hospital	878	403	Reference	498	357	Reference
Main regional hospital	1404	620	0.97 (0.85-1.11)	588	399	0.99 (0.84-1.18)
Tertiary cardiac hospital	1091	490	1.00 (0.86-1.15)	313	216	1.12 (0.92-1.38)
CABG	56	22	0.81 (0.49-1.34)	191	107	1.00 (0.80-1.25)
Heart failure	59	42	1.40 (0.94-2.08)	86	79	1.33 (0.98-1.81)
Stroke	97	56	1.34 (0.99-1.82)	101	77	1.11 (0.82-1.49)
Atrial fibrillation	92	68	1.88 (1.41-2.50)	94	81	1.27 (0.95-1.70)
Diabetes	411	229	1.23 (1.05-1.44)	258	196	0.96 (0.79-1.16)
Cancer	219	131	1.09 (0.88-1.34)	125	104	1.03 (0.80-1.33)
Major bleeding	67	39	1.07 (0.74-1.56)	53	36	1.20 (0.86-1.67)
Peripheral arterial disease	85	61	1.63 (1.20-2.20)	93	74	0.99 (0.72-1.36)

CI, confidence interval; Local hospital, hospital without catheterization laboratory; Main regional hospital, hospital with catheterization laboratory; Tertiary cardiac hospital, university hospital with catheterization laboratory; CABG, coronary artery bypass surgery

DISCUSSION

This nationwide observational study showed changes in the treatment of MI patients in Denmark from 2009 to 2012. In 2012, more patients are referred to coronary angiography and PCI, and a larger proportion of patients are discharged with DAPT compared to 2009. However, non-PCI patients were, to a large extent, discharged without DAPT, or received shorter duration of DAPT treatment as compared with PCI patients. Among PCI patients, age>75 years, atrial fibrillation, diabetes and peripheral arterial disease were all associated with a higher risk of treatment breaks, which might indicates a risk-treatment mismatch, as these patients have higher risk of recurrent events and might benefit from longer DAPT duration. During the observation period, the DAPT pattern shifted from merely clopidogrel treatment to more selective treatments with clopidogrel, prasugrel and ticagrelor for patient populations with varying characteristics.

Interpretation with reference to other studies

The underlying medical treatment of MI patients in Denmark, with more patients undergoing angiography and PCI over time, followed the same trend as seen in both earlier observations in Denmark and studies from other countries[19, 20, 21].

To our knowledge, national level data describing patient selection for different DAPT regimens and persistence with treatment in unselected populations are scarce. Publications based on data from cardiovascular quality registers, actively recruiting or selecting patients, report an overall DAPT usage for discharged patients with ACS in the range of approximately 60% to 80% depending on the observation period and the type of ACS event included[21, 23, 24, 25]. A recent Swedish nationwide study on MI patients, which may be considered comparable to the present nationwide data, reported a DAPT usage of 69% for patients discharged with MI in 2000-2011[26].

A previous similar Danish study, including all MI patients between 2000 and 2005, reported an increasing use of DAPT during the observation period[7]. However, for non-PCI patients there was a substantial underuse, especially among women and patients admitted to local hospitals. Although the observation period in the present study is more recent, many of these patients are still discharged without DAPT, although there is a markedly increased use of DAPT in these patient groups.

The observed overall adherence to DAPT (Figure 2), with more than 75% of patients completing more than 11 months of treatment, is noteworthy and comparable to what has been observed in randomized controlled trials[27, 28].

Medical history-related predictors of DAPT persistence

The non-DAPT-treated patients are of special interest, as in the present study they form a considerable proportion of patients discharged with first-time MI (27% in 2012), despite the decline in the relative number of patients discharged without DAPT during the observation period (Figure 2). A large

proportion of these patients received oral antiplatelet monotherapy with ASA or with prasugrel, ticagrelor or clopidogrel. Furthermore, there was a marked difference between patients who underwent PCI vs. those did no; a larger proportion of non-PCI patients were discharged without DAPT (in 2012: 9% vs. 49%, respectively). In addition, non-PCI patients had a shorter DAPT treatment duration in general, were on average 10 years older and with a large proportion having a risk profile with atrial fibrillation and history of bleedings where a shorter DAPT duration or no DAPT treatment may be appropriate. However, many of these patients had a high cardiovascular disease risk profile at baseline, suggesting a potential benefit of a longer DAPT treatment duration and more frequent use of beta-blockers, ACE inhibitors, and statins.

Thus, potentially there exists a risk-treatment mismatch with treatment being withheld from patients who might similar or more benefit of longer DAPT.

Comparison of adherence to different DAPT alternatives

A direct comparison of adherence and treatment length between the different DAPT alternatives after MI is complex because the treatments in clinical practice are prescribed to different patient populations. Even in comparable populations, it is difficult to standardize adherence in a multivariable model as underlying factors (such as tablet pack size and daily dosing patterns) may influence treatment length. Similarly, it is difficult to assess how these underlying factors influence the risk of having a calculated treatment break of 30 days.

Prasugrel is prescribed almost entirely for patients with PCI, whereas clopidogrel and ticagrelor are prescribed irrespective of PCI status. In patients with PCI, the adherence patterns did not differ between the respective DAPTs, whereas non-PCI patients had a generally shorter treatment length and those prescribed ticagrelor showed an increased risk of early treatment break compared with patients prescribed clopidogrel; some of these patients (11%) were switched to clopidogrel. We did not have access to data that would provide reasons for this shorter treatment length or treatment switch, such as if this switch was done in a hospital setting, by general practitioners, or in certain geographical locations. Moreover, a relatively large proportion (18%) of patients not undergoing PCI were already on clopidogrel before their MI event, indicating an underlying long term use not associated with the MI which may explain the longer observed treatment length in this group. In addition, it seems that a larger proportion of clopidogrel patients, both with and without PCI, are treated for more than 12 months after MI.

Strength and Limitations

Our data set is uniquely placed to examine DAPT adherence because it includes nationwide data from all patients hospitalized in Denmark for MI, allowing analyses on a complete and unselected cohort of patients. This reduces potential problems arising from selection bias due to inclusion of selected hospitals, regions, or healthcare insurance systems. We believe our results may be generalized to

societies with healthcare systems comparable to the Danish. However, the present study design also comes with certain limitations. A register-based analysis relies on ICD-10 codes for morbidity data and therefore, the possibility of coding errors cannot be ruled out. Therefore, patients with unstable angina pectoris diagnose was not included and sub-coding into STEMI and NSTEMI was not performed. However, the diagnoses covering MI have been shown to have high sensitivity and specificity[29] and treatment guidelines for DAPT initiation and treatment duration do not differ between STEMI and NSTEMI[5, 6].

Because our study is based on central registry data collected primarily for administrative purposes, it is not possible to include clinical data on smoking pattern, weight, blood pressure, laboratory data or socio economic status. Furthermore, data on events (recurrent MI, elective PCI, bleedings) during follow-up that might influence treatment length were not included in the current analysis because of the complexity of different patient baseline risks for the DAPTs.

Conclusions

The results from the present study show that the treatment of MI patients in Denmark has undergone major changes during 2009 to 2012. More patients undergo invasive procedures (coronary angiography and PCI), and the DAPT pattern has shifted from merely clopidogrel to different treatments for selected patient populations. The majority of patients are discharged with dual antiplatelet therapy and the overall treatment length is according to guidelines and in line with what has been observed in randomized controlled clinical trials. Still, there is a proportion of patients not undergoing PCI who are discharged without guideline recommended DAPT. If treated with DAPT, they have a shorter treatment length. The present findings may indicate the need for more careful attention with regard to DAPT for MI patients without PCI in Denmark.

Contributors

AG, PH and ME were involved in the study design; AP and AB performed the statistical analyses; AG, PH, TGD, GHG, AP and AB were involved in the interpretation of the results; PH and AG wrote the manuscript and AG, AP, AB, TGD, PH and GHG were involved in the critical comments on the manuscript. Mrs. Sabrina Imeroski has provided editorial assistance in the preparation of the manuscript.

Funding

This work was supported by AstraZeneca (study sponsor). The statistical analysis was agreed on by the study steering committee, and data analysis was performed by the study database owner in collaboration with AstraZeneca. As members of the study steering committee, AstraZeneca took part

in the interpretation of data and the drafting of the manuscript. Dr. Gislason is supported by an unrestricted clinical research scholarship from the Novo Nordisk Foundation.

Competing interests

Pål Hasvold and Thomas G Diness are full time employees at AstraZeneca. Martha Emneus and Anders Green are employed by the Institute of Applied Economics and Health Research. Dr. Gislason reports research grants from AstraZeneca, Pfizer, Bristol-Myers Squibb and Bayer. The authors report no other conflicts of interest in this work. Dr. Pottegård reports funding from Servier, Boehringer-Ingelheim, Astellas, AstraZeneca, Almirall and Alcon.

Data sharing statement

No additional data are available

REFERENCES

1. Dudas K, Lappas G, Rosengren A. Long-term prognosis after hospital admission for acute myocardial infarction from 1987 to 2006. *Int J Cardiol* 2012;155:400-405.
2. Fox KAA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *Br Med J* 2006;333:1091–1094.
3. Gulliksson M, Wedel H, Köster M, et al. Hazard function and secular trends in the risk of recurrent acute myocardial infarction: 30 years of follow-up of more than 775 000 incidents. *Circ Cardiovasc Qual Outcomes* 2009;2:178-185.
4. Jernberg T, Johanson P, Held C, et al. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. *JAMA* 2011;305:1677–1684.
5. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999-3054.
6. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Task force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *Eur Heart J* 2012;33:2569-2619.
7. Sørensen R, Gislason GH, Fosbøl EL, et al. Initiation and persistence with clopidogrel treatment after acute myocardial infarction: a nationwide study. *Br J Clin Pharmacol* 2008;66:875-884.
8. EMA (2015-08-11) Ticagrelor (Brilique) Summary of product characteristics. European Medicines Agency. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001241/WC500100494.pdf. Accessed 01.09.2015.
9. EMEA (2014-02-17) Prasugrel (Efient) Summary of product characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000984/WC500021971.pdf. Accessed 01.06.2015.
10. The national Danish ACS guidelines. Available at: http://nbv.cardio.dk/. Accessed 01.06.2015.
11. Thygesen LC, Ersbøll AK. Danish population-based registers for public health and health-related welfare research: introduction to the supplement. *Scand J Public Health* 2011;39:8–10.

12. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39:38–41.
13. Anatomic Therapeutic Chemical (ATC) index. Available at: www.whocc.no/filearchive/publications/1_2013guidelines.pdf. Accessed 01.06.2015
14. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30–33.
15. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39:22–25.
16. Thygesen LC, Daasnes C, Thaulow I, et al. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011;39:12–16.
17. Nordic Medico-Statistical Committee: Classification of Surgical Procedures, version 1.15. Copenhagen, Denmark 2010: Publication 93.
18. Gislason GH, Rasmussen JN, Abildstrøm SZ, et al. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J* 2006;27:1153-1158.
19. Mårtensson S, Gyrd-Hansen D, Prescott E, et al. Trends in time to invasive examination and treatment from 2001 to 2009 in patients admitted first time with non-ST elevation myocardial infarction or unstable angina in Denmark. *BMJ Open* 2014;9:e004052.
20. Fokkema ML, James SK, Albertsson P, et al. Population trends in percutaneous coronary intervention: 20-year results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). *J Am Coll Cardiol* 2013;61:1222-1230.
21. Vamos EP, Millett C, Parsons C, et al. Nationwide study on trends in hospital admissions for major cardiovascular events and procedures among people with and without diabetes in England, 2004-2009. *Diabetes Care* 2012;35:265-272.
22. SWEDEHEART 2014 Annual Report (English edition). http://www.ucr.uu.se/swedeheart/index.php/arsrapporter. Accessed 18.05.2015.
23. Erne P, Gutzwiller F, Urban P, et al. Characteristics and outcome in acute coronary syndrome patients with and without established modifiable cardiovascular risk factors: Insights from the nationwide AMIS Plus Registry 1997-2010. *Am J Cardiol* 2013;111:202-207.
24. Bajaj RR, Goodman SG, Yan RT, et al. Treatment and outcomes of patients with suspected acute coronary syndromes in relation to initial diagnostic impressions (insights from the Canadian Global Registry of Acute Coronary Events [GRACE] and Canadian Registry of Acute Coronary Events [CANRACE]). *Am J Cardiol* 2013;111:202-207.
25. Jortveit J, Govatsmark RE, Digre TA, et al. Myocardial infarction in Norway in 2013. *Tidsskr Nor Laegeforen* 2014;134:1841-1846.

26. Jernberg T, Hasvold P, Henriksson M, et al. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J* 2015;36:1163-1170.
27. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001-2015.
28. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-1057.
29. Joensen AM, Jensen MK, Overvad K, et al. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. *J Clin Epidemiol* 2009;62:188-194.

FIGURE LEGENDS

Figure 1 Proportion of first-time MI patients discharged alive with or without PCI and prescribed different types of dual antiplatelet therapy or no dual antiplatelet therapy 2009-2012

Figure 2 Persistence with different dual antiplatelet therapy in first-time MI patients with or without PCI 2009-2012

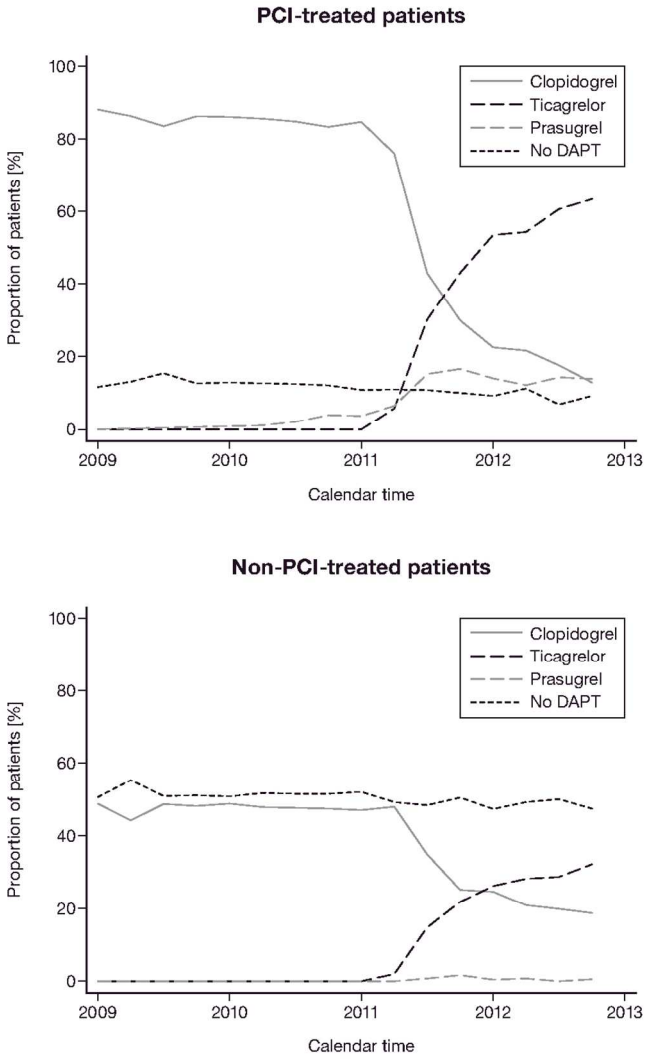

Figure 1 Proportion of first-time MI patients discharged alive with or without PCI and prescribed different types of dual antiplatelet therapy or no dual antiplatelet therapy 2009-2012
209x297mm (150 x 150 DPI)

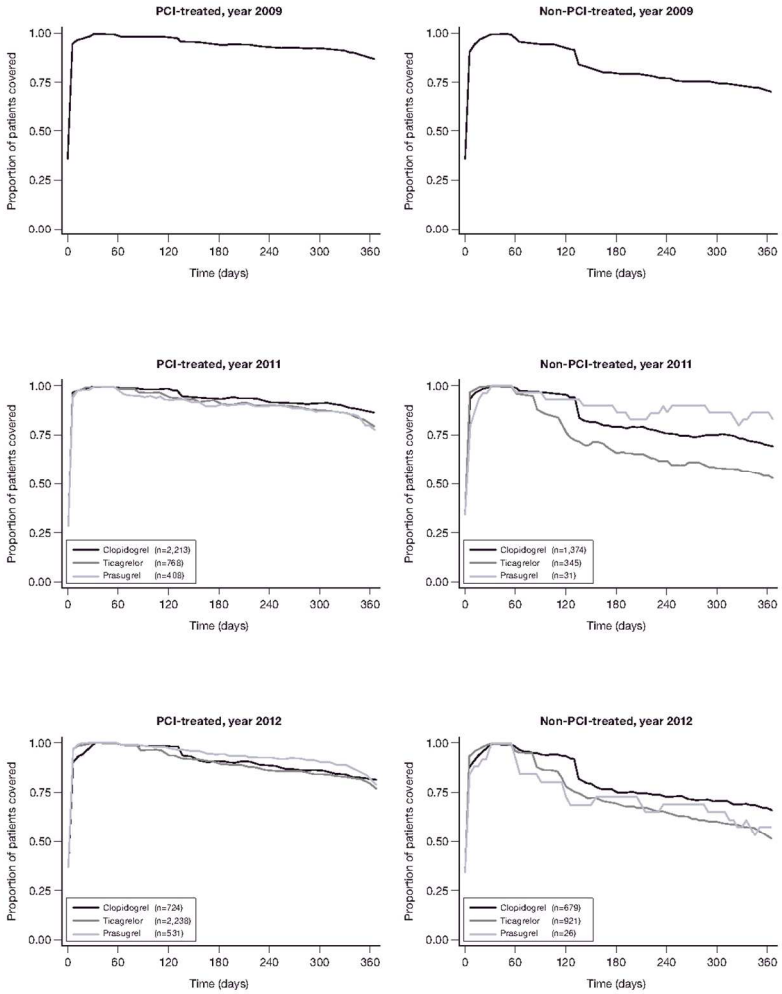

Figure 2 Persistence with different dual antiplatelet therapy in first-time MI patients with or without PCI 2009-2012
209x297mm (150 x 150 DPI)

Green et al.: "Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction – a Danish nationwide population based cohort study"

Appendix A: ICD10 and ATC codes used for the identification of conditions and diseases

Disease/conditions	Codes
Heart failure	I11.0, I13.0, I13.2, I50
Ischaemic heart disease	I21-I25
Previous myocardial infarctions	I21–I23
Previous unstable angina pectoris	I20.0
Peripheral arterial disease	I70, I71, I74
Stroke total	I60–I66 and G45
Non-ischaemic stroke	I60, I61, I62.0, I62
Ischaemic stroke	I63-I66 and G45
Atrial fibrillation	I48
Chronic renal dysfunction	I15.0, I15.1,N03, N04, N05, N11, N18.4, N18.5, Q60, Q61, Z49.1, Z99.2
Diabetes mellitus	E10-E14 and/or ATC A10
Major bleeding	D62.9, I60, I61, I62, I85.0, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0, K92.1, K92.2.
Moderate and severe liver disease	K71-K719, K721, K730-K768, R18
Bleeding diathesis/coagulation disease	D66, D67, D68, D68.0, D681, D68.2, D68.3, D68.4, D68.8, D68.9, D69, D69.1, D69.3, D69.4, D69.5, D69.6
Cancer	C00-C99

Appendix B: ATC codes used for the identification of drug treatment

Drug	Code
ACE-inhibitor	C09A/B
ARB	C09C/D
Beta-blocker	C07
Calcium channel blocker	C08
Insulin	A10A
Oral antidiabetic	A10B
Proton pump inhibitor	A02B C
Statin	C10AA
Warfarin/OAC	B01AA, B01AE, B01AF
NSAIDS	M01A
SSRI	N06A B

Green et al.:

Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction – a Danish nationwide population based cohort study

Supplementary tables

Supplementary Table 1 Baseline demographic and clinical characteristics for the total first-time MI population (2009-2012, incl.)

	Patients with PCI (N=14852, 52%)					Patients without PCI (N=13597, 48%)				
	All patients n=14852	**Clopidogrel n=9140**	**Ticagrelor n=2991**	**Prasugrel n=1030**	**No DAPT n=1691**	**All patients n=13597**	**Clopidogrel n=5513**	**Ticagrelor n=1221**	**Prasugrel n=62**	**No DAPT n=6801**
Age [median (IQR)]	65 (55 - 74)	65 (56 - 74)	65 (55 - 73)	60 (51 - 67)	67 (58 - 75)	74 (63 - 83)	74 (64 - 83)	71 (61 - 80)	60 (49 - 67)	74 (62 - 83)
Males	10,848 (73.0%)	6,642 (72.7%)	2,161 (72.3%)	833 (80.9%)	1,212 (71.7%)	7,358 (54.1%)	2,985 (54.1%)	662 (54.2%)	42 (67.7%)	3,669 (53.9%)
Type of hospital (at index MI event)										
Local hospital	3,797 (25.6%)	2,478 (27.1%)	707 (23.6%)	132 (12.8%)	480 (28.4%)	5,490 (40.4%)	2,074 (37.6%)	404 (33.1%)	13 (21.0%)	2,999 (44.1%)
Main regional hospital	5,463 (36.8%)	3,165 (34.6%)	1,331 (44.5%)	431 (41.8%)	536 (31.7%)	4,647 (34.2%)	2,083 (37.8%)	564 (46.2%)	24 (38.7%)	1,976 (29.1%)
Tertiary cardiac hospital	5,592 (37.7%)	3,497 (38.3%)	953 (31.9%)	467 (45.3%)	675 (39.9%)	3,460 (25.4%)	1,356 (24.6%)	253 (20.7%)	25 (40.3%)	1,826 (26.8%)
Procedures (at index event)										
CABG	328 (2.2%)	177 (1.9%)	28 (0.9%)	(n<=5)	119 (7.0%)	1,727 (12.7%)	660 (12.0%)	165 (13.5%)	(n<=5)	898 (13.2%)
Angiography	14,626 (98.5%)	9,009 (98.6%)	2,946 (98.5%)	1,012 (98.3%)	1,659 (98.1%)	7,330 (53.9%)	3,138 (56.9%)	865 (70.8%)	36 (58.1%)	3,291 (48.4%)
Previous diagnoses										
Heart failure	358 (2.4%)	211 (2.3%)	49 (1.6%)	12 (1.2%)	86 (5.1%)	1,185 (8.7%)	459 (8.3%)	53 (4.3%)	(n<=5)	671 (9.9%)
Ischaemic heart disease	985 (6.6%)	550 (6.0%)	152 (5.1%)	46 (4.5%)	237 (14.0%)	1,740 (12.8%)	658 (11.9%)	131 (10.7%)	11 (17.7%)	940 (13.8%)
Unstable angina	208 (1.4%)	117 (1.3%)	34 (1.1%)	11 (1.1%)	46 (2.7%)	365 (2.7%)	132 (2.4%)	15 (1.2%)	5 (8.1%)	213 (3.1%)
Peripheral arterial disease	442 (3.0%)	263 (2.9%)	67 (2.2%)	21 (2.0%)	91 (5.4%)	945 (7.0%)	397 (7.2%)	73 (6.0%)	(n<=5)	474 (7.0%)
Stroke total	520 (3.5%)	315 (3.4%)	89 (3.0%)	8 (0.8%)	108 (6.4%)	1,194 (8.8%)	527 (9.6%)	65 (5.3%)	0 (0.0%)	602 (8.9%)
Non-ischaemic stroke	38 (0.3%)	26 (0.3%)	6 (0.2%)	0 (0.0%)	6 (0.4%)	74 (0.5%)	25 (0.5%)	5 (0.4%)	0 (0.0%)	44 (0.6%)
Ischaemic stroke	495 (3.3%)	298 (3.3%)	85 (2.8%)	8 (0.8%)	104 (6.2%)	1,153 (8.5%)	512 (9.3%)	62 (5.1%)	0 (0.0%)	579 (8.5%)
Atrial fibrillation	539 (3.6%)	301 (3.3%)	80 (2.7%)	14 (1.4%)	144 (8.5%)	1,426 (10.5%)	445 (8.1%)	71 (5.8%)	0 (0.0%)	910 (13.4%)
Chronic renal dysfunction	95 (0.6%)	52 (0.6%)	17 (0.6%)	(n<=5)	24 (1.4%)	158 (1.2%)	57 (1.0%)	5 (0.4%)	(n<=5)	94 (1.4%)
Diabetes mellitus	1,871 (12.6%)	1,117 (12.2%)	374 (12.5%)	106 (10.3%)	274 (16.2%)	2,513 (18.5%)	1,048 (19.0%)	200 (16.4%)	9 (14.5%)	1,256 (18.5%)
Major bleeding	359 (2.4%)	226 (2.5%)	59 (2.0%)	12 (1.2%)	62 (3.7%)	713 (5.2%)	248 (4.5%)	41 (3.4%)	(n<=5)	423 (6.2%)
Liver disease	21 (0.1%)	10 (0.1%)	(n<=5)	(n<=5)	7 (0.4%)	23 (0.2%)	5 (0.1%)	(n<=5)	0 (0.0%)	17 (0.2%)
Coagulation disorders	45 (0.3%)	28 (0.3%)	5 (0.2%)	0 (0.0%)	12 (0.7%)	81 (0.6%)	18 (0.3%)	(n<=5)	0 (0.0%)	60 (0.9%)
Cancer	924 (6.2%)	556 (6.1%)	179 (6.0%)	49 (4.8%)	140 (8.3%)	1,330 (9.8%)	490 (8.9%)	116 (9.5%)	0 (0.0%)	724 (10.6%)
Drug use at discharge										
Total number of drugs [median (IQR)]	3 (1 - 6)	3 (1 - 6)	3 (1 - 6)	2 (0 - 4)	4 (2 - 8)	6 (3 - 10)	6 (3 - 10)	5 (2 - 9)	4 (1 - 7)	6 (3 - 11)
ACE-inhbitors and ARB	8,140 (54.8%)	5,106 (55.9%)	1,536 (51.4%)	538 (52.2%)	960 (56.8%)	7,610 (56.0%)	3,240 (58.8%)	668 (54.7%)	36 (58.1%)	3,666 (53.9%)

Acetyl salicylic acid	14,109 (95.0%)	9,140 (100.0%)	2,991 (100.0%)	1,030 (100.0%)	948 (56.1%)	11,166 (82.1%)	5,513 (100.0%)	1,221 (100.0%)	62 (100.0%)	4,370 (64.3%)
Betablocker	13,065 (88.0%)	8,093 (88.5%)	2,626 (87.8%)	948 (92.0%)	1,398 (82.7%)	9,719 (71.5%)	4,450 (80.7%)	997 (81.7%)	52 (83.9%)	4,220 (62.0%)
Calcium-channel blocker	3,259 (21.9%)	1,987 (21.7%)	646 (21.6%)	161 (15.6%)	465 (27.5%)	4,310 (31.7%)	1,763 (32.0%)	391 (32.0%)	24 (38.7%)	2,132 (31.3%)
Oral antidiabetics and insulin	1,728 (11.6%)	1,034 (11.3%)	355 (11.9%)	95 (9.2%)	244 (14.4%)	2,235 (16.4%)	952 (17.3%)	189 (15.5%)	9 (14.5%)	1,085 (16.0%)
Proton pump inhibitors	4,092 (27.6%)	2,433 (26.6%)	932 (31.2%)	204 (19.8%)	523 (30.9%)	5,151 (37.9%)	1,977 (35.9%)	429 (35.1%)	19 (30.6%)	2,726 (40.1%)
Statins	14,131 (95.1%)	8,748 (95.7%)	2,894 (96.8%)	1,011 (98.2%)	1,478 (87.4%)	9,599 (70.6%)	4,531 (82.2%)	1,062 (87.0%)	57 (91.9%)	3,949 (58.1%)
Anticoagulant	913 (6.1%)	488 (5.3%)	127 (4.2%)	35 (3.4%)	263 (15.6%)	1,742 (12.8%)	395 (7.2%)	92 (7.5%)	(n<=5)	1,254 (18.4%)
NSAIDs	2,562 (17.3%)	1,606 (17.6%)	506 (16.9%)	152 (14.8%)	298 (17.6%)	2,506 (18.4%)	1,005 (18.2%)	226 (18.5%)	12 (19.4%)	1,263 (18.6%)
Time until $P2Y_{12}$ antagonist prescription claimed										
Prior to MI	564 (3.8%)	349 (3.8%)	103 (3.4%)	36 (3.5%)	76 (4.5%)	704 (5.2%)	449 (8.1%)	60 (4.9%)	6 (9.7%)	189 (2.8%)
1-7 days	13,083 (88.1%)	8,512 (93.1%)	2,838 (94.9%)	977 (94.9%)	756 (44.7%)	6,589 (48.5%)	4,724 (85.7%)	1,114 (91.2%)	52 (83.9%)	699 (10.3%)
8-14 days	141 (0.9%)	94 (1.0%)	20 (0.7%)	11 (1.1%)	16 (0.9%)	205 (1.5%)	160 (2.9%)	25 (2.0%)	0 (0.0%)	20 (0.3%)
15-30 days	246 (1.7%)	185 (2.0%)	30 (1.0%)	6 (0.6%)	25 (1.5%)	238 (1.8%)	180 (3.3%)	22 (1.8%)	(n<=5)	32 (0.5%)
No prescription	818 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	818 (48.4%)	5,861 (43.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5,861 (86.2%)

Numbers in parentheses are percentages of total number of patients in the group; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; IQR, interquartile range; Local hospital, hospital without catheterization laboratory; Main regional hospital, hospital with catheterization laboratory; Tertiary cardiac hospital, university hospital with catheterization laboratory; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

Supplementary Table 2 Baseline demographic and clinical characteristics for the 2010 first-time MI population

	Patients with PCI (N=3673, 49%)					Patients without PCI (N=3754, 51%)				
	All patients n=3673	**Clopidogrel n=3127**	**Ticagrelor n=0**	**Prasugrel n=79**	**No DAPT n=467**	**All patients n=3754**	**Clopidogrel n=1830**	**Ticagrelor n=0**	**Prasugrel n=5**	**No DAPT n=1919**
Age [median (IQR)]	65 (56 - 73)	64 (56 - 73)	. (. - .)	61 (53 - 72)	66 (57 - 74)	73 (62 - 83)	73 (63 - 83)	. (. - .)	62 (61 - 65)	73 (61 - 83)
Males	2,682 (73.0%)	2,275 (72.8%)	0 (.%)	66 (83.5%)	341 (73.0%)	2,002 (53.3%)	996 (54.4%)	0 (.%)	(n<=5)	1,002 (52.2%)
Type of hospital (at index MI event)										
Local hospital	915 (24.9%)	792 (25.3%)	0 (.%)	10 (12.7%)	113 (24.2%)	1,502 (40.0%)	642 (35.1%)	0 (.%)	(n<=5)	857 (44.7%)
Main regional hospital	1,337 (36.4%)	1,178 (37.7%)	0 (.%)	21 (26.6%)	138 (29.6%)	1,280 (34.1%)	730 (39.9%)	0 (.%)	(n<=5)	549 (28.6%)
Tertiary cardiac hospital	1,421 (38.7%)	1,157 (37.0%)	0 (.%)	48 (60.8%)	216 (46.3%)	972 (25.9%)	458 (25.0%)	0 (.%)	(n<=5)	513 (26.7%)
Procedures (at index event)										
CABG	73 (2.0%)	43 (1.4%)	0 (.%)	0 (0.0%)	30 (6.4%)	417 (11.1%)	217 (11.9%)	0 (.%)	0 (0.0%)	200 (10.4%)
Angiography	3,620 (98.6%)	3,084 (98.6%)	0 (.%)	76 (96.2%)	460 (98.5%)	1,983 (52.8%)	1,094 (59.8%)	0 (.%)	(n<=5)	888 (46.3%)
Previous diagnoses										
Heart failure	89 (2.4%)	68 (2.2%)	0 (.%)	(n<=5)	20 (4.3%)	332 (8.8%)	136 (7.4%)	0 (.%)	0 (0.0%)	196 (10.2%)
Ischaemic heart disease	244 (6.6%)	176 (5.6%)	0 (.%)	9 (11.4%)	59 (12.6%)	466 (12.4%)	208 (11.4%)	0 (.%)	(n<=5)	257 (13.4%)
Unstable angina	51 (1.4%)	35 (1.1%)	0 (.%)	(n<=5)	13 (2.8%)	117 (3.1%)	41 (2.2%)	0 (.%)	0 (0.0%)	76 (4.0%)
Peripheral arterial disease	110 (3.0%)	90 (2.9%)	0 (.%)	(n<=5)	19 (4.1%)	262 (7.0%)	126 (6.9%)	0 (.%)	0 (0.0%)	136 (7.1%)
Stroke total	133 (3.6%)	106 (3.4%)	0 (.%)	0 (0.0%)	27 (5.8%)	346 (9.2%)	162 (8.9%)	0 (.%)	0 (0.0%)	184 (9.6%)
Non-ischaemic stroke	9 (0.2%)	7 (0.2%)	0 (.%)	0 (0.0%)	(n<=5)	24 (0.6%)	9 (0.5%)	0 (.%)	0 (0.0%)	15 (0.8%)
Ischaemic stroke	127 (3.5%)	101 (3.2%)	0 (.%)	0 (0.0%)	26 (5.6%)	332 (8.8%)	156 (8.5%)	0 (.%)	0 (0.0%)	176 (9.2%)
Atrial fibrillation	122 (3.3%)	93 (3.0%)	0 (.%)	(n<=5)	27 (5.8%)	389 (10.4%)	137 (7.5%)	0 (.%)	0 (0.0%)	252 (13.1%)
Chronic renal dysfunction	24 (0.7%)	21 (0.7%)	0 (.%)	0 (0.0%)	(n<=5)	39 (1.0%)	17 (0.9%)	0 (.%)	0 (0.0%)	22 (1.1%)
Diabetes mellitus	465 (12.7%)	392 (12.5%)	0 (.%)	13 (16.5%)	60 (12.8%)	697 (18.6%)	336 (18.4%)	0 (.%)	0 (0.0%)	361 (18.8%)
Major bleeding	88 (2.4%)	69 (2.2%)	0 (.%)	(n<=5)	17 (3.6%)	205 (5.5%)	88 (4.8%)	0 (.%)	(n<=5)	116 (6.0%)
Liver disease	6 (0.2%)	(n<=5)	0 (.%)	0 (0.0%)	(n<=5)	5 (0.1%)	(n<=5)	0 (.%)	0 (0.0%)	(n<=5)
Coagulation disorders	12 (0.3%)	10 (0.3%)	0 (.%)	0 (0.0%)	(n<=5)	26 (0.7%)	9 (0.5%)	0 (.%)	0 (0.0%)	17 (0.9%)
Cancer	224 (6.1%)	188 (6.0%)	0 (.%)	(n<=5)	33 (7.1%)	341 (9.1%)	153 (8.4%)	0 (.%)	0 (0.0%)	188 (9.8%)
Drug use at discharge										
Total number of drugs [median (IQR)]	3 (1 - 6)	3 (1 - 6)	. (. - .)	4 (1 - 7)	4 (1 - 8)	6 (3 - 10)	6 (3 - 10)	. (. - .)	3 (2 - 4)	6 (3 - 11)
ACE-inhbitors and ARB	2,051 (55.8%)	1,737 (55.5%)	0 (.%)	50 (63.3%)	264 (56.5%)	2,075 (55.3%)	1,067 (58.3%)	0 (.%)	(n<=5)	1,004 (52.3%)
Acetyl salicylic acid	3,485 (94.9%)	3,127 (100.0%)	0 (.%)	79 (100.0%)	279 (59.7%)	3,044 (81.1%)	1,830 (100.0%)	0 (.%)	5 (100.0%)	1,209 (63.0%)
Betablocker	3,239 (88.2%)	2,774 (88.7%)	0 (.%)	66 (83.5%)	399 (85.4%)	2,659 (70.8%)	1,496 (81.7%)	0 (.%)	5 (100.0%)	1,158 (60.3%)
Calcium-channel blocker	784 (21.3%)	656 (21.0%)	0 (.%)	23 (29.1%)	105 (22.5%)	1,180 (31.4%)	589 (32.2%)	0 (.%)	(n<=5)	590 (30.7%)

Oral antidiabetics and insulin	428 (11.7%)	362 (11.6%)	0 (.%)	11 (13.9%)	55 (11.8%)	611 (16.3%)	302 (16.5%)	0 (.%)	0 (0.0%)	309 (16.1%)
Proton pump inhibitors	912 (24.8%)	755 (24.1%)	0 (.%)	23 (29.1%)	134 (28.7%)	1,340 (35.7%)	613 (33.5%)	0 (.%)	(n<=5)	724 (37.7%)
Statins	3,517 (95.8%)	3,012 (96.3%)	0 (.%)	77 (97.5%)	428 (91.6%)	2,596 (69.2%)	1,514 (82.7%)	0 (.%)	5 (100.0%)	1,077 (56.1%)
Anticoagulant	189 (5.1%)	130 (4.2%)	0 (.%)	(n<=5)	55 (11.8%)	454 (12.1%)	119 (6.5%)	0 (.%)	0 (0.0%)	335 (17.5%)
NSAIDs	677 (18.4%)	576 (18.4%)	0 (.%)	9 (11.4%)	92 (19.7%)	734 (19.6%)	369 (20.2%)	0 (.%)	0 (0.0%)	365 (19.0%)
Time until $P2Y_{12}$ antagonist prescription claimed										
Prior to MI	131 (3.6%)	108 (3.5%)	0 (.%)	(n<=5)	19 (4.1%)	139 (3.7%)	101 (5.5%)	0 (.%)	0 (0.0%)	38 (2.0%)
1-7 days	3,207 (87.3%)	2,948 (94.3%)	0 (.%)	72 (91.1%)	187 (40.0%)	1,814 (48.3%)	1,636 (89.4%)	0 (.%)	(n<=5)	174 (9.1%)
8-14 days	29 (0.8%)	25 (0.8%)	0 (.%)	(n<=5)	(n<=5)	52 (1.4%)	44 (2.4%)	0 (.%)	0 (0.0%)	8 (0.4%)
15-30 days	53 (1.4%)	46 (1.5%)	0 (.%)	(n<=5)	5 (1.1%)	59 (1.6%)	49 (2.7%)	0 (.%)	(n<=5)	9 (0.5%)
No prescription	253 (6.9%)	0 (0.0%)	0 (.%)	0 (0.0%)	253 (54.2%)	1,690 (45.0%)	0 (0.0%)	0 (.%)	0 (0.0%)	1,690 (88.1%)

Numbers in parentheses are percentages of total number of patients in the group; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; IQR, interquartile range; Local hospital, hospital without catheterization laboratory; Main regional hospital, hospital with catheterization laboratory; Tertiary cardiac hospital, university hospital with catheterization laboratory; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs

Supplementary Table 3 Baseline demographic and clinical characteristics for the 2011 first-time MI population

	Patients with PCI (N=3782, 53%)					Patients without PCI (N=3334, 47%)				
	All patients n=3782	**Clopidogrel n=2204**	**Ticagrelor n=766**	**Prasugrel n=408**	**No DAPT n=404**	**All patients n=3334**	**Clopidogrel n=1327**	**Ticagrelor n=332**	**Prasugrel n=30**	**No DAPT n=1645**
Age [median (IQR)]	65 (55 - 74)	66 (56 - 75)	64 (55 - 73)	61 (51 - 67)	67 (59 - 74.5)	74 (63 - 83)	75 (65 - 84)	72 (62 - 81.5)	60.5 (51 - 67)	73 (63 - 83)
Males	2,744 (72.6%)	1,590 (72.1%)	554 (72.3%)	320 (78.4%)	280 (69.3%)	1,803 (54.1%)	708 (53.4%)	179 (53.9%)	20 (66.7%)	896 (54.5%)
Type of hospital (at index MI event)										
Local hospital	906 (24.0%)	590 (26.8%)	157 (20.5%)	50 (12.3%)	109 (27.0%)	1,354 (40.6%)	520 (39.2%)	96 (28.9%)	5 (16.7%)	733 (44.6%)
Main regional hospital	1,409 (37.3%)	781 (35.4%)	315 (41.1%)	171 (41.9%)	142 (35.1%)	1,132 (34.0%)	497 (37.5%)	162 (48.8%)	15 (50.0%)	458 (27.8%)
Tertiary cardiac hospital	1,467 (38.8%)	833 (37.8%)	294 (38.4%)	187 (45.8%)	153 (37.9%)	848 (25.4%)	310 (23.4%)	74 (22.3%)	10 (33.3%)	454 (27.6%)
Procedures (at index event)										
CABG	86 (2.3%)	47 (2.1%)	8 (1.0%)	(n<=5)	29 (7.2%)	449 (13.5%)	169 (12.7%)	35 (10.5%)	(n<=5)	242 (14.7%)
Angiography	3,712 (98.1%)	2,168 (98.4%)	746 (97.4%)	399 (97.8%)	399 (98.8%)	1,882 (56.4%)	779 (58.7%)	226 (68.1%)	18 (60.0%)	859 (52.2%)
Previous diagnoses										
Heart failure	89 (2.4%)	49 (2.2%)	17 (2.2%)	(n<=5)	19 (4.7%)	288 (8.6%)	110 (8.3%)	15 (4.5%)	(n<=5)	161 (9.8%)
Ischaemic heart disease	276 (7.3%)	134 (6.1%)	63 (8.2%)	20 (4.9%)	59 (14.6%)	395 (11.8%)	149 (11.2%)	35 (10.5%)	6 (20.0%)	205 (12.5%)
Unstable angina	57 (1.5%)	25 (1.1%)	14 (1.8%)	6 (1.5%)	12 (3.0%)	66 (2.0%)	23 (1.7%)	(n<=5)	(n<=5)	37 (2.2%)
Peripheral arterial disease	130 (3.4%)	70 (3.2%)	24 (3.1%)	14 (3.4%)	22 (5.4%)	231 (6.9%)	96 (7.2%)	21 (6.3%)	(n<=5)	113 (6.9%)
Stroke total	131 (3.5%)	75 (3.4%)	28 (3.7%)	(n<=5)	24 (5.9%)	276 (8.3%)	126 (9.5%)	26 (7.8%)	0 (0.0%)	124 (7.5%)
Non-ischaemic stroke	13 (0.3%)	12 (0.5%)	0 (0.0%)	0 (0.0%)	(n<=5)	14 (0.4%)	5 (0.4%)	(n<=5)	0 (0.0%)	7 (0.4%)
Ischaemic stroke	123 (3.3%)	68 (3.1%)	28 (3.7%)	(n<=5)	23 (5.7%)	269 (8.1%)	124 (9.3%)	25 (7.5%)	0 (0.0%)	120 (7.3%)
Atrial fibrillation	144 (3.8%)	71 (3.2%)	25 (3.3%)	7 (1.7%)	41 (10.1%)	353 (10.6%)	116 (8.7%)	24 (7.2%)	0 (0.0%)	213 (12.9%)
Chronic renal dysfunction	25 (0.7%)	12 (0.5%)	6 (0.8%)	(n<=5)	6 (1.5%)	37 (1.1%)	12 (0.9%)	(n<=5)	0 (0.0%)	24 (1.5%)
Diabetes mellitus	507 (13.4%)	284 (12.9%)	102 (13.3%)	40 (9.8%)	81 (20.0%)	641 (19.2%)	262 (19.7%)	66 (19.9%)	5 (16.7%)	308 (18.7%)
Major bleeding	91 (2.4%)	56 (2.5%)	18 (2.3%)	(n<=5)	14 (3.5%)	180 (5.4%)	64 (4.8%)	11 (3.3%)	0 (0.0%)	105 (6.4%)
Liver disease	(n<=5)	(n<=5)	0 (0.0%)	0 (0.0%)	(n<=5)	7 (0.2%)	(n<=5)	0 (0.0%)	0 (0.0%)	6 (0.4%)
Coagulation disorders	10 (0.3%)	5 (0.2%)	(n<=5)	0 (0.0%)	(n<=5)	17 (0.5%)	(n<=5)	(n<=5)	0 (0.0%)	12 (0.7%)
Cancer	236 (6.2%)	144 (6.5%)	37 (4.8%)	20 (4.9%)	35 (8.7%)	345 (10.3%)	135 (10.2%)	35 (10.5%)	0 (0.0%)	175 (10.6%)
Drug use at discharge										
Total number of drugs [median (IQR)]	3 (1 - 6)	3 (1 - 6)	3 (1 - 7)	2 (0 - 5)	5 (2 - 8)	6 (3 - 10)	6 (3 - 10)	5 (2.5 - 9)	4.5 (1 - 7)	7 (3 - 11)
ACE-inhbitors and ARB	2,087 (55.2%)	1,243 (56.4%)	403 (52.6%)	214 (52.5%)	227 (56.2%)	1,897 (56.9%)	785 (59.2%)	195 (58.7%)	17 (56.7%)	900 (54.7%)
Acetyl salicylic acid	3,600 (95.2%)	2,204 (100.0%)	766 (100.0%)	408 (100.0%)	222 (55.0%)	2,728 (81.8%)	1,327 (100.0%)	332 (100.0%)	30 (100.0%)	1,039 (63.2%)
Betablocker	3,311 (87.5%)	1,940 (88.0%)	676 (88.3%)	368 (90.2%)	327 (80.9%)	2,398 (71.9%)	1,068 (80.5%)	267 (80.4%)	27 (90.0%)	1,036 (63.0%)
Calcium-channel blocker	859 (22.7%)	492 (22.3%)	186 (24.3%)	59 (14.5%)	122 (30.2%)	1,091 (32.7%)	464 (35.0%)	95 (28.6%)	10 (33.3%)	522 (31.7%)

Oral antidiabetics and insulin	467 (12.3%)	266 (12.1%)	97 (12.7%)	35 (8.6%)	69 (17.1%)	561 (16.8%)	235 (17.7%)	62 (18.7%)	5 (16.7%)	259 (15.7%)
Proton pump inhibitors	1,077 (28.5%)	632 (28.7%)	255 (33.3%)	70 (17.2%)	120 (29.7%)	1,324 (39.7%)	487 (36.7%)	121 (36.4%)	6 (20.0%)	710 (43.2%)
Statins	3,593 (95.0%)	2,112 (95.8%)	739 (96.5%)	399 (97.8%)	343 (84.9%)	2,336 (70.1%)	1,076 (81.1%)	277 (83.4%)	29 (96.7%)	954 (58.0%)
Anticoagulant	238 (6.3%)	121 (5.5%)	35 (4.6%)	16 (3.9%)	66 (16.3%)	447 (13.4%)	102 (7.7%)	30 (9.0%)	(n<=5)	314 (19.1%)
NSAIDs	658 (17.4%)	382 (17.3%)	142 (18.5%)	60 (14.7%)	74 (18.3%)	646 (19.4%)	256 (19.3%)	71 (21.4%)	(n<=5)	315 (19.1%)
Time until $P2Y_{12}$ antagonist prescription claimed										
Prior to MI	148 (3.9%)	90 (4.1%)	24 (3.1%)	15 (3.7%)	19 (4.7%)	192 (5.8%)	116 (8.7%)	19 (5.7%)	5 (16.7%)	52 (3.2%)
1-7 days	3,389 (89.6%)	2,085 (94.6%)	727 (94.9%)	387 (94.9%)	190 (47.0%)	1,689 (50.7%)	1,150 (86.7%)	308 (92.8%)	23 (76.7%)	208 (12.6%)
8-14 days	28 (0.7%)	13 (0.6%)	9 (1.2%)	(n<=5)	(n<=5)	38 (1.1%)	30 (2.3%)	(n<=5)	0 (0.0%)	(n<=5)
15-30 days	29 (0.8%)	16 (0.7%)	6 (0.8%)	(n<=5)	(n<=5)	40 (1.2%)	31 (2.3%)	(n<=5)	(n<=5)	6 (0.4%)
No prescription	188 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	188 (46.5%)	1,375 (41.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1,375 (83.6%)

Numbers in parentheses are percentages of total number of patients in the group; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; IQR, interquartile range; Local hospital, hospital without catheterization laboratory; Main regional hospital, hospital with catheterization laboratory; Tertiary cardiac hospital, university hospital with catheterization laboratory; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

STROBE Statement—checklist of items that should be included in reports of observational studies
Green et al.: "Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction – a Danish nationwide population based cohort study"
N.A.: Not applicable

	Item No	Recommendation
Title and abstract	1 P 1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	P 2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 P 3-4	Explain the scientific background and rationale for the investigation being reported
Objectives	3 P 4	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 P 4-5	Present key elements of study design early in the paper
Setting	5 P 4-5K	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 P 6 (cohort study) N.A.	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7 P 5	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* P 4-5	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 P 6 (sensitivity analyses)	Describe any efforts to address potential sources of bias
Study size	10 N.A.	Explain how the study size was arrived at
Quantitative variables	11 N.A.	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 P 6 P. 5	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was

	addressed
N.A.	*Case-control study*—If applicable, explain how matching of cases and controls was addressed
N.A.	*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
P 6	(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13* N.A.	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* Tables 1,2; Suppl.tables 1,2,3	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* P 12, Figs 1, 2, Tab 3	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 Tab 4	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
	Not applicable	(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 N.A.	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 P 15	Summarise key results with reference to study objectives
Limitations	19 P 17	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 P 17	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 P 16-17	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 P 17-18	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction – a Danish nationwide population based cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-010880.R1
Article Type:	Research
Date Submitted by the Author:	09-Apr-2016
Complete List of Authors:	Green, Anders; Institute of Clinical Research, University of Southern Denmark, Odense Patient data Exploratory Network (OPEN) Pottegard, Anton; University of Southern Denmark, Clinical Pharmacology, Institute of Public Health Broe, Anne Diness, Thomas; AstraZeneca Emneus, Martha; Institute of Applied Economics and Health Research Hasvold, Lars Pål; AstraZeneca Nordic, Medical department Gislason, Gunnar; Copenhagen University Hospital Gentofte, Department of Cardiology
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Myocardial infarction < CARDIOLOGY, dual antiplatelet therapy, persistence, health registers, real-life data

Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction – a Danish nationwide population based cohort study

Key words: Myocardial infarction; dual antiplatelet therapy, persistence; Danish nationwide health registries; real-life data

Anders Green, MD, PhD, DMSc [1, 2], Anton Pottegård, MScPharm, PhD [3], Anne Broe, MD [3], Thomas Goldin Diness, MScPharm, PhD [4], Martha Emneus [2], Pål Hasvold, MScPharm [4], Gunnar H. Gislason, MD, PhD, FACC, FAHA, FESC [5]

[1] Institute of Applied Economics and Health Research, Copenhagen, Denmark

[2] OPEN, Odense Patient Data Explorative Network, Odense University Hospital/Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[3] Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, Odense, Denmark

[4] AstraZeneca, Södertälje, SE-151 85 Sweden

[5] Copenhagen University Hospital Gentofte, 2900 Hellerup, Denmark

Total word count: 3687

Address for correspondence:

Prof. Anders Green, MD, PhD, DMSc
Institute of Applied Economics and Health Research
Ewaldsgade 3, DK-2200 Copenhagen N, Denmark
E-mail: anders.green@dadlnet.dk
Phone: +45 4088 7775 (mobile) FAX: Not available

Author emails:
Anders Green: agreen@dadlnet.dk
Anton Pottegård: apottegaard@health.sdu.dk
Anne Broe: annebroe@gmail.com
Thomas Goldin Diness: Thomas.diness@astrazeneca.com
Martha Emneus: martha.emneus@appliedeconomics.dk
Pål Hasvold: Paal.hasvold@astrazeneca.com
Gunnar Gislason: Gunnar.Gislason@regionh.dk

ABSTRACT

Objectives: The study investigated DAPT patterns over time and patient characteristics associated with the various treatments in an MI population.

Design: A registry-based observational cohort study was performed using antecedent data.

Setting: This study linked morbidity, mortality, and medication data from Danish national registries.

Participants: All 28,449 patients admitted to a Danish hospital with a first time MI and alive at discharge from 2009 through 2012 were included.

Primary and secondary outcome measures: Primary outcome was initiation of DAPT and secondary outcomes comprised persistence in DAPT treatment and switches between DAPT treatments.

Results: The overall proportion of patients prescribed DAPT increased from 68% (C.L.95%: 67% - 69%) to 73% (C.L.95%: 67% - 69%) from 2009 to 2012. For patients treated with and without percutaneous coronary intervention (PCI), the corresponding numbers were from 87% (C.L.95%: 86% - 88%) to 91% (C.L.95%: 90% - 92%) and from 49% (C.L.95%: 47% - 50%) to 52% (C.L.95%: 51% - 54%), respectively. Non-PCI patients had higher cardiovascular risk compared with PCI patients. Among PCI patients, age >75 years, atrial fibrillation, diabetes, and peripheral arterial disease were associated with a higher risk of treatment breaks for DAPT. Among patients without PCI, ticagrelor treatment was associated with an increased risk of treatment breaks during the first 12 months compared with clopidogrel treatment.

Conclusions: From 2009 to 2012, there was an increase in the proportion of MI patients receiving DAPT, and a longer duration of DAPT. Still, a large proportion of patients without PCI are discharged either without DAPT or with a short DAPT duration. These findings may indicate the need for more careful attention to DAPT for MI patients not undergoing PCI in Denmark.

Strength and limitations of this study

- Our study describes dual antiplatelet treatment in Danish patients after myocardial infarction during 2009-2012, making use of the nationwide and complete health registers that may be linked at individual level by means of the unique personal identification system covering all Danish citizens.
- The registry data available for our study are collected for administrative purposes, thereby reducing potential sources of bias otherwise introduced by selection of particular hospitals or healthcare insurance systems.
- Even though coding errors cannot be ruled out in the registry data previous studies have demonstrated high levels of sensitivity and specificity for cardiovascular outcomes in the Danish health registers.
- Our study is limited by not including information on unstable angina, STEMI , NSTEMI, blood pressure, smoking habits, lipid profiles and socioeconomic status.

INTRODUCTION

Platelet activation and subsequent aggregation represent the key targets in the management of acute coronary syndromes (ACS) to prevent recurrent events. However, the incidence of ACS has declined over time supporting the notion that contemporary treatment effectively improves outcomes after an MI[1, 2, 3, 4]. European guidelines recommend initiation of dual antiplatelet therapy (DAPT) with low-dose acetyl salicylic acid (ASA) and a $P2Y_{12}$ antagonist to reduce the risk of both acute ischemic complications and recurrent atherothrombotic events[5]. This treatment is recommended for up to 12 months in patients with ACS, irrespective of whether the patient undergoes revascularization with percutaneous coronary intervention (PCI) or not[5, 6].

Previously, a nationwide Danish study described initiation and persistence patterns for DAPT with clopidogrel and ASA after myocardial infarction (MI) in the years 2000-2005[7]. The study showed a high persistence with clopidogrel treatment among PCI treated patients as compared with non-PCI patients, and a lower degree of clopidogrel use among women and patients admitted to local hospitals[7].

New $P2Y_{12}$ antagonists have recently been introduced in the treatment of ACS patients; prasugrel received European Medicines Agency (EMA) approval in 2009 and ticagrelor in 2011. Ticagrelor, co-administered with ASA, is indicated for patients with ACS, including patients managed medically, and those who are managed with PCI or coronary artery by-pass grafting (CABG)[8]. Prasugrel, co-administered with ASA is indicated for patients with ACS undergoing PCI[9].

In 2011, ticagrelor was recommended as first-line treatment in the national Danish ACS guidelines across sub-diagnoses[10]. How these new multiple DAPT options are used in contemporary clinical practice in Denmark and how guideline recommendations are implemented are not known. Also, as the indication for the different $P2Y_{12}$ antagonists differ, it is likely that the populations treated with the respective $P2Y_{12}$ antagonists diverge with respect to their baseline characteristics. To our knowledge, this has not been investigated in a large scale study. Furthermore, it is of clinical relevance to describe treatment persistence and patient characteristics that are associated with reduced persistence.

The aim of this study was to describe the DAPT pattern in Danish patients with MI during 2009-2012, with focus on comparing treatment in 2009 and 2012, ie, before and after the introduction of prasugrel and ticagrelor, by combining data from nationwide registries on hospital admissions, prescription drug use and date of mortality.

METHODS

Data sources

Data were obtained from Danish nationwide compulsory registries on hospital admissions and prescribed drugs. As virtually all medical care in Denmark is provided by the national health authorities, these data sources allow true population-based studies with national coverage and high levels of completeness[11].

The Danish National Prescription Registry[12] contains data on all prescribed drugs dispensed from Danish community pharmacies since 1995. Prescription data include type of drug, date of dispensing and quantity and are categorized according to the Anatomic Therapeutic Chemical (ATC) index[13]. Drug expenses are partially reimbursed by the Danish health-care authorities.

The Danish National Patient Registry contains data on all somatic hospitalizations in Denmark since 1977 and on outpatient visits since 1995[14]. Hospital discharge and outpatient contact diagnoses are coded according to the International Classification of Diseases (ICD-10) from 1994 onward.

All data sources were linked by means of the personal identification number, a unique identifier encoding gender and date of birth, assigned by the Danish Civil Registration System to all Danish residents since 1968[15]. The Civil Registration System contains continuously updated data on address, date of death, and migration to and from Denmark. All record linkage was performed by Statistics Denmark.

Study design and study population

Patients who experienced a first time ever hospital admission related to acute MI within the observation period 1 January 2009 to 31 December 2012 were eligible for inclusion. A MI event was defined as having an admission with a primary or secondary diagnosis ICD-10 code of I21. Patients with a diagnosis of unstable angina pectoris (ICD-10 code I20.0) were not included. Further, sub classification into ST segment elevation MI (STEMI) and non-segment ST elevation MI (NSTEMI) was not performed since ICD-10 coding specification at this level has not been validated.

An MI episode may present as a sequence of admissions to more than one hospital department and was defined as one admission if the interval was not more than one day between discharge from one hospital and admission date at the next hospital. Only the first episode for each individual within the observation period was included. We also required that individuals were discharged alive. Patients had to be Danish residents with a Danish permanent address at the time of admission.

The study was approved by the Danish Data Protection Agency. According to Danish law, ethical approval is not required for registry-based studies[16].

ANALYSIS

All individuals were classified according to whether they had been dispensed DAPT or not. The use of DAPT was analyzed among individuals experiencing MI in 2009 and 2012, respectively. All analyses were stratified by type of DAPT, study year and whether or not the patient underwent PCI in relation to the index event.

Baseline characteristics of subjects initiating DAPT following MI

Individuals were described regarding age and gender, the type of hospital at index event, procedures during index event, previous diagnoses and dispensed drugs at the time of admission.

(1) Classification according to admission by type of hospital according to degree of cardiological expertise available was: local hospital, hospital without catheterization laboratory (level 1); main regional hospital, hospital with catheterization laboratory (level 2); tertiary cardiac hospital, university hospital with catheterization laboratory (level 3).

(2) Procedures during index event included angiography (UXAC85), PCI (procedure code FNG) and CABG (procedure code FNA-FNE). We included CABG performed up to 30 days after discharge. Throughout the study period, procedures were coded according to the Nordic classification scheme[17].

(3) Previous diagnoses (other than those related to MI) registered in the Patient Registry up to 5 years prior to the admission for index MI were included. For a full list of diagnoses and definitions, see Appendix A.

(4) Drug use were defined as having filled a prescription for the given drug according to the Prescription Registry within 180 days prior to the index admission and up to 30 days following discharge. For a full list of drugs included, see Appendix B.

Persistence to DAPT following treatment initiation

DAPTs were defined as concomitant use of low-dose ASA and a $P2Y_{12}$ antagonist, and were further subcategorized by the specific $P2Y_{12}$ antagonists. The main drugs examined were the three $P2Y_{12}$ antagonists currently available in Denmark, ie, clopidogrel (ATC B01AC04), prasugrel (B01AC22) and ticagrelor (B01AC24), as well as low-dose ASA (B01AC06 or N02BA01). For all four drugs, use was defined as having filled a prescription for the given drug within 90 days prior to the admission to 30 days after the admission. Individuals filling prescriptions for two different $P2Y_{12}$ antagonists within this interval were classified according to the last prescription filled. Individuals failing to fill a prescription for either a $P2Y_{12}$ antagonist or ASA within 30 days after index MI were classified as not using DAPT.

Persistence with treatment was analyzed during a period of 365 days following the index MI using the 'proportion of patients covered' (PPC) method[18]. In brief, all subjects were followed starting 30 days after discharge from the index event. Over time, we estimated the proportion of all subjects still alive and not migrated and using the same $P2Y_{12}$ antagonist as at discharge. A subject was considered a current user of a given $P2Y_{12}$ antagonist from the day of filling a prescription for that drug and for a number of days corresponding to either the number of tablets for clopidogrel and prasugrel (used once daily) or half the number of tablets for ticagrelor (used twice daily). Finally, a 30-day grace period was added to the estimated duration to account for minor non-compliance and irregular prescription refills. A sensitivity analysis with a grace period of 90 days was also performed. An individual could be regarded as dropped out of treatment at one point in time and later be re-classified as a current user upon filling a new prescription. In the Cox regression analysis for having a treatment break larger than the 30-day grace period, the type of DAPT treatment, age and gender, type of treating hospital department and selected comorbidities were chosen as covariates.

Frequency of switch between different DAPT regimens

To estimate switch patterns, we estimated the proportion of all subjects who within the first year following discharge filled a $P2Y_{12}$ antagonist other than the one they first used following discharge. The observation period for this analysis commenced 30 days after discharge with the index admission of MI.

Statistical program

All calculations were performed using STATA Release 13.0 (StataCorp, College Station, TX, USA).

RESULTS

Overall, 97% (28,449 patients) of all patients admitted to the hospital with a first-time MI during 2009–2012 were alive 30 days after discharge and included in this study. The baseline characteristics for the years 2009 and 2012 are shown in Table 1 and Table 2. Baseline characteristics for the toal material as well as for the years 2010 and 2011 are contained Supplementary Tables 1, 2 and 3, respectively.

Patient characteristics 2009

Of the first time MI patients (median age 69 years [interquartile range (IQR) 59-79 years]; 36% women), 73% underwent angiography and 53% PCI, and a majority of patients (67%) were discharged with DAPT (Table 1 and Figure 1). A larger proportion of patients with PCI were discharged with DAPT (87%) compared with the patients without PCI (51%). The PCI patients were younger and more frequently men than the non-PCI patients. A majority of these patients received ASA, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and statins at discharge, which is in line with guideline recommendations. Among the non-PCI patients, a considerably larger proportion underwent CABG, had a diagnosis of atrial fibrillation, and/or had a history of major bleedings compared with the PCI patients. Notably, a larger proportion of non-PCI patients were discharged without beta-blockers, ACE inhibitors and statins.

Patient characteristics 2012

The median age of first time MI patients was 69 years [IQR, 58-78 years], and 36% were women (Table 2). Overall, 79% underwent angiography and 55% PCI, and the majority (73%) were discharged with DAPT (Table 2 and Figure 1). Still, a large proportion (49%) of the non-PCI patients were discharged without DAPT and other guideline recommended drug therapies compared with the PCI patients. In general, marked differences in patient characteristic were observed dependent on the choice of $P2Y_{12}$ antagonist used in the DAPT regimens. Patients treated with prasugrel were 11 years younger (median), more commonly men, and the majority underwent PCI (84%) compared with the total MI patient population. Most of the prasugrel-treated patients were either managed at a main regional hospital or at a university hospital with a catheterization laboratory.

The proportion of patients prescribed DAPT with ticagrelor increased quickly after its introduction in 2011. By the end of 2012, ticagrelor was the most common $P2Y_{12}$ antagonist in both patients with and without PCI (Figure 1). More patients in the ticagrelor group underwent PCI (71%) compared with clopidogrel treated patients (52%). Ticagrelor-treated patients were 7 years younger and more commonly men. Patients treated with clopidogrel had in general a more severe disease burden at baseline, with additional diagnoses of heart failure, stroke, or atrial fibrillation compared with the other DAPT-treated patients (Table 2).

Table 1 Baseline demographic and clinical characteristics for the 2009 first-time MI population

	Patients with PCI (N=3576, 50%)					Patients without PCI (N=3528, 50%)				
	All patients n=3576	**Clopidogrel n=3087**	**Ticagrelor n=0**	**Prasugrel n=13**	**No DAPT n=476**	**All patients n=3528**	**Clopidogrel n=1712**	**Ticagrelor n=0**	**Prasugrel n=1**	**No DAPT n=1815**
Age [median (IQR)]	64 (55 - 73)	64 (55 - 73)	. (. - .)	57 (50 - 64)	68 (59 - 75)	74 (64 - 83)	74 (64 - 83)	. (. - .)	49 (49 - 49)	74 (63 - 84)
Males	2,643 (73.9%)	2,289 (74.1%)	0 (.%)	8 (61.5%)	346 (72.7%)	1,951 (55.3%)	956 (55.8%)	0 (.%)	0 (0.0%)	995 (54.8%)
Type of hospital (at index MI event)										
Local hospital	946 (26.5%)	805 (26.1%)	0 (.%)	5 (38.5%)	136 (28.6%)	1,440 (40.8%)	659 (38.5%)	0 (.%)	<5	780 (43.0%)
Main regional hospital	1,149 (32.1%)	1,005 (32.6%)	0 (.%)	5 (38.5%)	139 (29.2%)	1,150 (32.6%)	616 (36.0%)	0 (.%)	0 (0.0%)	534 (29.4%)
Tertiary cardiac hospital	1,481 (41.4%)	1,277 (41.4%)	0 (.%)	<5	201 (42.2%)	938 (26.6%)	437 (25.5%)	0 (.%)	0 (0.0%)	501 (27.6%)
Procedures (at index event)										
CABG	80 (2.2%)	47 (1.5%)	0 (.%)	0 (0.0%)	33 (6.9%)	412 (11.7%)	197 (11.5%)	0 (.%)	0 (0.0%)	215 (11.8%)
Angiography	3,535 (98.9%)	3,055 (99.0%)	0 (.%)	13 (100.0%)	467 (98.1%)	1,761 (49.9%)	932 (54.4%)	0 (.%)	<5	828 (45.6%)
Previous diagnoses										
Heart failure	100 (2.8%)	71 (2.3%)	0 (.%)	0 (0.0%)	29 (6.1%)	343 (9.7%)	148 (8.6%)	0 (.%)	0 (0.0%)	195 (10.7%)
Ischaemic heart disease	256 (7.2%)	181 (5.9%)	0 (.%)	<5	74 (15.5%)	488 (13.8%)	199 (11.6%)	0 (.%)	0 (0.0%)	289 (15.9%)
Unstable angina	55 (1.5%)	43 (1.4%)	0 (.%)	0 (0.0%)	12 (2.5%)	107 (3.0%)	50 (2.9%)	0 (.%)	0 (0.0%)	57 (3.1%)
Peripheral arterial disease	94 (2.6%)	67 (2.2%)	0 (.%)	0 (0.0%)	27 (5.7%)	246 (7.0%)	118 (6.9%)	0 (.%)	0 (0.0%)	128 (7.1%)
Stroke total	132 (3.7%)	98 (3.2%)	0 (.%)	<5	33 (6.9%)	338 (9.6%)	160 (9.3%)	0 (.%)	0 (0.0%)	178 (9.8%)
Non-ischaemic stroke	<5	<5	0 (.%)	0 (0.0%)	<5	19 (0.5%)	7 (0.4%)	0 (.%)	0 (0.0%)	12 (0.7%)
Ischaemic stroke	130 (3.6%)	96 (3.1%)	0 (.%)	<5	33 (6.9%)	328 (9.3%)	155 (9.1%)	0 (.%)	0 (0.0%)	173 (9.5%)
Atrial fibrillation	125 (3.5%)	93 (3.0%)	0 (.%)	0 (0.0%)	32 (6.7%)	375 (10.6%)	132 (7.7%)	0 (.%)	0 (0.0%)	243 (13.4%)
Chronic renal dysfunction	16 (0.4%)	11 (0.4%)	0 (.%)	0 (0.0%)	5 (1.1%)	43 (1.2%)	18 (1.1%)	0 (.%)	0 (0.0%)	25 (1.4%)
Diabetes mellitus	396 (11.1%)	327 (10.6%)	0 (.%)	<5	68 (14.3%)	625 (17.7%)	304 (17.8%)	0 (.%)	0 (0.0%)	321 (17.7%)
Major bleeding	93 (2.6%)	75 (2.4%)	0 (.%)	0 (0.0%)	18 (3.8%)	189 (5.4%)	67 (3.9%)	0 (.%)	0 (0.0%)	122 (6.7%)
Liver disease	<5	<5	0 (.%)	0 (0.0%)	0 (0.0%)	5 (0.1%)	<5	0 (.%)	0 (0.0%)	<5
Coagulation disorders	9 (0.3%)	8 (0.3%)	0 (.%)	0 (0.0%)	<5	21 (0.6%)	<5	0 (.%)	0 (0.0%)	17 (0.9%)
Cancer	193 (5.4%)	158 (5.1%)	0 (.%)	<5	34 (7.1%)	333 (9.4%)	146 (8.5%)	0 (.%)	0 (0.0%)	187 (10.3%)
Drug use at discharge										
Total number of drugs [median (IQR)]	3 (1 - 6)	3 (1 - 6)	. (. - .)	4 (0 - 8)	4 (2 - 8)	6 (3 - 10)	6 (3 - 10)	. (. - .)	13 (13 - 13)	7 (3 - 11)
ACE-inhbitors and ARB	1,948 (54.5%)	1,678 (54.4%)	0 (.%)	7 (53.8%)	263 (55.3%)	1,984 (56.2%)	992 (57.9%)	0 (.%)	0 (0.0%)	992 (54.7%)

Acetyl salicylic acid	3,379 (94.5%)	3,087 (100.0%)	0 (.%)	13 (100.0%)	279 (58.6%)	2,962 (84.0%)	1,712 (100.0%)	0 (.%)	<5	1,249 (68.8%)
Betablocker	3,170 (88.6%)	2,760 (89.4%)	0 (.%)	12 (92.3%)	398 (83.6%)	2,537 (71.9%)	1,389 (81.1%)	0 (.%)	0 (0.0%)	1,148 (63.3%)
Calcium-channel blocker	749 (20.9%)	621 (20.1%)	0 (.%)	<5	127 (26.7%)	1,027 (29.1%)	474 (27.7%)	0 (.%)	<5	552 (30.4%)
Oral antidiabetics and insulin	369 (10.3%)	308 (10.0%)	0 (.%)	<5	60 (12.6%)	562 (15.9%)	277 (16.2%)	0 (.%)	0 (0.0%)	285 (15.7%)
Proton pump inhibitors	916 (25.6%)	772 (25.0%)	0 (.%)	<5	140 (29.4%)	1,302 (36.9%)	579 (33.8%)	0 (.%)	<5	722 (39.8%)
Statins	3,379 (94.5%)	2,954 (95.7%)	0 (.%)	12 (92.3%)	413 (86.8%)	2,523 (71.5%)	1,427 (83.4%)	0 (.%)	<5	1,095 (60.3%)
Anticoagulant	224 (6.3%)	162 (5.2%)	0 (.%)	<5	61 (12.8%)	415 (11.8%)	113 (6.6%)	0 (.%)	0 (0.0%)	302 (16.6%)
NSAIDs	613 (17.1%)	531 (17.2%)	0 (.%)	5 (38.5%)	77 (16.2%)	606 (17.2%)	280 (16.4%)	0 (.%)	0 (0.0%)	326 (18.0%)
Time until $P2Y_{12}$ antagonist prescription claimed										
Prior to MI	122 (3.4%)	103 (3.3%)	0 (.%)	<5	18 (3.8%)	167 (4.7%)	125 (7.3%)	0 (.%)	0 (0.0%)	42 (2.3%)
1-7 days	3,033 (84.8%)	2,825 (91.5%)	0 (.%)	11 (84.6%)	197 (41.4%)	1,600 (45.4%)	1,438 (84.0%)	0 (.%)	<5	161 (8.9%)
8-14 days	52 (1.5%)	48 (1.6%)	0 (.%)	0 (0.0%)	<5	69 (2.0%)	65 (3.8%)	0 (.%)	0 (0.0%)	<5
15-30 days	120 (3.4%)	111 (3.6%)	0 (.%)	<5	8 (1.7%)	91 (2.6%)	84 (4.9%)	0 (.%)	0 (0.0%)	7 (0.4%)
No prescription	249 (7.0%)	0 (0.0%)	0 (.%)	0 (0.0%)	249 (52.3%)	1,601 (45.4%)	0 (0.0%)	0 (.%)	0 (0.0%)	1,601 (88.2%)

Numbers in parentheses are percentages of total number of patients in the group; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; IQR, interquartile range; Local hospital, hospital without catheterization laboratory; Main regional hospital, hospital with catheterization laboratory; Tertiary cardiac hospital, university hospital with catheterization laboratory; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2 Baseline demographic and clinical characteristics for the 2012 first-time MI population

	Patients with PCI (n=3852, 55%)					Non-PCI patients (n=3164, 45%)				
	All patients n=3852	**Clopidogrel n=724**	**Ticagrelor n=2238**	**Prasugrel n=531**	**No DAPT n=359**	**All patients n=3164**	**Clopidogrel n=679**	**Ticagrelor n=921**	**Prasugrel n=26**	**No DAPT n=1538**
Age [median (IQR)]	65 (55 - 74)	68 (58 - 79)	65 (55 - 74)	58 (51 - 66)	69 (59 - 77)	74 (63 - 83)	77 (67 - 86)	71 (61 - 80)	52.5 (48 - 67)	75 (64 - 84)
Males	2800 (72.7)	490 (67.7)	1615 (72.2)	440 (82.9)	255 (71.0)	1684 (53.2)	337 (49.6)	500 (54.3)	18 (69.2)	829 (53.9)
Type of hospital (at index MI event)										
Local hospital	1037 (26.9)	291 (40.2)	552 (24.7)	68 (12.8)	126 (35.1)	1285 (40.6)	277 (40.8)	318 (34.5)	<5	686 (44.6)
Main regional hospital	1579 (41.0)	202 (27.9)	1021 (45.6)	234 (44.1)	122 (34.0)	1144 (36.2)	247 (36.4)	417 (45.3)	8 (30.8)	472 (30.7)
Tertiary cardiac hospital	1236 (32.1)	231 (31.9)	665 (29.7)	229 (43.1)	111 (30.9)	735 (23.2)	155 (22.8)	186 (20.2)	14 (53.8)	380 (24.7)
Procedures (at index MI event)										
CABG	93 (2.4)	40 (5.5)	20 (0.9)	<5	30 (8.4)	453 (14.3)	77 (11.3)	130 (14.1)	<5	245 (15.9)
Angiography	3790 (98.4)	704 (97.2)	2213 (98.9)	525 (98.9)	348 (96.9)	1740 (55.0)	340 (50.1)	649 (70.5)	16 (61.5)	735 (47.8)
Previous diagnoses										
Heart failure	83 (2.2)	23 (3.2)	34 (1.5)	7 (1.3)	19 (5.3)	234 (7.4)	67 (9.9)	41 (4.5)	0 (0.0)	126 (8.2)
Ischaemic heart disease	210 (5.5)	59 (8.1)	90 (4.0)	16 (3.0)	45 (12.5)	413 (13.1)	108 (15.9)	101 (11.0)	<5	200 (13.0)
Unstable angina pectoris	46 (1.2)	14 (1.9)	21 (0.9)	<5	9 (2.5)	77 (2.4)	18 (2.7)	14 (1.5)	<5	43 (2.8)
Peripheral arterial disease	110 (2.9)	36 (5.0)	44 (2.0)	6 (1.1)	24 (6.7)	224 (7.1)	61 (9.0)	55 (6.0)	0 (0.0)	108 (7.0)
Stroke total	126 (3.3)	36 (5.0)	62 (2.8)	<5	25 (7.0)	257 (8.1)	86 (12.7)	40 (4.3)	0 (0.0)	131 (8.5)
Non-ischaemic stroke	12 (0.3)	<5	6 (0.3)	0 (0.0)	<5	22 (0.7)	5 (0.7)	<5	0 (0.0)	14 (0.9)
Ischaemic stroke	117 (3.0)	33 (4.6)	58 (2.6)	<5	23 (6.4)	243 (7.7)	83 (12.2)	38 (4.1)	0 (0.0)	122 (7.9)
Atrial fibrillation	150 (3.9)	44 (6.1)	56 (2.5)	5 (0.9)	45 (12.5)	335 (10.6)	63 (9.3)	49 (5.3)	0 (0.0)	223 (14.5)
Chronic renal dysfunction	30 (0.8)	8 (1.1)	11 (0.5)	<5	10 (2.8)	41 (1.3)	11 (1.6)	<5	<5	24 (1.6)
Diabetes mellitas	512 (13.3)	114 (15.7)	279 (12.5)	53 (10.0)	66 (18.4)	585 (18.5)	157 (23.1)	140 (15.2)	<5	284 (18.5)
Major bleeding	88 (2.3)	26 (3.6)	41 (1.8)	7 (1.3)	14 (3.9)	155 (4.9)	33 (4.9)	33 (3.6)	0 (0.0)	89 (5.8)
Liver disease	9 (0.2)	<5	<5	<5	<5	7 (0.2)	<5	<5	0 (0.0)	<5
Coagulation disorders	15 (0.4)	5 (0.7)	<5	0 (0.0)	6 (1.7)	17 (0.5)	<5	<5	0 (0.0)	14 (0.9)
Cancer	278 (7.2)	66 (9.1)	145 (6.5%)	25 (4.7)	42 (11.7)	339 (10.7)	63 (9.3)	86 (9.3)	0 (0.0)	190 (12.4)

Drug use at discharge										
Total number of drugs [median (IQR)]	3 (1 - 6)	4 (1 - 8)	3 (1 - 6)	2 (0 - 4)	5 (2 - 8)	6 (3 - 10)	7 (4 - 11)	5 (2 - 9)	4.5 (1 - 6)	7 (3 - 11)
ACE-inhibitors and ARB	2076 (53.9)	450 (62.2)	1145 (51.2)	268 (50.5)	213 (59.3)	1748 (55.2)	417 (61.4)	495 (53.7)	15 (57.7)	821 (53.4)
Acetyl salicylic acid	3666 (95.2)	724 (100.0)	2238 (100.0)	531 (100.0)	173 (48.2)	2568 (81.2)	679 (100.0)	921 (100.0)	26 (100.0)	942 (61.2)
Beta-blocker	3364 (87.3)	621 (85.8)	1959 (87.5)	503 (94.7)	281 (78.3)	2226 (70.4)	517 (76.1)	754 (81.9)	20 (76.9)	935 (60.8)
Calcium-channel blocker	877 (22.8)	218 (30.1)	463 (20.7)	79 (14.9)	117 (32.6)	1073 (33.9)	247 (36.4)	305 (33.1)	12 (46.2)	509 (33.1)
Oral antidiabetics and insulin	473 (12.3)	98 (13.5)	265 (11.8)	49 (9.2)	61 (17.0)	532 (16.8)	147 (21.6)	133 (14.4)	<5	248 (16.1)
Proton pump inhibitors	1195 (31.0)	275 (38.0)	680 (30.4)	108 (20.3)	132 (36.8)	1280 (40.5)	322 (47.4)	323 (35.1)	9 (34.6)	626 (40.7)
Statins	3661 (95.0)	672 (92.8)	2165 (96.7)	524 (98.7)	300 (83.6)	2219 (70.1)	529 (77.9)	802 (87.1)	22 (84.6)	866 (56.3)
Anticoagulant	266 (6.9)	76 (10.5)	94 (4.2)	14 (2.6)	82 (22.8)	445 (14.1)	65 (9.6)	63 (6.8)	0 (0.0)	317 (20.6)
NSAIDs	624 (16.2)	118 (16.3)	367 (16.4)	79 (14.9)	60 (16.7)	539 (17.0)	104 (15.3)	159 (17.3)	8 (30.8)	268 (17.4)
Time until $P2Y_{12}$ antagonist –prescription claimed										
Prior to MI	165 (4.3)	48 (6.6)	80 (3.6)	16 (3.0)	21 (5.8)	228 (7.2)	121 (17.8)	45 (4.9)	<5	61 (4.0)
1-7 days	3472 (90.1)	656 (90.6)	2123 (94.9)	508 (95.7)	185 (51.5)	1543 (48.8)	521 (76.7)	833 (90.4)	24 (92.3)	165 (10.7)
8-14 days	32 (0.8)	8 (1.1)	11 (0.5)	7 (1.3)	6 (1.7)	46 (1.5)	21 (3.1)	21 (2.3)	0 (0.0)	<5
15-30 days	44 (1.1)	12 (1.7)	24 (1.1)	0 (0.0)	8 (2.2)	49 (1.5)	16 (2.4)	22 (2.4)	<5	10 (0.7)
No prescription	139 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	139 (38.7)	1298 (41.0)	0 (0.0)	0 (0.0)	0 (0.0)	1298 (84.4)

Numbers in parentheses are percentages of total number of patients in the group; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; IQR, interquartile range; Local hospital, hospital without catheterization laboratory; Main regional hospital, hospital with catheterization laboratory; Tertiary cardiac hospital, university hospital with catheterization laboratory; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs

In 2012, the proportion of patients discharged with DAPT was 6% higher compared with that in 2009. The non-DAPT-treated patients were older (+9 years, median age difference) and more commonly women (+20% difference) compared with the DAPT treated patients. Among non-DAPT treated patients, invasive treatment within 30 days from admission was received by relatively few patients; 57% underwent angiography and 19% PCI. A larger proportion of non-DAPT treated patients underwent CABG, were diagnosed with atrial fibrillation, and were treated with warfarin or new oral anticoagulants (NOAC) compared with the DAPT-treated patients. More patients had a prior diagnosis of heart failure, cancer and/or a history of major bleeds or coagulation disorders.

A smaller proportion of the non-DAPT treated patients received ACE inhibitors/ angiotensin receptor blockers (ARBs), beta-blockers, and statins at discharge compared with DAPT-treated patients. Of these, 49% received ASA as mono therapy, and 13% and10% of non-DAPT treated patients were treated with clopidogrel or ticagrelor, respectively, as mono therapies.

Medical history-related predictors of DAPT persistence

Overall persistence was very high among patients initiated on DAPT (Figure 2).

Within the first year post- MI in 2012, 6% of the prasugrel treated patients were switched to another $P2Y_{12}$ antagonist; 11% from the ticagrelor group and 3% from clopidogrel group (Table 3).

Patients undergoing PCI had an overall longer DAPT duration compared with patients not undergoing PCI, and age >75 years and diagnosis of atrial fibrillation, diabetes, and peripheral arterial disease were associated with a higher risk of treatment breaks (Table 4). Furthermore, there was a trend toward increased risk for treatment breaks for PCI patients with heart failure and stroke. For patients not undergoing PCI we did not observe any association between any major baseline diseases and risk for treatment breaks.

Among PCI patients, treatment with prasugrel or ticagrelor compared with clopidogrel was associated with an increased risk of a 30-day treatment break within 365 days after MI (Table 4). However, this risk was not present when extending the grace period to 60 days (data not shown).

For non-PCI patients, ticagrelor compared to clopidogrel treatment was associated with an increased risk of having a 30-day treatment break. This finding was also present when expanding the grace period to 60 days, during which 11% of these patients were switched to clopidogrel after a median of 107 days.

Table 3 MI patients discharged in 2012: switch pattern for dual antiplatelet therapy during the first 365 days after MI

	Drug treatment	No of discharged patients	No of patients switching	Median time (days) to switch	No of patients switching to clopidogrel	No of patients switching to ticagrelor	No of patients switching to prasugrel
PCI treated patients	Clopidogrel	719	25	73 (44-119)	0	18	7
	Ticagrelor	2198	214	110 (62-209)	210	0	<5
	Prasugrel	524	33	147 (90-230)	29	<5	0
	Clopidogrel without ASA	74	<5	83 (12-90)	0	<5	<5
	Ticagrelor without ASA	110	18	84 (57-210)	18	0	0
	Prasugrel without ASA	29	<5	200 (149-310)	<5	0	0
	No $P2Y_{12}$ antagonist only ASA	118	29	49 (15-119)	13	7	9
	No $P2Y_{12}$ antagonist or ASA	24	14	34 (14-136)	8	<5	<5
Non-PCI treated patients	Clopidogrel	635	14	148 (73-213)	0	13	<5
	Ticagrelor	868	102	107 (49-208)	102	0	0
	Prasugrel	25	<5	52 (52-52)	0	<5	0
	Clopidogrel without ASA	161	<5	44 (33-106)	0	<5	0
	Ticagrelor without ASA	68	11	133 (108-154)	10	0	<5
	No $P2Y_{12}$ antagonist only ASA	765	83	77 (13-167)	58	22	<5
	No $P2Y_{12}$ antagonist or ASA	424	21	92 (55-178)	16	5	0

Table 4 MI patients discharged in 2012: Cox regression analysis: hazard ratio for having a break in $P2Y_{12}$ antagonist treatment >30 days with or without PCI

	Patients with PCI			Non-PCI patients		
	No of patients	No of patients with breaks	Hazard ratio (95% CI)	No of patients	No of patients with breaks	Hazard ratio (95% CI)
All patients	3373	1,513		1399	972	
Clopidogrel	697	317	Reference	579	411	Reference
Ticagrelor	2164	937	1.20 (1.03-1.39)	800	552	1.48 (1.27-1.72)
Prasugrel	512	259	1.48 (1.24-1.78)	20	9	0.86 (0.47-1.58)
Female	911	398	Reference	666	481	Reference
Male	2462	1115	1.00 (0.88-1.13)	733	491	0.91 (0.78-1.05)
<60 years	1216	503	1.01 (0.90-1.14)	277	168	1.18 (0.97-1.43)
60-75 years	1481	648	Reference	554	344	Reference
>75 years	676	362	1.15 (1.00-1.34)	568	460	1.02 (0.86-1.21)
Local hospital	878	403	Reference	498	357	Reference
Main regional hospital	1404	620	0.97 (0.85-1.11)	588	399	0.99 (0.84-1.18)
Tertiary cardiac hospital	1091	490	1.00 (0.86-1.15)	313	216	1.12 (0.92-1.38)
CABG	56	22	0.81 (0.49-1.34)	191	107	1.00 (0.80-1.25)
Heart failure	59	42	1.40 (0.94-2.08)	86	79	1.33 (0.98-1.81)
Stroke	97	56	1.34 (0.99-1.82)	101	77	1.11 (0.82-1.49)
Atrial fibrillation	92	68	1.88 (1.41-2.50)	94	81	1.27 (0.95-1.70)
Diabetes	411	229	1.23 (1.05-1.44)	258	196	0.96 (0.79-1.16)
Cancer	219	131	1.09 (0.88-1.34)	125	104	1.03 (0.80-1.33)
Major bleeding	67	39	1.07 (0.74-1.56)	53	36	1.20 (0.86-1.67)
Peripheral arterial disease	85	61	1.63 (1.20-2.20)	93	74	0.99 (0.72-1.36)

CI, confidence interval; Local hospital, hospital without catheterization laboratory; Main regional hospital, hospital with catheterization laboratory; Tertiary cardiac hospital, university hospital with catheterization laboratory; CABG, coronary artery bypass surgery

DISCUSSION

This nationwide observational study showed changes in the treatment of MI patients in Denmark from 2009 to 2012. In 2012, more patients are referred to coronary angiography and PCI, and a larger proportion of patients are discharged with DAPT compared to 2009. However, non-PCI patients were, to a large extent, discharged without DAPT, or received shorter duration of DAPT treatment as compared with PCI patients. Among PCI patients, age>75 years, atrial fibrillation, diabetes and peripheral arterial disease were all associated with a higher risk of treatment breaks, which might indicates a risk-treatment mismatch, as these patients have higher risk of recurrent events and might benefit from longer DAPT duration. During the observation period, the DAPT pattern shifted from merely clopidogrel treatment to more selective treatments with clopidogrel, prasugrel and ticagrelor for patient populations with varying characteristics.

Interpretation with reference to other studies

The underlying medical treatment of MI patients in Denmark, with more patients undergoing angiography and PCI over time, followed the same trend as seen in both earlier observations in Denmark and studies from other countries[19, 20, 21].

To our knowledge, national level data describing patient selection for different DAPT regimens and persistence with treatment in unselected populations are scarce. Publications based on data from cardiovascular quality registers, actively recruiting or selecting patients, report an overall DAPT usage for discharged patients with ACS in the range of approximately 60% to 80% depending on the observation period and the type of ACS event included[21, 22, 23, 24, 25]. A recent Swedish nationwide study on MI patients, which may be considered comparable to the present nationwide data, reported a DAPT usage of 69% for patients discharged with MI in 2000-2011[26].

A previous similar Danish study, including all MI patients between 2000 and 2005, reported an increasing use of DAPT during the observation period[7]. However, for non-PCI patients there was a substantial underuse, especially among women and patients admitted to local hospitals. Although the observation period in the present study is more recent, many of these patients are still discharged without DAPT, although there is a markedly increased use of DAPT in these patient groups.

The observed overall adherence to DAPT (Figure 2), with more than 75% of patients completing more than 11 months of treatment, is noteworthy and comparable to what has been observed in randomized controlled trials[27, 28].

Medical history-related predictors of DAPT persistence

The non-DAPT-treated patients are of special interest, as in the present study they form a considerable proportion of patients discharged with first-time MI (27% in 2012), despite the decline in the relative number of patients discharged without DAPT during the observation period (Figure 2). A large

proportion of these patients received oral antiplatelet monotherapy with ASA or with prasugrel, ticagrelor or clopidogrel. Furthermore, there was a marked difference between patients who underwent PCI vs. those did no; a larger proportion of non-PCI patients were discharged without DAPT (in 2012: 9% vs. 49%, respectively). In addition, non-PCI patients had a shorter DAPT treatment duration in general, were on average 10 years older and with a large proportion having a risk profile with atrial fibrillation and history of bleedings where a shorter DAPT duration or no DAPT treatment may be appropriate. However, many of these patients had a high cardiovascular disease risk profile at baseline, suggesting a potential benefit of a longer DAPT treatment duration and more frequent use of beta-blockers, ACE inhibitors, and statins.

Thus, potentially there exists a risk-treatment mismatch with treatment being withheld from patients who might similar or more benefit of longer DAPT.

Comparison of adherence to different DAPT alternatives

A direct comparison of adherence and treatment length between the different DAPT alternatives after MI is complex because the treatments in clinical practice are prescribed to different patient populations. Even in comparable populations, it is difficult to standardize adherence in a multivariable model as underlying factors (such as tablet pack size and daily dosing patterns) may influence treatment length. Similarly, it is difficult to assess how these underlying factors influence the risk of having a calculated treatment break of 30 days.

Prasugrel is prescribed almost entirely for patients with PCI, whereas clopidogrel and ticagrelor are prescribed irrespective of PCI status. In patients with PCI, the adherence patterns did not differ between the respective DAPTs, whereas non-PCI patients had a generally shorter treatment length and those prescribed ticagrelor showed an increased risk of early treatment break compared with patients prescribed clopidogrel; some of these patients (11%) were switched to clopidogrel. We did not have access to data that would provide reasons for this shorter treatment length or treatment switch, such as if this switch was done in a hospital setting, by general practitioners, or in certain geographical locations. Moreover, a relatively large proportion (18%) of patients not undergoing PCI were already on clopidogrel before their MI event, indicating an underlying long term use not associated with the MI which may explain the longer observed treatment length in this group. In addition, it seems that a larger proportion of clopidogrel patients, both with and without PCI, are treated for more than 12 months after MI.

Strength and Limitations

Our data set is uniquely placed to examine DAPT adherence because it includes nationwide data from all patients hospitalized in Denmark for MI, allowing analyses on a complete and unselected cohort of patients. This reduces potential problems arising from selection bias due to inclusion of selected hospitals, regions, or healthcare insurance systems. We believe our results may be generalized to

societies with healthcare systems comparable to the Danish. However, the present study design also comes with certain limitations. A register-based analysis relies on ICD-10 codes for morbidity data and therefore, the possibility of coding errors cannot be ruled out. Therefore, patients with unstable angina pectoris diagnose was not included and sub-coding into STEMI and NSTEMI was not performed. However, the diagnosis of MI in the Danish National Patient Registry has previously been shown to have both high sensitivity and high specificity [29]. Further, treatment guidelines for DAPT initiation and treatment duration do not differ between STEMI and NSTEMI[5, 6].

Because our study is based on central registry data collected primarily for administrative purposes, it is not possible to include clinical data on smoking pattern, weight, blood pressure, laboratory data or socio economic status. Furthermore, data on events (recurrent MI, elective PCI, bleedings) during follow-up that might influence treatment length were not included in the current analysis because of the complexity of different patient baseline risks for the DAPTs.

Conclusions

The results from the present study show that the treatment of MI patients in Denmark has undergone major changes during 2009 to 2012. More patients undergo invasive procedures (coronary angiography and PCI), and the DAPT pattern has shifted from merely clopidogrel to different treatments for selected patient populations. The majority of patients are discharged with dual antiplatelet therapy and the overall treatment length is according to guidelines and in line with what has been observed in randomized controlled clinical trials. Still, there is a proportion of patients not undergoing PCI who are discharged without guideline recommended DAPT. If treated with DAPT, they have a shorter treatment length. The present findings may indicate the need for more careful attention with regard to DAPT for MI patients without PCI in Denmark.

Contributors

AG, PH and ME were involved in the study design; AP and AB performed the statistical analyses; AG, PH, TGD, GHG, AP and AB were involved in the interpretation of the results; PH and AG wrote the manuscript and AG, AP, AB, TGD, PH and GHG were involved in the critical comments on the manuscript. Mrs. Sabrina Imeroski has provided editorial assistance in the preparation of the manuscript.

Funding

This work was supported by AstraZeneca (study sponsor). The statistical analysis was agreed on by the study steering committee, and data analysis was performed by the study database owner in collaboration with AstraZeneca. As members of the study steering committee, AstraZeneca took part

in the interpretation of data and the drafting of the manuscript. Dr. Gislason is supported by an unrestricted clinical research scholarship from the Novo Nordisk Foundation.

Competing interests

Pål Hasvold and Thomas G Diness are full time employees at AstraZeneca. Martha Emneus and Anders Green are employed by the Institute of Applied Economics and Health Research. Dr. Gislason reports research grants from AstraZeneca, Pfizer, Bristol-Myers Squibb and Bayer. The authors report no other conflicts of interest in this work. Dr. Pottegård reports funding from Servier, Boehringer-Ingelheim, Astellas, AstraZeneca, Almirall and Alcon.

Data sharing statement

No additional data are available

REFERENCES

1. Dudas K, Lappas G, Rosengren A. Long-term prognosis after hospital admission for acute myocardial infarction from 1987 to 2006. *Int J Cardiol* 2012;155:400-405.
2. Fox KAA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *Br Med J* 2006;333:1091–1094.
3. Gulliksson M, Wedel H, Köster M, et al. Hazard function and secular trends in the risk of recurrent acute myocardial infarction: 30 years of follow-up of more than 775 000 incidents. *Circ Cardiovasc Qual Outcomes* 2009;2:178-185.
4. Jernberg T, Johanson P, Held C, et al. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. *JAMA* 2011;305:1677–1684.
5. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999-3054.
6. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Task force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *Eur Heart J* 2012;33:2569-2619.
7. Sørensen R, Gislason GH, Fosbøl EL, et al. Initiation and persistence with clopidogrel treatment after acute myocardial infarction: a nationwide study. *Br J Clin Pharmacol* 2008;66:875-884.
8. EMA (2015-08-11) Ticagrelor (Brilique) Summary of product characteristics. European Medicines Agency. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001241/WC500100494.pdf. Accessed 01.09.2015.
9. EMEA (2014-02-17) Prasugrel (Efient) Summary of product characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000984/WC500021971.pdf. Accessed 01.06.2015.
10. The national Danish ACS guidelines. Available at: http://nbv.cardio.dk/. Accessed 01.06.2015.
11. Thygesen LC, Ersbøll AK. Danish population-based registers for public health and health-related welfare research: introduction to the supplement. *Scand J Public Health* 2011;39:8–10.

12. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39:38–41.
13. Anatomic Therapeutic Chemical (ATC) index. Available at: www.whocc.no/filearchive/publications/1_2013guidelines.pdf. Accessed 01.06.2015
14. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30–33.
15. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39:22–25.
16. Thygesen LC, Daasnes C, Thaulow I, et al. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011;39:12–16.
17. Nordic Medico-Statistical Committee: Classification of Surgical Procedures, version 1.15. Copenhagen, Denmark 2010: Publication 93.
18. Gislason GH, Rasmussen JN, Abildstrøm SZ, et al. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J* 2006;27:1153-1158.
19. Mårtensson S, Gyrd-Hansen D, Prescott E, et al. Trends in time to invasive examination and treatment from 2001 to 2009 in patients admitted first time with non-ST elevation myocardial infarction or unstable angina in Denmark. *BMJ Open* 2014;9:e004052.
20. Fokkema ML, James SK, Albertsson P, et al. Population trends in percutaneous coronary intervention: 20-year results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). *J Am Coll Cardiol* 2013;61:1222-1230.
21. Vamos EP, Millett C, Parsons C, et al. Nationwide study on trends in hospital admissions for major cardiovascular events and procedures among people with and without diabetes in England, 2004-2009. *Diabetes Care* 2012;35:265-272.
22. SWEDEHEART 2014 Annual Report (English edition). http://www.ucr.uu.se/swedeheart/index.php/arsrapporter. Accessed 18.05.2015.
23. Erne P, Gutzwiller F, Urban P, et al. Characteristics and outcome in acute coronary syndrome patients with and without established modifiable cardiovascular risk factors: Insights from the nationwide AMIS Plus Registry 1997-2010. *Am J Cardiol* 2013;111:202-207.
24. Bajaj RR, Goodman SG, Yan RT, et al. Treatment and outcomes of patients with suspected acute coronary syndromes in relation to initial diagnostic impressions (insights from the Canadian Global Registry of Acute Coronary Events [GRACE] and Canadian Registry of Acute Coronary Events [CANRACE]). *Am J Cardiol* 2013;111:202-207.
25. Jortveit J, Govatsmark RE, Digre TA, et al. Myocardial infarction in Norway in 2013. *Tidsskr Nor Laegeforen* 2014;134:1841-1846.

26. Jernberg T, Hasvold P, Henriksson M, et al. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J* 2015;36:1163-1170.
27. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001-2015.
28. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-1057.
29. Schmidt M, Schmidt SAJ, Sandegaard JL, et al. The Danish National Patient Registry: A Review of Content, Data Quality, and Research Potential. *Clin Epidemiol* 2015;7:449–90.

FIGURE LEGENDS

Figure 1 Proportion of first-time MI patients discharged alive with or without PCI and prescribed different types of dual antiplatelet therapy or no dual antiplatelet therapy 2009-2012

Figure 2 Persistence with different dual antiplatelet therapy in first-time MI patients with or without PCI 2009-2012

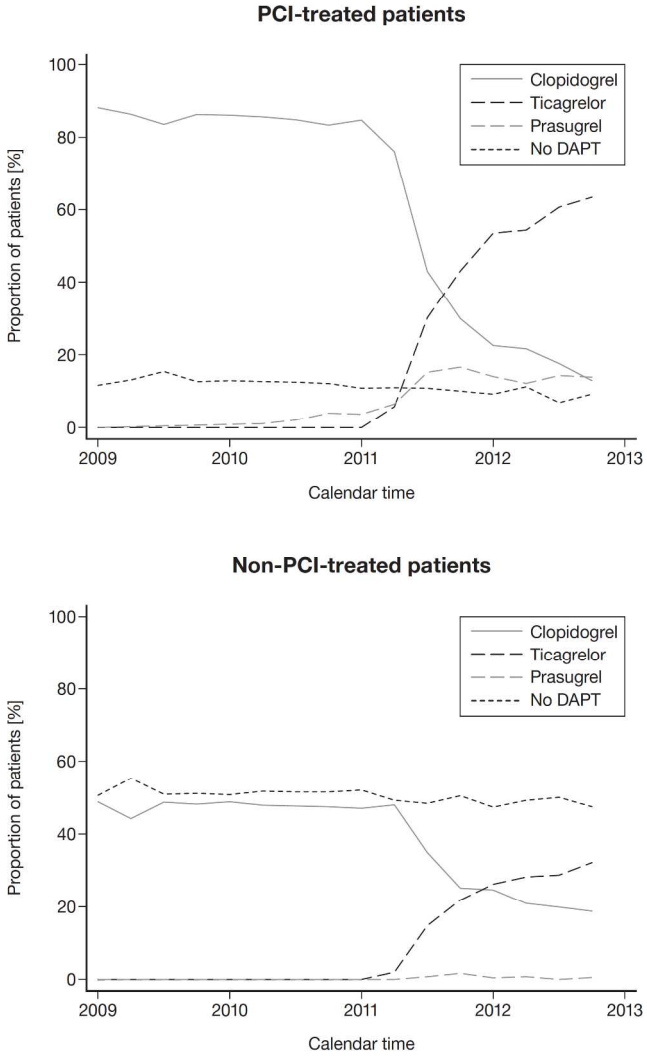

Figure 1 Proportion of first-time MI patients discharged alive with or without PCI and prescribed different types of dual antiplatelet therapy or no dual antiplatelet therapy 2009-2012
297x420mm (300 x 300 DPI)

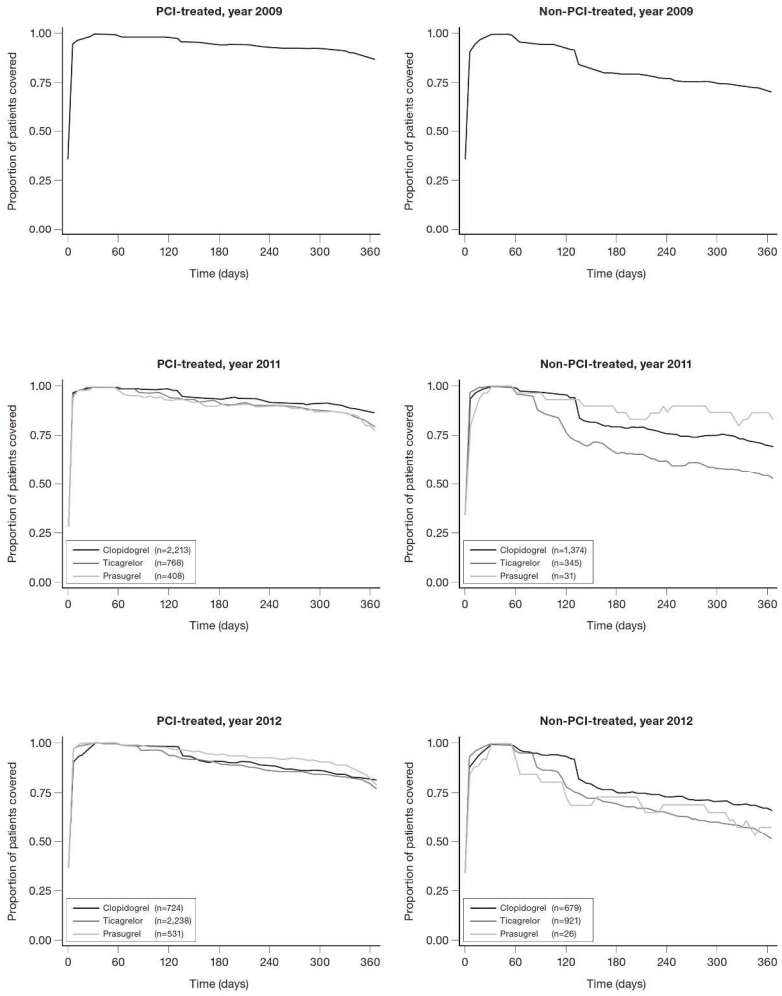

Figure 2 Persistence with different dual antiplatelet therapy in first-time MI patients with or without PCI 2009-2012
297x420mm (300 x 300 DPI)

Green et al.: "Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction – a Danish nationwide population based cohort study"

Appendix A: ICD10 and ATC codes used for the identification of conditions and diseases

Disease/conditions	Codes
Heart failure	I11.0, I13.0, I13.2, I50
Ischaemic heart disease	I21-I25
Previous myocardial infarctions	I21–I23
Previous unstable angina pectoris	I20.0
Peripheral arterial disease	I70, I71, I74
Stroke total	I60–I66 and G45
Non-ischaemic stroke	I60, I61, I62.0, I62
Ischaemic stroke	I63-I66 and G45
Atrial fibrillation	I48
Chronic renal dysfunction	I15.0, I15.1,N03, N04, N05, N11, N18.4, N18.5, Q60, Q61, Z49.1, Z99.2
Diabetes mellitus	E10-E14 and/or ATC A10
Major bleeding	D62.9, I60, I61, I62, I85.0, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0, K92.1, K92.2.
Moderate and severe liver disease	K71-K719, K721, K730-K768, R18
Bleeding diathesis/coagulation disease	D66, D67, D68, D68.0, D681, D68.2, D68.3, D68.4, D68.8, D68.9, D69, D69.1, D69.3, D69.4, D69.5, D69.6
Cancer	C00-C99

Appendix B: ATC codes used for the identification of drug treatment

Drug	Code
ACE-inhibitor	C09A/B
ARB	C09C/D
Beta-blocker	C07
Calcium channel blocker	C08
Insulin	A10A
Oral antidiabetic	A10B
Proton pump inhibitor	A02B C
Statin	C10AA
Warfarin/OAC	B01AA, B01AE, B01AF
NSAIDS	M01A
SSRI	N06A B

Green et al.:

Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction – a Danish nationwide population based cohort study

Supplementary tables

Supplementary Table 1 Baseline demographic and clinical characteristics for the total first-time MI population (2009-2012, incl.)

	Patients with PCI (N=14852, 52%)					Patients without PCI (N=13597, 48%)				
	All patients n=14852	**Clopidogrel n=9140**	**Ticagrelor n=2991**	**Prasugrel n=1030**	**No DAPT n=1691**	**All patients n=13597**	**Clopidogrel n=5513**	**Ticagrelor n=1221**	**Prasugrel n=62**	**No DAPT n=6801**
Age [median (IQR)]	65 (55 - 74)	65 (56 - 74)	65 (55 - 73)	60 (51 - 67)	67 (58 - 75)	74 (63 - 83)	74 (64 - 83)	71 (61 - 80)	60 (49 - 67)	74 (62 - 83)
Males	10,848 (73.0%)	6,642 (72.7%)	2,161 (72.3%)	833 (80.9%)	1,212 (71.7%)	7,358 (54.1%)	2,985 (54.1%)	662 (54.2%)	42 (67.7%)	3,669 (53.9%)
Type of hospital (at index MI event)										
Local hospital	3,797 (25.6%)	2,478 (27.1%)	707 (23.6%)	132 (12.8%)	480 (28.4%)	5,490 (40.4%)	2,074 (37.6%)	404 (33.1%)	13 (21.0%)	2,999 (44.1%)
Main regional hospital	5,463 (36.8%)	3,165 (34.6%)	1,331 (44.5%)	431 (41.8%)	536 (31.7%)	4,647 (34.2%)	2,083 (37.8%)	564 (46.2%)	24 (38.7%)	1,976 (29.1%)
Tertiary cardiac hospital	5,592 (37.7%)	3,497 (38.3%)	953 (31.9%)	467 (45.3%)	675 (39.9%)	3,460 (25.4%)	1,356 (24.6%)	253 (20.7%)	25 (40.3%)	1,826 (26.8%)
Procedures (at index event)										
CABG	328 (2.2%)	177 (1.9%)	28 (0.9%)	(n<=5)	119 (7.0%)	1,727 (12.7%)	660 (12.0%)	165 (13.5%)	(n<=5)	898 (13.2%)
Angiography	14,626 (98.5%)	9,009 (98.6%)	2,946 (98.5%)	1,012 (98.3%)	1,659 (98.1%)	7,330 (53.9%)	3,138 (56.9%)	865 (70.8%)	36 (58.1%)	3,291 (48.4%)
Previous diagnoses										
Heart failure	358 (2.4%)	211 (2.3%)	49 (1.6%)	12 (1.2%)	86 (5.1%)	1,185 (8.7%)	459 (8.3%)	53 (4.3%)	(n<=5)	671 (9.9%)
Ischaemic heart disease	985 (6.6%)	550 (6.0%)	152 (5.1%)	46 (4.5%)	237 (14.0%)	1,740 (12.8%)	658 (11.9%)	131 (10.7%)	11 (17.7%)	940 (13.8%)
Unstable angina	208 (1.4%)	117 (1.3%)	34 (1.1%)	11 (1.1%)	46 (2.7%)	365 (2.7%)	132 (2.4%)	15 (1.2%)	5 (8.1%)	213 (3.1%)
Peripheral arterial disease	442 (3.0%)	263 (2.9%)	67 (2.2%)	21 (2.0%)	91 (5.4%)	945 (7.0%)	397 (7.2%)	73 (6.0%)	(n<=5)	474 (7.0%)
Stroke total	520 (3.5%)	315 (3.4%)	89 (3.0%)	8 (0.8%)	108 (6.4%)	1,194 (8.8%)	527 (9.6%)	65 (5.3%)	0 (0.0%)	602 (8.9%)
Non-ischaemic stroke	38 (0.3%)	26 (0.3%)	6 (0.2%)	0 (0.0%)	6 (0.4%)	74 (0.5%)	25 (0.5%)	5 (0.4%)	0 (0.0%)	44 (0.6%)
Ischaemic stroke	495 (3.3%)	298 (3.3%)	85 (2.8%)	8 (0.8%)	104 (6.2%)	1,153 (8.5%)	512 (9.3%)	62 (5.1%)	0 (0.0%)	579 (8.5%)
Atrial fibrillation	539 (3.6%)	301 (3.3%)	80 (2.7%)	14 (1.4%)	144 (8.5%)	1,426 (10.5%)	445 (8.1%)	71 (5.8%)	0 (0.0%)	910 (13.4%)
Chronic renal dysfunction	95 (0.6%)	52 (0.6%)	17 (0.6%)	(n<=5)	24 (1.4%)	158 (1.2%)	57 (1.0%)	5 (0.4%)	(n<=5)	94 (1.4%)
Diabetes mellitus	1,871 (12.6%)	1,117 (12.2%)	374 (12.5%)	106 (10.3%)	274 (16.2%)	2,513 (18.5%)	1,048 (19.0%)	200 (16.4%)	9 (14.5%)	1,256 (18.5%)
Major bleeding	359 (2.4%)	226 (2.5%)	59 (2.0%)	12 (1.2%)	62 (3.7%)	713 (5.2%)	248 (4.5%)	41 (3.4%)	(n<=5)	423 (6.2%)
Liver disease	21 (0.1%)	10 (0.1%)	(n<=5)	(n<=5)	7 (0.4%)	23 (0.2%)	5 (0.1%)	(n<=5)	0 (0.0%)	17 (0.2%)
Coagulation disorders	45 (0.3%)	28 (0.3%)	5 (0.2%)	0 (0.0%)	12 (0.7%)	81 (0.6%)	18 (0.3%)	(n<=5)	0 (0.0%)	60 (0.9%)
Cancer	924 (6.2%)	556 (6.1%)	179 (6.0%)	49 (4.8%)	140 (8.3%)	1,330 (9.8%)	490 (8.9%)	116 (9.5%)	0 (0.0%)	724 (10.6%)
Drug use at discharge										
Total number of drugs [median (IQR)]	3 (1 - 6)	3 (1 - 6)	3 (1 - 6)	2 (0 - 4)	4 (2 - 8)	6 (3 - 10)	6 (3 - 10)	5 (2 - 9)	4 (1 - 7)	6 (3 - 11)
ACE-inhbitors and ARB	8,140 (54.8%)	5,106 (55.9%)	1,536 (51.4%)	538 (52.2%)	960 (56.8%)	7,610 (56.0%)	3,240 (58.8%)	668 (54.7%)	36 (58.1%)	3,666 (53.9%)

Acetyl salicylic acid	14,109 (95.0%)	9,140 (100.0%)	2,991 (100.0%)	1,030 (100.0%)	948 (56.1%)	11,166 (82.1%)	5,513 (100.0%)	1,221 (100.0%)	62 (100.0%)	4,370 (64.3%)
Betablocker	13,065 (88.0%)	8,093 (88.5%)	2,626 (87.8%)	948 (92.0%)	1,398 (82.7%)	9,719 (71.5%)	4,450 (80.7%)	997 (81.7%)	52 (83.9%)	4,220 (62.0%)
Calcium-channel blocker	3,259 (21.9%)	1,987 (21.7%)	646 (21.6%)	161 (15.6%)	465 (27.5%)	4,310 (31.7%)	1,763 (32.0%)	391 (32.0%)	24 (38.7%)	2,132 (31.3%)
Oral antidiabetics and insulin	1,728 (11.6%)	1,034 (11.3%)	355 (11.9%)	95 (9.2%)	244 (14.4%)	2,235 (16.4%)	952 (17.3%)	189 (15.5%)	9 (14.5%)	1,085 (16.0%)
Proton pump inhibitors	4,092 (27.6%)	2,433 (26.6%)	932 (31.2%)	204 (19.8%)	523 (30.9%)	5,151 (37.9%)	1,977 (35.9%)	429 (35.1%)	19 (30.6%)	2,726 (40.1%)
Statins	14,131 (95.1%)	8,748 (95.7%)	2,894 (96.8%)	1,011 (98.2%)	1,478 (87.4%)	9,599 (70.6%)	4,531 (82.2%)	1,062 (87.0%)	57 (91.9%)	3,949 (58.1%)
Anticoagulant	913 (6.1%)	488 (5.3%)	127 (4.2%)	35 (3.4%)	263 (15.6%)	1,742 (12.8%)	395 (7.2%)	92 (7.5%)	(n<=5)	1,254 (18.4%)
NSAIDs	2,562 (17.3%)	1,606 (17.6%)	506 (16.9%)	152 (14.8%)	298 (17.6%)	2,506 (18.4%)	1,005 (18.2%)	226 (18.5%)	12 (19.4%)	1,263 (18.6%)
Time until $P2Y_{12}$ antagonist prescription claimed										
Prior to MI	564 (3.8%)	349 (3.8%)	103 (3.4%)	36 (3.5%)	76 (4.5%)	704 (5.2%)	449 (8.1%)	60 (4.9%)	6 (9.7%)	189 (2.8%)
1-7 days	13,083 (88.1%)	8,512 (93.1%)	2,838 (94.9%)	977 (94.9%)	756 (44.7%)	6,589 (48.5%)	4,724 (85.7%)	1,114 (91.2%)	52 (83.9%)	699 (10.3%)
8-14 days	141 (0.9%)	94 (1.0%)	20 (0.7%)	11 (1.1%)	16 (0.9%)	205 (1.5%)	160 (2.9%)	25 (2.0%)	0 (0.0%)	20 (0.3%)
15-30 days	246 (1.7%)	185 (2.0%)	30 (1.0%)	6 (0.6%)	25 (1.5%)	238 (1.8%)	180 (3.3%)	22 (1.8%)	(n<=5)	32 (0.5%)
No prescription	818 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	818 (48.4%)	5,861 (43.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5,861 (86.2%)

Numbers in parentheses are percentages of total number of patients in the group; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; IQR, interquartile range; Local hospital, hospital without catheterization laboratory; Main regional hospital, hospital with catheterization laboratory; Tertiary cardiac hospital, university hospital with catheterization laboratory; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

Supplementary Table 2 Baseline demographic and clinical characteristics for the 2010 first-time MI population

	Patients with PCI (N=3673, 49%)					Patients without PCI (N=3754, 51%)				
	All patients n=3673	**Clopidogrel n=3127**	**Ticagrelor n=0**	**Prasugrel n=79**	**No DAPT n=467**	**All patients n=3754**	**Clopidogrel n=1830**	**Ticagrelor n=0**	**Prasugrel n=5**	**No DAPT n=1919**
Age [median (IQR)]	65 (56 - 73)	64 (56 - 73)	. (. - .)	61 (53 - 72)	66 (57 - 74)	73 (62 - 83)	73 (63 - 83)	. (. - .)	62 (61 - 65)	73 (61 - 83)
Males	2,682 (73.0%)	2,275 (72.8%)	0 (.%)	66 (83.5%)	341 (73.0%)	2,002 (53.3%)	996 (54.4%)	0 (.%)	(n<=5)	1,002 (52.2%)
Type of hospital (at index MI event)										
Local hospital	915 (24.9%)	792 (25.3%)	0 (.%)	10 (12.7%)	113 (24.2%)	1,502 (40.0%)	642 (35.1%)	0 (.%)	(n<=5)	857 (44.7%)
Main regional hospital	1,337 (36.4%)	1,178 (37.7%)	0 (.%)	21 (26.6%)	138 (29.6%)	1,280 (34.1%)	730 (39.9%)	0 (.%)	(n<=5)	549 (28.6%)
Tertiary cardiac hospital	1,421 (38.7%)	1,157 (37.0%)	0 (.%)	48 (60.8%)	216 (46.3%)	972 (25.9%)	458 (25.0%)	0 (.%)	(n<=5)	513 (26.7%)
Procedures (at index event)										
CABG	73 (2.0%)	43 (1.4%)	0 (.%)	0 (0.0%)	30 (6.4%)	417 (11.1%)	217 (11.9%)	0 (.%)	0 (0.0%)	200 (10.4%)
Angiography	3,620 (98.6%)	3,084 (98.6%)	0 (.%)	76 (96.2%)	460 (98.5%)	1,983 (52.8%)	1,094 (59.8%)	0 (.%)	(n<=5)	888 (46.3%)
Previous diagnoses										
Heart failure	89 (2.4%)	68 (2.2%)	0 (.%)	(n<=5)	20 (4.3%)	332 (8.8%)	136 (7.4%)	0 (.%)	0 (0.0%)	196 (10.2%)
Ischaemic heart disease	244 (6.6%)	176 (5.6%)	0 (.%)	9 (11.4%)	59 (12.6%)	466 (12.4%)	208 (11.4%)	0 (.%)	(n<=5)	257 (13.4%)
Unstable angina	51 (1.4%)	35 (1.1%)	0 (.%)	(n<=5)	13 (2.8%)	117 (3.1%)	41 (2.2%)	0 (.%)	0 (0.0%)	76 (4.0%)
Peripheral arterial disease	110 (3.0%)	90 (2.9%)	0 (.%)	(n<=5)	19 (4.1%)	262 (7.0%)	126 (6.9%)	0 (.%)	0 (0.0%)	136 (7.1%)
Stroke total	133 (3.6%)	106 (3.4%)	0 (.%)	0 (0.0%)	27 (5.8%)	346 (9.2%)	162 (8.9%)	0 (.%)	0 (0.0%)	184 (9.6%)
Non-ischaemic stroke	9 (0.2%)	7 (0.2%)	0 (.%)	0 (0.0%)	(n<=5)	24 (0.6%)	9 (0.5%)	0 (.%)	0 (0.0%)	15 (0.8%)
Ischaemic stroke	127 (3.5%)	101 (3.2%)	0 (.%)	0 (0.0%)	26 (5.6%)	332 (8.8%)	156 (8.5%)	0 (.%)	0 (0.0%)	176 (9.2%)
Atrial fibrillation	122 (3.3%)	93 (3.0%)	0 (.%)	(n<=5)	27 (5.8%)	389 (10.4%)	137 (7.5%)	0 (.%)	0 (0.0%)	252 (13.1%)
Chronic renal dysfunction	24 (0.7%)	21 (0.7%)	0 (.%)	0 (0.0%)	(n<=5)	39 (1.0%)	17 (0.9%)	0 (.%)	0 (0.0%)	22 (1.1%)
Diabetes mellitus	465 (12.7%)	392 (12.5%)	0 (.%)	13 (16.5%)	60 (12.8%)	697 (18.6%)	336 (18.4%)	0 (.%)	0 (0.0%)	361 (18.8%)
Major bleeding	88 (2.4%)	69 (2.2%)	0 (.%)	(n<=5)	17 (3.6%)	205 (5.5%)	88 (4.8%)	0 (.%)	(n<=5)	116 (6.0%)
Liver disease	6 (0.2%)	(n<=5)	0 (.%)	0 (0.0%)	(n<=5)	5 (0.1%)	(n<=5)	0 (.%)	0 (0.0%)	(n<=5)
Coagulation disorders	12 (0.3%)	10 (0.3%)	0 (.%)	0 (0.0%)	(n<=5)	26 (0.7%)	9 (0.5%)	0 (.%)	0 (0.0%)	17 (0.9%)
Cancer	224 (6.1%)	188 (6.0%)	0 (.%)	(n<=5)	33 (7.1%)	341 (9.1%)	153 (8.4%)	0 (.%)	0 (0.0%)	188 (9.8%)
Drug use at discharge										
Total number of drugs [median (IQR)]	3 (1 - 6)	3 (1 - 6)	. (. - .)	4 (1 - 7)	4 (1 - 8)	6 (3 - 10)	6 (3 - 10)	. (. - .)	3 (2 - 4)	6 (3 - 11)
ACE-inhbitors and ARB	2,051 (55.8%)	1,737 (55.5%)	0 (.%)	50 (63.3%)	264 (56.5%)	2,075 (55.3%)	1,067 (58.3%)	0 (.%)	(n<=5)	1,004 (52.3%)
Acetyl salicylic acid	3,485 (94.9%)	3,127 (100.0%)	0 (.%)	79 (100.0%)	279 (59.7%)	3,044 (81.1%)	1,830 (100.0%)	0 (.%)	5 (100.0%)	1,209 (63.0%)
Betablocker	3,239 (88.2%)	2,774 (88.7%)	0 (.%)	66 (83.5%)	399 (85.4%)	2,659 (70.8%)	1,496 (81.7%)	0 (.%)	5 (100.0%)	1,158 (60.3%)
Calcium-channel blocker	784 (21.3%)	656 (21.0%)	0 (.%)	23 (29.1%)	105 (22.5%)	1,180 (31.4%)	589 (32.2%)	0 (.%)	(n<=5)	590 (30.7%)

Oral antidiabetics and insulin	428 (11.7%)	362 (11.6%)	0 (.%)	11 (13.9%)	55 (11.8%)	611 (16.3%)	302 (16.5%)	0 (.%)	0 (0.0%)	309 (16.1%)
Proton pump inhibitors	912 (24.8%)	755 (24.1%)	0 (.%)	23 (29.1%)	134 (28.7%)	1,340 (35.7%)	613 (33.5%)	0 (.%)	(n<=5)	724 (37.7%)
Statins	3,517 (95.8%)	3,012 (96.3%)	0 (.%)	77 (97.5%)	428 (91.6%)	2,596 (69.2%)	1,514 (82.7%)	0 (.%)	5 (100.0%)	1,077 (56.1%)
Anticoagulant	189 (5.1%)	130 (4.2%)	0 (.%)	(n<=5)	55 (11.8%)	454 (12.1%)	119 (6.5%)	0 (.%)	0 (0.0%)	335 (17.5%)
NSAIDs	677 (18.4%)	576 (18.4%)	0 (.%)	9 (11.4%)	92 (19.7%)	734 (19.6%)	369 (20.2%)	0 (.%)	0 (0.0%)	365 (19.0%)
Time until $P2Y_{12}$ antagonist prescription claimed										
Prior to MI	131 (3.6%)	108 (3.5%)	0 (.%)	(n<=5)	19 (4.1%)	139 (3.7%)	101 (5.5%)	0 (.%)	0 (0.0%)	38 (2.0%)
1-7 days	3,207 (87.3%)	2,948 (94.3%)	0 (.%)	72 (91.1%)	187 (40.0%)	1,814 (48.3%)	1,636 (89.4%)	0 (.%)	(n<=5)	174 (9.1%)
8-14 days	29 (0.8%)	25 (0.8%)	0 (.%)	(n<=5)	(n<=5)	52 (1.4%)	44 (2.4%)	0 (.%)	0 (0.0%)	8 (0.4%)
15-30 days	53 (1.4%)	46 (1.5%)	0 (.%)	(n<=5)	5 (1.1%)	59 (1.6%)	49 (2.7%)	0 (.%)	(n<=5)	9 (0.5%)
No prescription	253 (6.9%)	0 (0.0%)	0 (.%)	0 (0.0%)	253 (54.2%)	1,690 (45.0%)	0 (0.0%)	0 (.%)	0 (0.0%)	1,690 (88.1%)

Numbers in parentheses are percentages of total number of patients in the group; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; IQR, interquartile range; Local hospital, hospital without catheterization laboratory; Main regional hospital, hospital with catheterization laboratory; Tertiary cardiac hospital, university hospital with catheterization laboratory; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs

Supplementary Table 3 Baseline demographic and clinical characteristics for the 2011 first-time MI population

	Patients with PCI (N=3782, 53%)					Patients without PCI (N=3334, 47%)				
	All patients n=3782	**Clopidogrel n=2204**	**Ticagrelor n=766**	**Prasugrel n=408**	**No DAPT n=404**	**All patients n=3334**	**Clopidogrel n=1327**	**Ticagrelor n=332**	**Prasugrel n=30**	**No DAPT n=1645**
Age [median (IQR)]	65 (55 - 74)	66 (56 - 75)	64 (55 - 73)	61 (51 - 67)	67 (59 - 74.5)	74 (63 - 83)	75 (65 - 84)	72 (62 - 81.5)	60.5 (51 - 67)	73 (63 - 83)
Males	2,744 (72.6%)	1,590 (72.1%)	554 (72.3%)	320 (78.4%)	280 (69.3%)	1,803 (54.1%)	708 (53.4%)	179 (53.9%)	20 (66.7%)	896 (54.5%)
Type of hospital (at index MI event)										
Local hospital	906 (24.0%)	590 (26.8%)	157 (20.5%)	50 (12.3%)	109 (27.0%)	1,354 (40.6%)	520 (39.2%)	96 (28.9%)	5 (16.7%)	733 (44.6%)
Main regional hospital	1,409 (37.3%)	781 (35.4%)	315 (41.1%)	171 (41.9%)	142 (35.1%)	1,132 (34.0%)	497 (37.5%)	162 (48.8%)	15 (50.0%)	458 (27.8%)
Tertiary cardiac hospital	1,467 (38.8%)	833 (37.8%)	294 (38.4%)	187 (45.8%)	153 (37.9%)	848 (25.4%)	310 (23.4%)	74 (22.3%)	10 (33.3%)	454 (27.6%)
Procedures (at index event)										
CABG	86 (2.3%)	47 (2.1%)	8 (1.0%)	(n<=5)	29 (7.2%)	449 (13.5%)	169 (12.7%)	35 (10.5%)	(n<=5)	242 (14.7%)
Angiography	3,712 (98.1%)	2,168 (98.4%)	746 (97.4%)	399 (97.8%)	399 (98.8%)	1,882 (56.4%)	779 (58.7%)	226 (68.1%)	18 (60.0%)	859 (52.2%)
Previous diagnoses										
Heart failure	89 (2.4%)	49 (2.2%)	17 (2.2%)	(n<=5)	19 (4.7%)	288 (8.6%)	110 (8.3%)	15 (4.5%)	(n<=5)	161 (9.8%)
Ischaemic heart disease	276 (7.3%)	134 (6.1%)	63 (8.2%)	20 (4.9%)	59 (14.6%)	395 (11.8%)	149 (11.2%)	35 (10.5%)	6 (20.0%)	205 (12.5%)
Unstable angina	57 (1.5%)	25 (1.1%)	14 (1.8%)	6 (1.5%)	12 (3.0%)	66 (2.0%)	23 (1.7%)	(n<=5)	(n<=5)	37 (2.2%)
Peripheral arterial disease	130 (3.4%)	70 (3.2%)	24 (3.1%)	14 (3.4%)	22 (5.4%)	231 (6.9%)	96 (7.2%)	21 (6.3%)	(n<=5)	113 (6.9%)
Stroke total	131 (3.5%)	75 (3.4%)	28 (3.7%)	(n<=5)	24 (5.9%)	276 (8.3%)	126 (9.5%)	26 (7.8%)	0 (0.0%)	124 (7.5%)
Non-ischaemic stroke	13 (0.3%)	12 (0.5%)	0 (0.0%)	0 (0.0%)	(n<=5)	14 (0.4%)	5 (0.4%)	(n<=5)	0 (0.0%)	7 (0.4%)
Ischaemic stroke	123 (3.3%)	68 (3.1%)	28 (3.7%)	(n<=5)	23 (5.7%)	269 (8.1%)	124 (9.3%)	25 (7.5%)	0 (0.0%)	120 (7.3%)
Atrial fibrillation	144 (3.8%)	71 (3.2%)	25 (3.3%)	7 (1.7%)	41 (10.1%)	353 (10.6%)	116 (8.7%)	24 (7.2%)	0 (0.0%)	213 (12.9%)
Chronic renal dysfunction	25 (0.7%)	12 (0.5%)	6 (0.8%)	(n<=5)	6 (1.5%)	37 (1.1%)	12 (0.9%)	(n<=5)	0 (0.0%)	24 (1.5%)
Diabetes mellitus	507 (13.4%)	284 (12.9%)	102 (13.3%)	40 (9.8%)	81 (20.0%)	641 (19.2%)	262 (19.7%)	66 (19.9%)	5 (16.7%)	308 (18.7%)
Major bleeding	91 (2.4%)	56 (2.5%)	18 (2.3%)	(n<=5)	14 (3.5%)	180 (5.4%)	64 (4.8%)	11 (3.3%)	0 (0.0%)	105 (6.4%)
Liver disease	(n<=5)	(n<=5)	0 (0.0%)	0 (0.0%)	(n<=5)	7 (0.2%)	(n<=5)	0 (0.0%)	0 (0.0%)	6 (0.4%)
Coagulation disorders	10 (0.3%)	5 (0.2%)	(n<=5)	0 (0.0%)	(n<=5)	17 (0.5%)	(n<=5)	(n<=5)	0 (0.0%)	12 (0.7%)
Cancer	236 (6.2%)	144 (6.5%)	37 (4.8%)	20 (4.9%)	35 (8.7%)	345 (10.3%)	135 (10.2%)	35 (10.5%)	0 (0.0%)	175 (10.6%)
Drug use at discharge										
Total number of drugs [median (IQR)]	3 (1 - 6)	3 (1 - 6)	3 (1 - 7)	2 (0 - 5)	5 (2 - 8)	6 (3 - 10)	6 (3 - 10)	5 (2.5 - 9)	4.5 (1 - 7)	7 (3 - 11)
ACE-inhbitors and ARB	2,087 (55.2%)	1,243 (56.4%)	403 (52.6%)	214 (52.5%)	227 (56.2%)	1,897 (56.9%)	785 (59.2%)	195 (58.7%)	17 (56.7%)	900 (54.7%)
Acetyl salicylic acid	3,600 (95.2%)	2,204 (100.0%)	766 (100.0%)	408 (100.0%)	222 (55.0%)	2,728 (81.8%)	1,327 (100.0%)	332 (100.0%)	30 (100.0%)	1,039 (63.2%)
Betablocker	3,311 (87.5%)	1,940 (88.0%)	676 (88.3%)	368 (90.2%)	327 (80.9%)	2,398 (71.9%)	1,068 (80.5%)	267 (80.4%)	27 (90.0%)	1,036 (63.0%)
Calcium-channel blocker	859 (22.7%)	492 (22.3%)	186 (24.3%)	59 (14.5%)	122 (30.2%)	1,091 (32.7%)	464 (35.0%)	95 (28.6%)	10 (33.3%)	522 (31.7%)

Oral antidiabetics and insulin	467 (12.3%)	266 (12.1%)	97 (12.7%)	35 (8.6%)	69 (17.1%)	561 (16.8%)	235 (17.7%)	62 (18.7%)	5 (16.7%)	259 (15.7%)
Proton pump inhibitors	1,077 (28.5%)	632 (28.7%)	255 (33.3%)	70 (17.2%)	120 (29.7%)	1,324 (39.7%)	487 (36.7%)	121 (36.4%)	6 (20.0%)	710 (43.2%)
Statins	3,593 (95.0%)	2,112 (95.8%)	739 (96.5%)	399 (97.8%)	343 (84.9%)	2,336 (70.1%)	1,076 (81.1%)	277 (83.4%)	29 (96.7%)	954 (58.0%)
Anticoagulant	238 (6.3%)	121 (5.5%)	35 (4.6%)	16 (3.9%)	66 (16.3%)	447 (13.4%)	102 (7.7%)	30 (9.0%)	(n<=5)	314 (19.1%)
NSAIDs	658 (17.4%)	382 (17.3%)	142 (18.5%)	60 (14.7%)	74 (18.3%)	646 (19.4%)	256 (19.3%)	71 (21.4%)	(n<=5)	315 (19.1%)
Time until $P2Y_{12}$ antagonist prescription claimed										
Prior to MI	148 (3.9%)	90 (4.1%)	24 (3.1%)	15 (3.7%)	19 (4.7%)	192 (5.8%)	116 (8.7%)	19 (5.7%)	5 (16.7%)	52 (3.2%)
1-7 days	3,389 (89.6%)	2,085 (94.6%)	727 (94.9%)	387 (94.9%)	190 (47.0%)	1,689 (50.7%)	1,150 (86.7%)	308 (92.8%)	23 (76.7%)	208 (12.6%)
8-14 days	28 (0.7%)	13 (0.6%)	9 (1.2%)	(n<=5)	(n<=5)	38 (1.1%)	30 (2.3%)	(n<=5)	0 (0.0%)	(n<=5)
15-30 days	29 (0.8%)	16 (0.7%)	6 (0.8%)	(n<=5)	(n<=5)	40 (1.2%)	31 (2.3%)	(n<=5)	(n<=5)	6 (0.4%)
No prescription	188 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	188 (46.5%)	1,375 (41.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1,375 (83.6%)

Numbers in parentheses are percentages of total number of patients in the group; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; IQR, interquartile range; Local hospital, hospital without catheterization laboratory; Main regional hospital, hospital with catheterization laboratory; Tertiary cardiac hospital, university hospital with catheterization laboratory; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

STROBE Statement—checklist of items that should be included in reports of observational studies
Green et al.: "Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction – a Danish nationwide population based cohort study"
N.A.: Not applicable

	Item No	Recommendation
Title and abstract	1 P 1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	P 2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 P 3-4	Explain the scientific background and rationale for the investigation being reported
Objectives	3 P 4	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 P 4-5	Present key elements of study design early in the paper
Setting	5 P 4-5K	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 P 6 (cohort study) N.A.	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7 P 5	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* P 4-5	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 P 6 (sensitivity analyses)	Describe any efforts to address potential sources of bias
Study size	10 N.A.	Explain how the study size was arrived at
Quantitative variables	11 N.A.	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 P 6 P. 5	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was

	addressed
N.A.	*Case-control study*—If applicable, explain how matching of cases and controls was addressed
N.A.	*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
P 6	(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13* N.A.	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* Tables 1,2; Suppl.tables 1,2,3	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* P 12, Figs 1, 2, Tab 3	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 Tab 4	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
	Not applicable	(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 N.A.	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 P 15	Summarise key results with reference to study objectives
Limitations	19 P 17	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 P 17	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 P 16-17	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 P 17-18	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.