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Initiation and duration of dual antiplatelet therapy after inpatient percutaneous coronary intervention with stent implantation in Germany: an electronic healthcare database cohort study

Initiierung und Dauer der dualen Thrombozytenaggregationshemmung nach stationärer perkutaner koronarer Intervention mit Stentimplantation in Deutschland: eine Kohortenstudie auf der Grundlage von Abrechnungsdaten

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ABSTRACT

Background: Studies assessing the routine outpatient dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) in Germany are scarce. The aim of this study was (i) to investigate the initiation and duration of DAPT after inpatient PCI with stent implantation in Germany, and (ii) to identify factors associated with DAPT discontinuation during the recommended treatment period.
Methods: This retrospective cohort study was based on data from a large German electronic healthcare database of the years 2004 to 2009. The study population comprised four groups of patients with acute coronary syndrome (ACS) or stable angina pectoris undergoing inpatient PCI with either bare metal stent (BMS) or drug eluting stent (DES) implantation between 2005 and 2008. Initiation of outpatient DAPT within a period from 100 days before the PCI to 60 days after the PCI was ascertained. Time until end of treatment was analysed using the Kaplan-Meier method. Factors potentially associated with DAPT discontinuation, like sex, age, cardiovascular comorbidity, contraindications, and other antithrombotic drugs were analysed in a Cox proportional hazard model.
Results: The cohort comprised 37,001 patients. Depending on the type of stent and the indication for the PCI, DAPT was initiated in 85 % (ACS/BMS) and 95 % (AP/DES) of all patients. Of those, 12 % (AP/DES) and 64 % (ACS/BMS) discontinued DAPT during the recommended treatment duration. An age of over 80 years (OR 1.2–1.5 compared to patients aged 0-49 years) and the use of phenprocoumon (OR 2.7–5.0 compared to no phenprocoumon) were associated with an increased risk of DAPT discontinuation.

Abbreviations: ACS, Acute coronary syndrome; AP, Angina pectoris; ASA, Acetylsalicylic acid; ATC, Anatomical-therapeutical-chemical classification; BMS, Bare metal stent; CAD, Coronary artery disease; DAPT, Dual antiplatelet therapy; DDD, Defined daily dose; DES, Drug eluting stent; ESC, European Society of Cardiology; GePaRD, German Pharmacoepidemiological Research Database; PCI, Percutaneous coronary intervention; SHI, Statutory health insurance; VKA, Vitamin K antagonists.

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Conclusions: A high proportion of patients with coronary artery disease undergoing inpatient PCI with stent implantation received DAPT. However, DAPT discontinuation during the recommended time span was frequent, particularly in patients suffering from ACS. On the other hand, especially patients with AP and DES were often treated longer than recommended.

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ZUSAMMENFASSUNG

Hintergrund: Studien, in denen der ambulante Einsatz der dualen Thrombozytenaggregationshemmung (DTAH) nach einer stationären perkutanen koronaren Intervention (PCI) im klinischen Alltag bewertet wird, sind in Deutschland selten. Ziel dieser Studie war es, die Initiierung und die Dauer der DTAH nach stationärer PCI mit Stentimplantation in Deutschland zu untersuchen und Faktoren zu identifizieren, die mit einem Abbruch der DTAH im empfohlenen Therapiezeitraum assoziiert waren.
Methodik: Diese retrospektive Kohortenstudie basiert auf Routinedaten der gesetzlichen Krankenversicherung aus den Jahren 2004 bis 2009. Die Studienpopulation bestand aus vier Gruppen von Patienten mit akutem Koronarsyndrom (ACS) bzw. stabiler Angina pectoris (AP), die sich zwischen 2005 und 2008 einer stationären PCI mit Implantation eines „bare metal stent" (BMS) oder eines „drug eluting stent" (DES) unterzogen. Die Initiierung der ambulanten DTAH wurde innerhalb von 100 Tagen vor und 60 Tagen nach PCI bestimmt. Die Zeit bis zum Abbruch der Therapie wurde mittels Kaplan-Meier-Methode bestimmt. In einem Cox-Regressionsmodell wurde der Einfluss von Geschlecht, Alter, kardiovaskulärer Komorbidität, Kontraindikationen und anderen antithrombotischen Medikamenten auf die Wahrscheinlichkeit eines Therapieabbruchs untersucht.
Ergebnisse: Die Kohorte bestand aus 37.001 Patienten. Je nach Stenttyp und Indikation für die PCI wurde die DTAH in 85 % (ACS/BMS) bzw. 95 % (AP/DES) aller Patienten initiiert. Von diesen beendeten 12 % (ACS/BMS) bzw. 64% (AP/DES) die DTAH noch während des empfohlenen Zeitraums. Ein Alter über 80 Jahren (OR 1,2–1,5 verglichen mit 0- bis 49-jährigen Patienten) und der Gebrauch von Phenprocoumon (OR 2,7–5,0 verglichen mit Patienten ohne Phenprocoumon) waren mit einem erhöhten Risiko für einen Abbruch der DTAH assoziiert.
Schlussfolgerungen: Ein großer Anteil von Patienten erhält nach einer PCI mit Stentimplantation eine DTAH. Dennoch konnte häufig ein Abbruch der DTAH innerhalb des empfohlenen Zeitraums beobachtet werden, besonders bei Patienten mit einem ACS. Auf der anderen Seite werden besonders Patienten mit AP und DES häufiger länger behandelt, als in der Leitlinie empfohlen.

Introduction

Coronary artery disease (CAD) is the most common cause of death in industrialized countries. In 2012, 15% of all deaths occured due to CAD in Germany [1]. The lifetime prevalence of CAD in German individuals aged 65 years or older is 15% and increases with advancing age [2]. Percutaneous coronary interventions (PCIs) are increasingly used in the therapy of CAD. Over the last decade, the number of PCIs in Germany rose from 180,000 in 2000 to over 335,000 in 2010 with an increasing proportion of PCIs with implantation of bare metal stents (BMS) or drug eluting stents (DES) [3–5]. To prevent stent thrombosis after PCI, dual antiplatelet therapy (DAPT) is recommended. This comprises lifelong acetylsalicylic acid (ASA) and a thienopyridine (e.g. clopidogrel or, less commonly, ticlopidine) for a limited period of time [6]. The duration of DAPT currently recommended by the European Society of Cardiology (ESC) depends on the type of stent and the indication for the PCI. In patients with acute coronary syndrome (ACS), DAPT should be given for a period of twelve months after the intervention, independently of the type of the stent. The recommended duration of DAPT after PCI in patients with stable angina pectoris (AP) is one month for BMS and six months for DES. However, during the whole study period the ESC-guideline published in 2005 was valid. The recommendations differed only for patients with ACS, who should get DAPT nine to twelve months instead of twelve months generally. The recommended duration of DAPT after PCI in patients with AP was still one month for BMS and six months for DES [7].

These recommendations are based on the observation that DAPT reduces major adverse cardiac events after PCI in patients with both stable angina and ACS as compared with ASA alone, or ASA in combination with a vitamin-K-antagonist [8]. Treatment with DAPT after PCI with stent implantation is critical to prevent early and late stent thrombosis and in-stent restenosis, which may be caused via intravascular clot formation or intimal hyperplasia on the surface of the stent [9,10]. DAPT discontinuation in the first 30 days after DES implantation was associated with an 8-fold increased risk of stent thrombosis compared to patients without therapy discontinuation [11].

In Germany, only few studies have assessed drug treatment after PCI. These studies were either conducted before the publication of current guidelines [12], only covered drug treatment in the inpatient setting [13], or were limited to a small and regional sample [14].

Up to date evidence from health care services research on medical treatment of patients undergoing PCI is essential to evaluate the adequacy of drug treatment, particularly in the context of an aging society and the associated increasing numbers of patients suffering from CAD.

The aims of this study were to (i) investigate the initiation and duration of outpatient DAPT in patients with ACS or stable AP, undergoing inpatient PCI with stent implantation in Germany and (ii) to identify factors associated with the discontinuation of DAPT.

Methods

Data source

This study was based on data from the German Pharmacoepidemiological Research Database (GePaRD). GePaRD currently comprises claims data from four statutory health insurances (SHIs) including data of more than 20 million insurants. The database has

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been described in detail elsewhere [15–17]. In short, the database contains demographic variables such as age, sex, and region of residence of the insurants. Besides, GePaRD contains information on outpatient physician visits, hospital admissions including diagnoses, treatments and procedures, and outpatient prescriptions of reimbursed drugs. Outpatient prescriptions comprise the dates of prescription and dispensation, the specialty of the prescribing physician, and the pharmaceutical reference number. On the basis of the pharmaceutical reference number, prescriptions can be linked to a pharmaceutical reference database, which includes, among others, information on anatomical-therapeutical-chemical code (ATC-Code), defined daily dose (DDD), packaging size, drug strength, and generic and brand name of the drug.

The SHIs contributing data to the database as well as the governing local or federal authorities needed to approve the use of the data. Due to approval from three SHIs, we were able to include data of more than nine million insurance members during the study period. In accordance with the Code of Social Law (Section 75, Book 10), informed consent of involved insurants was not required. Since the study was based on routinely collected pseudonymized data delivered by the SHIs, a vote of the ethics committee was not needed.

Study design and study population

The study was conducted in a retrospective cohort design and comprised patients with ACS or stable AP, who received inpatient PCI with stent implantation between 2005 and 2008, preceded by a one-year continuous insurance period without inpatient or outpatient PCIs.

Patients without valid information on the year of birth, sex, or region of residence were excluded from the study population. Since this study focussed on outpatient DAPT, patients dying in hospital after PCI, were excluded from the study population.

Cohort entry and cohort exit

Cohort entry was defined as the date of the first PCI between 2005 and 2008 (index-PCI), preceded by a one-year continuous insurance period without inpatient or outpatient PCIs. Patients remained in the cohort until the end of the insurance period (incl. death), the date of the end of the drug therapy or the end of the follow-up (maximum of 365 days after index-PCI) whichever was the earliest.

Ascertainment of interventions and comorbidity

Inpatient PCIs with stent implantation were identified by using the respective codes for the reimbursement of PCIs with BMS implantation, PCIs with DES implantation, PCIs with implantation of BMS for bifurcation lesions, and PCIs with implantation of DES for bifurcation lesions (**supplementary material**).

To describe the study population, a broad range of comorbidities, which are either risk factors for the development of CAD, secondary diseases of CAD, or relevant regarding the drug therapy, were ascertained. Comorbidities of the patients were identified by using confirmed outpatient diagnoses, as well as hospital main discharge and secondary diagnoses in the year prior to the index-PCI. Diagnoses of acute bleeding, renal disease, or liver disease, which are absolute or relative contraindications for the initiation of DAPT, were ascertained in the three months prior to the index-PCI.

Information on the comorbidities of the patients was used to determine whether ACS or stable AP was the indication for index-PCI. The diagnosis dated closest to the index-PCI was defined as the indication for the index-PCI. In case of diagnoses of stable AP and ACS in the same hospital stay, ACS was considered the primary indication for the index-PCI. Depending on the indication for the index-PCI and the type of stent, the study population was divided into four subpopulations: ACS with BMS, ACS with DES, stable AP with BMS, and stable AP with DES. A list of the considered diseases and corresponding ICD-10-GM-codes can be found in the **supplementary material**.

Ascertainment of drug therapy

For each study participant, dispensations of clopidogrel (ATC-code: B01AC04) and ticlopidine (ATC-code: B01AC05) were identified during the follow-up period of the study. The initiation of drug treatment was defined as the first dispensation of clopidogrel or ticlopidine within a period from 100 days before the PCI to 60 days after the PCI. As patients might already have received clopidogrel or ticlopidine due to other indications or due to an elective PCI, DAPT might have been initiated in advance of the studied PCI. Therefore, the time period preceding the PCI was also taken into account when defining the initiation of DAPT, but only if the supply of prescription was high enough to reach the period after PCI. Days between prescription date and PCI were subtracted from the supplied days of a prescription before the PCI. The duration of drug treatment was calculated by multiplying the packaging size by the number of DDD of one tablet.

Continuation of drug treatment was defined as a further dispensation of clopidogrel or ticlopidine during treatment duration or within a period after half of the treatment duration of the previous package. When a further package of clopidogrel or ticlopidine was dispensed during the treatment period covered by the previous dispensation, the overlapping days under treatment were added to the duration of the following dispensation. Drug treatment was considered discontinued if no further dispensation of clopidogrel or ticlopidine occurred during the 1.5 treatment duration of the last prescription. The end of drug therapy was defined as the end of the duration of the last clopidogrel or ticlopidine dispensation.

Other platelet inhibitors such as prasugrel or ticagrelor were not evaluated in our study, as they were not approved during the time period under study. Although low dose ASA is reimbursed in CAD patients, dispensations of ASA are likely underrepresented in German SHI data, since ASA can be bought as an over-the-counter medication. However, since patients who receive clopidogrel or ticlopidine after inpatient PCI are likely to receive also ASA, DAPT was assumed in case of a clopidogrel or ticlopidine dispensation.

The simultaneous use of DAPT and Vitamin K antagonists (VKA) is only recommended for a short period of time and therefore might lead to a discontinuation of DAPT [18]. Therefore use of phenprocoumon (ATC-code: B01AA04) and warfarin (ATC-code: B01AA03) in the last 100 days were included as time-dependent covariables in the multivariable Cox proportional hazards model for discontinuation of DAPT. All other medications which were also considered in the multivariable models were assessed on the basis of dispensations during the year preceding cohort entry.

Statistical analysis

The time until end of treatment was analysed using the Kaplan-Meier method (y-axis shows cumulative probability of discontinuation). Patients who continued with DAPT beyond the recommended period were censored at the end of the insurance period (insurance change or death) or the end of the follow-up, whichever came first. For each of the four subpopulations defined by type of the stent and CAD, a Kaplan-Meier analysis was carried out stratified by age-group (0-49 years, 50-59 years, 60-69 years, 70-79 years, ≥80 years). Differences in time between the age groups were evaluated using the log rank test ($p <= 0.05$).

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Table 1
Characteristics of the cohort.

Characteristics	Stable angina pectoris & bare metal stent (n = 6,845)		Stable angina pectoris & drug eluting stent (n = 4,477)		Acute coronary syndrome & bare metal stent (n = 17,535)		Acute coronary syndrome & drug eluting stent (n = 8,144)	
Age groups (n, %)								
0-49	236	3.4	241	5.4	1,884	10.7	873	10.7
50-59	1,015	14.8	815	18.2	3,763	21.5	1,813	22.3
60-69	2,649	38.7	1,866	41.7	5,738	32.7	2,937	36.1
70-79	2,438	35.6	1,392	31.1	4,673	26.6	2,113	26.2
≥80	507	7.4	163	3.6	1,477	8.4	408	5.0
Age (Mean, SD)	67.4	8.8	65.6	8.8	64.6	11.1	63.7	10.5
Sex (n, %)								
Women	1,115	16.3	665	14.9	3021	17.2	1,329	16.3
Men	5,730	83.7	3,812	85.1	14,514	82.8	6,815	83.7
Mean follow up in days (Mean, SD)	357.7	42.8	360.4	33.8	354.8	51.6	359.4	38.3
Cardiovascular comorbidity (n, %)*								
Atrial fibrillation	1,356	19.8	559	12.5	2,192	12.5	808	9.9
Dyslipidaemia	5,381	78.6	3,650	81.5	13,237	75.5	6,650	81.7
Heart failure	2,214	32.3	1,232	27.5	5478	31.2	2,606	32.0
Hypertension	6,175	90.2	4,022	89.8	14,415	82.2	7,058	86.7
Mechanical heart valve	100	1.5	38	0.8	129	0.8	67	0.8
Other comorbidity (n, %)*								
Deep vein thrombosis	121	1.8	56	1.3	283	1.6	111	1.4
Dementia	105	1.5	50	1.1	324	1.8	104	1.3
Diabetes mellitus	2,031	29.7	1,429	32.0	4,389	25.0	2,389	29.3
Ischaemic stroke	350	5.1	184	4.1	750	4.3	336	4.1
Obesity	1,761	25.7	1,136	25.4	4,031	23.0	1,960	24.1
Contraindications (n, %)*								
Acute haemorrhage	56	0.8	26	0.6	129	0.7	58	0.7
Liver disease	143	2.1	92	2.1	368	2.1	181	2.2
Renal disease	565	8.3	290	6.5	1,042	5.9	541	6.6
Drugs (n, %)*								
Unfractionated heparin	10	0.0	2	0.0	8	0.0	2	0.0
Low molecular weight heparin	570	8.3	135	3.0	633	3.6	197	2.4
Non-steroidal anti-inflammatory drugs	2,242	32.8	1,417	31.7	5,752	32.8	2,614	32.1
Phenprocoumon	508	7.5	152	3.5	692	4.0	206	2.5
Warfarin	5	0.0	2	0.0	8	0.0	3	0.0

* Since patients could have more than one comorbidity, the percentages do not add up to 100%.

In a multivariable Cox proportional hazards model, we determined factors associated with DAPT discontinuation during the recommended treatment duration separately for each subpopulation. Sex, age (ten-year age categories), all comorbidities, contraindications, and drugs (as shown in Table 1) were included as independent variables in the full model. Both, the Kaplan-Meier analyses and the Cox proportional hazards model were only based on patients in whom DAPT was initiated.

Results

Cohort characteristics

The cohort comprised 37,001 patients with an inpatient PCI with stent implantation, of whom 24,380 patients (65.9%) underwent BMS implantation. In 69.4% of all patients, ACS was determined as the indication for the PCI (Table 1). Patients receiving DES were somewhat younger than patients receiving BMS. The distributions of sex and mean follow-up times were similar for all four subpopulations. Hypertension and dyslipidaemia were with prevalences of up to 90% and 82% the most frequent comorbidities in all groups. Patients showed a pronounced cardiovascular risk profile with considerable percentages of concomitant heart failure, obesity, and diabetes mellitus. The prevalences of most of the diseases and drugs were similar between the four subpopulations (Table 1). Atrial fibrillation and dispensations of low molecular weight heparin or phenprocoumon were more often observed in patients with stable AP and BMS.

Initiation of dual antiplatelet therapy in the study period

Overall, 88.4% of the study population received at least one clopidogrel or ticlopidine prescription within the period from 100 days before the PCI (5.7%) to 60 days after the PCI (94.3%). Of these, only 0.01% received ticlopidine. The proportion of patients with DAPT was 85.3% in patients with ACS and BMS implantation, 93.3% in patients with ACS and DES implantation, 86.0% in patients with stable AP and BMS implantation, and 94.5% in patients with stable AP and DES implantation.

Duration of dual antiplatelet therapy

The mean treatment duration of all 32,722 treated patients (initiated in the 100 days before and 60 days after PCI) was 208.8 days after the PCI (median of 216) (SD: 134.5). The probability of treatment discontinuation differed between the four subgroups and the age of the patients (Figure 1**a-d**). In patients with ACS and BMS implantation (n = 14,958) (mean treatment duration of 186.2 days (median of 153) (SD: 133.6)), the probabilities of treatment discontinuation after one, six, nine and twelve months were 6.0%, 51.7%, 63.6%, and 80.0%, respectively. In this group, the probability of treatment discontinuation increased sharply after the first month of the follow-up to about 25%. 62.3% of the patients got only one prescription (Figure 1**a**).

Patients with ACS and DES implantation (n = 7,648) (mean treatment duration of 291.4 days (median of 343) (SD: 96.2)) had a longer treatment duration with clopidogrel or ticlopidine in the follow-up. In this group, the probabilities of treatment

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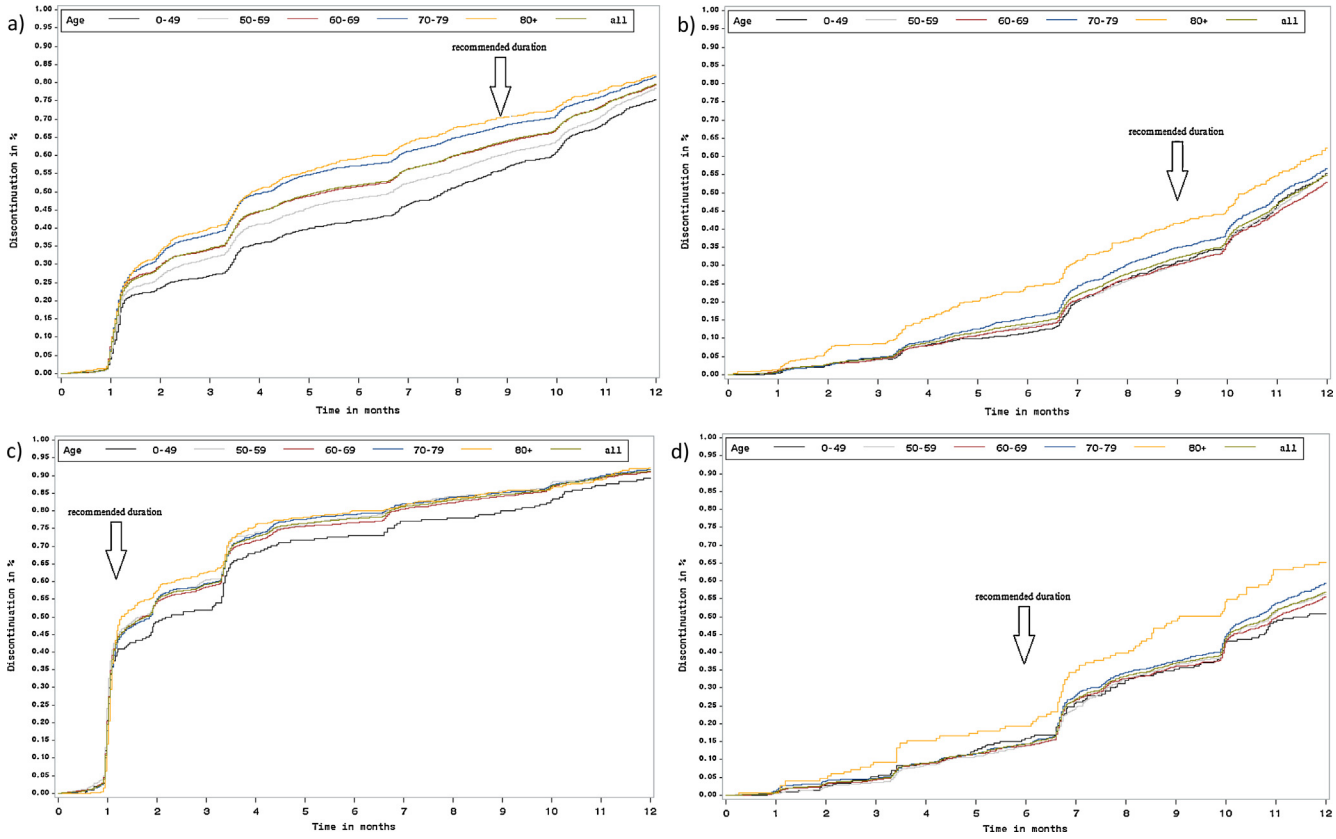

Figure 1. Age-stratified probability for end of treatment of dual antiplatelet therapy for patients with inpatient PCI due to a) acute coronary syndrome with bare metal stent implantation, b) acute coronary syndrome with drug eluting stent implantation, c) stable angina pectoris with bare metal stent implantation and d) stable angina pectoris with drug eluting stent implantation.

discontinuation after one, six, nine, and twelve months were 0.0%, 13.9%, 31.7%, and 54.9%, respectively. The probability of treatment discontinuation increased particularly after the sixth month to about 22%. Generally, the probability of treatment discontinuation increased more strongly in the last six months of the follow up compared to the first six months. 33.3% of the patients got only one prescription (Figure 1**b**).

In patients with stable AP and BMS implantation (n = 5,886) (mean treatment duration of 110.9 days (median of 53) (SD: 112.7)), the probabilities of treatment discontinuation were 19.6%, 77.8%, 84.5%, and 91.3% after one, six, nine, and twelve months, respectively. The probability of discontinuation increased sharply after the first and third month of follow up to about 47% and 67%, respectively. Afterwards, the Kaplan Meier curve showed a continuous increase of the probability for DAPT discontinuation to up to 91.3%. 84.0% of the patients got only one prescription (Figure 1**c**).

The Kaplan Meier curve for patients with stable AP and DES implantation (n = 4,230) (mean treatment duration of 283.4 days (median of 329) (SD: 97.1)) was similar to that of patients with ACS and DES implantation. However, the leap of the Kaplan Meier curve after six months of follow-up was more pronounced in patients with stable AP and DES implantation (Figure 1**d**). Particularly patients with DES implantation often received DAPT beyond the recommended period of time. 32.8% of the patients got only one prescription.

The log rank test indicated a significant difference between age-groups in the distributions of discontinuation time of DAPT in patients with ACS and BMS implantation ($p < 0.0001$) and in patients with DES implantation ($p < 0.0001$ for ACS and $p = 0.0115$ for stable AP, respectively) but not for patients with stable AP and BMS ($p = 0.0501$).

Predictors of DAPT discontinuation

Results of the multivariable Cox proportional hazard model showed that higher age was associated with an increased risk of DAPT discontinuation in patients with BMS implantation, regardless of the indication for the PCI (Table 2). Use of phenprocoumon and warfarin in the 100 days before discontinuation was associated with an increased risk of DAPT discontinuation. Heparin and NSAIDs showed no effect on the risk of discontinuation, the same was true for cardiovascular and other comorbidities. Contraindications to DAPT were largely associated with an increased risk of DAPT discontinuation, but in most cases the association was not statistically significant (Table 2).

Discussion

Based on German health insurance data, we investigated antiplatelet drug treatment in routine care in a sample of patients undergoing inpatient PCI with stent implantation. Depending on the type of the stent and the indication for the PCI, DAPT was initiated in 85-95% of patients, with the lowest proportion being observed in patients with ACS and BMS implantation. Depending on the subcohort, 36-88% of the patients received DAPT for the recommended duration. The risk of DAPT discontinuation increased with advancing age, especially in patients with BMS, irrespective of the indication for the PCI, and with the use of phenprocoumon.

Initiation of dual antiplatelet therapy

In our study, DAPT was initiated in 85-95% of all patients. Two registry-based studies investigating inpatient DAPT initiation

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Table 2
Risk of discontinuation of dual antiplatelet therapy after inpatient percutaneous coronary intervention with stent implantation.

	Hazard ratio (95% Confidence interval)			
	Stable angina pectoris & bare metal stent	Stable angina pectoris & drug eluting stent	Acute coronary syndrome & bare metal stent	Acute coronary syndrome & drug eluting stent
Age (Reference = 0-49 years)				
50-59 years	1.2 (1.0 - 1.4)	1.1 (0.9 - 1.4)	**1.1 (1.0 - 1.2)**	1.0 (0.9 - 1.1)
60-69 years	1.1 (1.0 - 1.3)	1.1 (0.9 - 1.3)	**1.2 (1.1 - 1.2)**	0.9 (0.8 - 1.0)
70-79 years	1.1 (1.0 - 1.3)	**1.2 (1.0 - 1.5)**	**1.2 (1.2 - 1.3)**	1.0 (0.9 - 1.2)
≥80 years	**1.2 (1.0 - 1.4)**	**1.5 (1.1 - 1.9)**	**1.3 (1.2 - 1.4)**	**1.3 (1.1 - 1.5)**
Sex (Reference = male)	**1.1 (1.0 - 1.2)**	1.0 (0.9 - 1.1)	**1.1 (1.0 - 1.1)**	1.0 (0.9 - 1.1)
Cardiovascular comorbidity*				
Atrial fibrillation	0.8 (0.8 - 0.9)	0.9 (0.8 - 1.0)	1.0 (0.9 - 1.0)	1.0 (0.9 - 1.1)
Dyslipidaemia	0.9 (0.9 - 1.0)	0.9 (0.8 – 1.0)	1.0 (0.9 - 1.0)	1.0 (0.9 - 1.1)
Heart failure	0.9 (0.8 - 0.9)	0.9 (0.9 - 1.0)	0.9 (0.9 - 0.9)	1.0 (0.9 - 1.1)
Hypertension	1.0 (0.9 - 1.1)	1.0 (0.8- 1.1)	1.0 (1.0 - 1.1)	1.0 (0.9 - 1.1)
Mechanical heart valve	0.8 (0.7 - 1.1)	1.5 (1.0 - 2.2)	1.2 (1.0 - 1.5)	1.4 (1.1 - 2.0)
Other comorbidity*				
Deep vein thrombosis	0.9 (0.8 - 1.2)	1.0 (0.7 - 1.5)	1.0 (0.8 - 1.1)	1.1 (0.8 - 1.5)
Dementia	0.8 (0.6 – 1.0)	1.2 (0.8 - 1.7)	1.1 (0.9 - 1.2)	1.1 (0.8 - 1.4)
Diabetes mellitus	0.9 (0.9 - 1.0)	1.0 (0.9 - 1.1)	1.0 (1.0 - 1.1)	1.0 (0.9 - 1.0)
Ischaemic stroke	0.8 (0.7 - 0.9)	1.0 (0.8 - 1.3)	**0.9 (0.8 - 1.0)**	1.1 (0.9 - 1.2)
Obesity	1.0 (0.9 - 1.0)	1.1 (1.0 - 1.2)	1.0 (0.9 - 1.0)	**1.1 (1.0 - 1.2)**
Contraindications*				
Acute haemorrhage	1.0 (0.6 - 1.6)	**2.3 (1.0 - 5.2)**	1.0 (0.7 - 1.4)	**1.6 (1.0 - 2.6)**
Liver disease	0.8 (0.5 - 1.3)	**2.2 (1.1 - 4.3)**	1.2 (0.9 - 1.6)	1.3 (0.8 - 2.1)
Renal disease	0.7 (0.4 - 1.1)	**2.4 (1.2 - 4.9)**	1.1 (0.8 - 1.5)	1.3 (0.8 - 2.1)
Drugs*				
Unfractionated heparin	1.1 (0.6 - 2.2)	0.8 (0.1 - 5.4)	1.6 (0.8 - 3.4)	-
Low molecular weight heparin	**1.2 (1.1 - 1.4)**	**1.2 (1.0 - 1.5)**	**1.4 (1.3 - 1.5)**	**1.5 (1.2 - 1.8)**
Non-steroidal anti-inflammatory drugs	1.1 (1.0 - 1.1)	1.0 (0.9 - 1.1)	0.9 (0.9 - 1.0)	0.9 (0.8 - 1.0)
Phenprocoumon	**2.7 (2.4 -3.0)**	**5.0 (4.0 - 6.1)**	**4.2 (3.8 -4.6)**	**4.6 (3.6 - 5.2)**
Warfarin	2.1 (0.9 - 5.1)	2.2 (0.3 - 15.5)	3.6 (1.8 – 7.2)	**8.9 (2.8 - 27.8)**

* Reference = not having the disease or not receiving the drug

found similar proportions of DAPT initiation than in our study. Zeymer and colleagues [14] used data from the European Antiplatelet Therapy Observational Registry (APTOR), a non-interventional, prospective cohort study which included patients undergoing PCI with stent implantation due to ACS to evaluate subsequent drug treatment in these patients. This study showed that 96% of the 500 German patients included in this registry received DAPT at hospital discharge. In a further German study based on the prospective, hospital-based, multicentre registry of the so-called 'Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte' (ALKK-registry), DAPT was studied in all patients in whom PCIs had been carried out [13]. This study observed inpatient DAPT initiation in 76-88% of all patients. However, these studies do not provide information on the proportion of patients continuing DAPT in the outpatient setting after discharge from hospital. Therefore, the comparability of the studies is limited. Furthermore, the voluntary participation of physicians and patients and therefore the awareness of being part of a study (volunteer bias) could influence the results in the registry-based studies [13,14]. On the contrary, our study is more likely to reflect routine DAPT after inpatient PCI.

Duration of dual antiplatelet therapy

According to the guideline valid during the study period [7], patients with ACS and PCI with BMS implantation were supposed to receive DAPT for nine to twelve months. However, in our study, the proportion of patients with DAPT discontinuation during the recommended time span was highest in this particular sub-group of patients with a sharp decrease of supplied patients after one month. Furthermore, in patients with ACS and DES implantation who should have received DAPT for nine to twelve months during the study period, we observed a high DAPT supply during the first six to seven months. Afterwards, the proportion of treated patients decreased sharply with 69% receiving DAPT longer than nine months. Both findings suggest that physicians are probably more prone towards providing DAPT based on the stent type than on the indication.

Patients with PCI due to stable AP more often received DAPT during the recommended period of time. Our study showed a comparably high proportion of patients receiving DAPT during the first month in patients with BMS implantation and during the first six months in patients with DES implantation, which was the guideline-recommended period of time for DAPT treatment during the study period. In patients with PCI due to stable AP, we observed DAPT durations beyond the recommended time span, with 53% of patients with BMS implantation receiving DAPT longer than one month and 76% of patients with DES implantation receiving DAPT longer than six month. This might reflect other indications requiring antithrombotic treatment. Of patients with AP and prolonged treatment, 33% with BMS implantation and 25% with DES implantation were diagnosed with other indications requiring antithrombotic treatment (peripheral artery disease, stroke, or atrial fibrillation) during the baseline period or between PCI and the end of the recommended duration of DAPT treatment, which might partly explain the observed prolonged DAPT. However, as clopidogrel, which was defined as DAPT in our study, is only given in case of a VKA or ASA intolerance, the proportion of patients receiving prolonged clopidogrel due to other indications is likely to be rather small. Thus, our results point towards an overtreatment particularly in patients with PCI due to stable AP.

Several reasons might explain the frequent DAPT discontinuation observed in our study. One explanation might be the simultaneous use of oral anticoagulant therapy and DAPT, which is associated with a high bleeding risk [19]. The so-called 'triple therapy' should be limited to a short period of time which could have contributed to the frequent DAPT discontinuation [19]. This is supported by the fact that our multivariable analyses revealed a statistically significant increased risk of DAPT discontinuation in patients receiving phenprocoumon in all of the four subpopulations. However, this can only partly explain the frequent DAPT

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discontinuation, since only 4.2% of the whole study population received phenprocoumon during the 100 days preceding discontinuation. Another reason could be intolerance to clopidogrel or ticlopidine. A total of 33 to 84% got only one prescription. How much patients discontinue their DAPT because of intolerance is not clear. It remains to be seen, if the concomitant use of novel oral anticoagulant drugs will have a different influence on the duration of DAPT after PCI. Up to now, only limited data are available regarding this issue.

In addition, other contraindications or higher age and therefore an increased bleeding risk likely were associated with an increased risk of DAPT discontinuation. Furthermore, there is an ongoing debate on the optimal duration of DAPT after DES implantation with arguments favouring also shorter or longer durations than recommended by guidelines [20]. This heterogeneous evidence might have contributed to non-adherence with recommended treatment durations after DES implantation, but does not explain non-adherence with guidelines after BMS implantation.

Our results regarding DAPT duration in patients with ACS are in line with those observed in another German study based on health insurance data including patients with acute myocardial infarction between 2001 and 2006 [12]. The authors showed that only around 40% of patients with BMS implantation and around 70% of patients with DES implantation received DAPT during the first nine months after the PCI. In our study, the proportion of supplied patients during the first nine months was 38% in patients with an ACS and BMS implantation and 68% in patients with an ACS and DES implantation, thus indicating no improvement over time.

One of the registry-based studies also analysed DAPT in patients with PCI due to ACS and observed that 77% of all patients received DAPT during the first twelve months after the PCI [14]. The higher proportion of patients receiving DAPT during the recommended period of time might mainly be due to the awareness of physicians and patients of taking part in a study which likely led to higher physicians' adherence to the guidelines and higher patients' adherence to the recommended treatment regime.

Strengths and limitations

The main limitation of our study is the fact that dispensations of ASA are underrepresented in German SHI data, as ASA is available as an over-the-counter medication. Of patients receiving clopidogrel or ticlopidine only 25.0% also received ASA dispensations during this time period. However, since patients who receive clopidogrel or ticlopidine after an inpatient PCI are likely to also receive ASA, an overestimation of DAPT is assumed to be small. However, the duration of DAPT is only an estimate, because we have no data on compliance. Because data on inpatient drugs were not available, we do not know, if patients got their DAPT during hospital stays from the hospital or use their own. However, the mean duration of hospital stays in the year after the PCI was 9 days, so there would be only a slightly underestimation of DAPT duration, even if every patient got DAPT from the hospital.

Since this study is based on administrative data, recall bias or selection bias (e.g. due to voluntary participation of patients or physicians) could be avoided. Hence, the results most likely reflect the routine practice of DAPT in Germany. Furthermore, a major strength of this study is the large and supraregional sample of patients with inpatient PCI and stent implantation.

Conclusions

Our study showed that a high proportion of patients undergoing inpatient PCI with stent implantation receive DAPT. We also observed that especially patients with ACS do not receive DAPT over the recommended period of time (undertreatment), whereas patients with stable AP often received DAPT beyond the recommended time span. If this has to be interpreted as an overtreatment is debateable. Further research is needed to evaluate the influence of newer antiplatelet and anticoagulant drugs and new stent types on DAPT initiation and duration after PCI.

Declarations

Conflict of interest

Edeltraut Garbe is a member of the scientific advisory board of the project "Versorgungsatlas" by the Central Research Institute of Ambulatory Health Care in the Federal Republic of Germany. Dirk Enders is employee of an institute that occasionally performs studies sponsored by pharmaceutical industries. These companies include Bayer, Celegne, GSK, Mundipharma, Novartis, Sanofi, Sanofi Pasteur MSD, and STADA. All other authors declare that they have no conflict of interest in the context of this study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.zefq.2016.12.007.

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