# Inpatient prescribing of dual antiplatelet therapy according to the guidelines

Moerlie, Ashwin R.; van Uden, Renate C.; Mantel-Teeuwisse, Aukje K.; Van den Bemt, Patricia; Becker, Matthijs L.

*Published in:*
Pharmacy practice

*DOI:*
10.18549/PharmPract.2020.2.1803

Moerlie AR, van Uden RC, Mantel-Teeuwisse AK, van den Bemt P, Becker ML. Inpatient prescribing of dual antiplatelet therapy according to the guidelines: a prospective intervention study. Pharmacy Practice 2020 Apr-Jun;18(2):1803.
https://doi.org/10.18549/PharmPract.2020.2.1803

**Original Research**

# Inpatient prescribing of dual antiplatelet therapy according to the guidelines: a prospective intervention study

Ashwin R. MOERLIE, Renate C. VAN UDEN, Aukje K. MANTEL-TEEUWISSE, Patricia VAN DEN BEMT, Matthijs L. BECKER.

Received (first version): 9-Jan-2020 Accepted: 31-May-2020 Published online: 10-Jun-2020

## Abstract

**Background**: In dual antiplatelet therapy (DAPT), low-dose acetylsalicylic acid is combined with a P2Y12 inhibitor. However, combining antithrombotic agents increases the risk of bleeding. Guidelines on DAPT recommend using this combination for a limited period of between three weeks and 30 months. This implies the risk of DAPT being erroneously continued after the intended stop date.

**Objective**: The primary objective of this study is to assess the proportion of hospitalized patients treated with DAPT whose treatment deviated erroneously and unintentionally from the guidelines. We also assessed risk factors and the effect of a pharmacist intervention.

**Methods**: All patients admitted to the Spaarne Gasthuis (Haarlem/ Hoofddorp, the Netherlands) who used DAPT between March 25th, 2019, and June 14th, 2019, were, in addition to receiving regular care, reviewed to assess whether their therapy was in line with the guidelines' recommendation and whether deviations were unintended and erroneous. In the event of an unintended deviation, the pharmacist intervened by contacting the prescriber by phone and giving advice to adjust the antithrombotic therapy in line with the guideline.

**Results**: We included 411 patients, of whom 21 patients (5.1%) had a treatment that deviated from the guidelines. For 11 patients (2.7%), the deviation was unintended and erroneous. The major risk factor for erroneous deviation was the use of DAPT before hospital admission (OR 18.7; 95%CI 4.79–72.7). In patients who used DAPT before admission, 18 out of 58 (31.0%) had a deviation from the guidelines of whom 8 (13.8%) were erroneous. For these eight patients, the pharmacist contacted the prescriber, and in these cases the therapy was adjusted in line with the guidelines.

**Conclusions**: Adherence to the guidelines recommending DAPT was high within the hospital. However, patients who used DAPT before hospital admission had a higher risk of erroneous prescription of DAPT. Intervention by a pharmacist increased adherence to guidelines and may reduce the number of preventable bleeding cases.

## Keywords

Platelet Aggregation Inhibitors; Fibrinolytic Agents; Guideline Adherence; Medication Errors; Hemorrhage; Risk Factors; Pharmacists; Clinical Audit; Netherlands



## INTRODUCTION

The use of antithrombotic agents involves a delicate balance between the risk of bleeding and the risk of thrombotic events.[1] Thrombocyte aggregation inhibitors (TARs) are used to prevent thrombo-embolic events. Dual antiplatelet therapy (DAPT) is the simultaneous use of two TARs and is recommended for various cardiologic, neurologic and surgical indications in which the need to prevent thrombo-embolic events outweighs the increased risk of bleeding (Table 1).[2-9] The use of both acetylsalicylic acid and clopidogrel is associated with a 1.4 to 1.6 times greater risk of bleeding compared to acetylsalicylic acid monotherapy and a 1.5 times increased risk of fatal bleeding.[10-13] In the guidelines, DAPT is only recommended for a restricted time depending on the indication, the individual risk of thrombo-embolic events and the individual risk of bleeding (Table 1).

In the first period after events such as myocardial infarctions and cerebrovascular accident or after interventions such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting, the risk of thrombo-embolic events is the highest, and treatment with DAPT is indicated. However, DAPT is not intended to be continued indefinitely, implying a risk of erroneous continuation beyond the intended stop date. Continuation results in an increased risk of bleeding with no added benefit for the patient. These errors negatively affect the benefit-to-risk ratio of DAPT, so non-adherence to the guidelines should be avoided.[14,15] In a study by Warlé-van Herwaarden *et al*. in a Dutch community pharmacy, 24% of all therapies with DAPT were found to not be prescribed in accordance with the guidelines.[16] Nearly half of these non-adhering therapies were a result of DAPT continuation beyond the recommended treatment period. Breuckmann *et al*. found a 38.2% level of compliance with European Society of Cardiology (ESC) guidelines for unstable angina pectoris in German hospitals.[17]

**Ashwin W. Rabin MOERLIE**. Pharmacy Foundation of Haarlem Hospitals. Haarlem (The Netherlands). a.w.r.moerlie@students.uu.nl
**Renate Cornelia VAN UDEN**. PharmD. Hospital Pharmacist. Pharmacy Foundation of Haarlem Hospitals. Haarlem (The Netherlands). ruden@sahz.nl
**Aukje Kaija MANTEL-TEEUWISSE**. PharmD, PhD. Professor of Pharmacy and Global Health. Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University. Utrecht (The Netherlands). A.K.Mantel@uu.nl
**Patricia M. L. A. VAN DEN BEMT**. PharmD, PhD. Hospital Pharmacist, Professor in Medication Safety. Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen. Groningen (The Netherlands). p.m.l.a.van.den.bemt@umcg.nl
**Matthijs Lambertus BECKER**. PharmD, PhD. Hospital Pharmacist, Researcher, Pharmacy Foundation of Haarlem Hospitals. Haarlem (The Netherlands). mbecker@sahz.nl

Table 1. Guidelines with the recommendations for dual antiplatelet therapy

| Indication for DAPT | Recommended duration of DAPT | Guideline (reference #) |
|---|---|---|
| Minor non-cardioembolic ischemic stroke (NIHSS score≤3) who did not receive IV alteplase | ASA + clopidogrel; 21 days | 2,3 |
| Acute coronary syndrome | DAPT; 3-36 months, in general 12 months | 4 |
| PCI in stable CAD setting | DAPT; 1-12 months | 4 |
| TAVI without high bleeding risk | ASA + clopidogrel; 3-6 months | 5 |
| Below the knee bypass with a prosthetic graft | ASA + clopidogrel; at least 1 year | 6,7 |
| Carotid artery stenting | ASA + clopidogrel; at least 1 month | 8 |
| Revascularization percutaneous in patients with lower extremity artery disease or infra-inguinal stent implementation | ASA + clopidogrel; at least 1 month | 6,7,9 |

DAPT: dual antiplatelet therapy; NIHSS: National Institutes of Health Stroke Scale; PCI: Percutaneous Coronary Intervention; CAD: Coronary artery disease; TAVI: Transcatheter aortic valve implantation; ASA: acetylsalicylic acid

The majority of therapies with DAPT begin during hospital admission and continue after discharge. It is a pharmacist's duty to prevent medication errors and to reduce erroneous non-adherence with guidelines in patients using DAPT. However, it is unknown whether deviations occur due to erroneous initiation of DAPT during admission or whether deviations occur due to erroneous continuation of DAPT after the intended stop date. To distinguish between erroneous initiation during hospital admission and erroneous continuation after the intended stop date, we reviewed all patients using DAPT during their hospital stay. The primary objective of this study was to assess the proportion of hospitalized patients treated with DAPT whose treatment deviated erroneously and unintentionally from the guidelines outlined in Table 1. The secondary objectives were to assess potential risk factors for erroneous deviation from the guidelines and to assess the impact of a pharmacist's intervention on adherence to the guidelines.

## METHODS

### Study population

This prospective intervention study was initiated by the Pharmacy Foundation of Haarlem Hospitals (Haarlem, the Netherlands), the hospital pharmacy providing pharmaceutical care for the teaching hospital Spaarne Gasthuis (Haarlem/ Hoofddorp, the Netherlands). All patients over the age of 18 admitted between March 25$^{th}$, 2019, and June 14$^{th}$, 2019, to the Spaarne Gasthuis and using low-dose acetylsalicylic acid or carbasalate calcium (≤ 100 mg/day) and a P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor) were included in this study. Carbasalate calcium is a chelate of calcium acetylsalicylate and urea and is converted into acetylsalicylic acid in the gastrointestinal tract. Patients using carbasalate calcium were therefore analyzed as acetylsalicylic acid users. Patients using vitamin K antagonists, direct oral anticoagulants (DOACs), heparin or therapeutic doses of low-molecular-weight heparin (nadroparin >5700 IE/day or equivalent doses) as therapeutic anticoagulants in addition to DAPT were excluded from this study. We excluded these patients because the combination of DAPT with an anti-coagulant is used for the treatment of at least two indications, making the therapy much more complex and not comparable to treatment with DAPT alone. For patients who were readmitted during the study period only the first admission was included.

### Study design and flow

At Spaarne Gasthuis, the hospital information system Epic, version 2019 (Epic, Verona, WI), featuring integrated computerized physician order entry, is used. In Epic, we built a patient list that presents all inpatients using DAPT. The medical records of these patients, including the physician's notes and the prescribed medications, were reviewed daily during weekdays by a pharmacist or pharmacist in training on top of regular medication surveillance. Patients admitted during the weekend or on a holiday were reviewed the next working day if they were still hospitalized. All pharmacists and pharmacists in training were trained in the indications and treatment guidelines for DAPT in advance. Regular medication surveillance consists of surveillance for drug-drug interactions and duplicate medication alerts, among others, using the database built and maintained by the Royal Dutch Association for the Advancement of Pharmacy. These alerts are shown to the physician during order entry and are subsequently reviewed by a pharmacist. During the study period, for all patients on the patient list, potential indications for DAPT were searched for in the patient's medical records. Both the medical history as described in the notes of the admitting physician and the notes of previous admissions were searched. During admission, the patient's medical history is written in the admission note, including information from previous admissions and information from the general practitioner and the patient. If the information was insufficient, the physician was contacted and asked to contact the patient's previous healthcare providers for more information. Subsequently, the potential indications for DAPT were compared with the indications as described in the guidelines in Table 1.[5-9] If a deviation was present, the patient's medical record was searched for notes of whether there was a reason to intentionally deviate from the guidelines. The pharmacist in training discussed with a pharmacist whether the reason to deviate was clinically sound. In case of disagreement, a third pharmacist decided. If there was a deviation and no clinically sound reason to intentionally deviate from the guidelines was found in the patient's medical record, an intervention was performed. In the intervention, the treating physician was contacted by telephone. The physician was informed about the indication and duration of DAPT, how this treatment deviated from the guidelines and that a potential reason was not found in the patient's medical record to deviate from the guidelines. A recommendation was given to adjust the therapy to comply with the guidelines outlined in Table 1.[5-9] If the physician

| Table 2 baseline characteristics of patients using dual antiplatelet therapy during hospitalization (n=411) | |
|---|---|
| Male | 244 (59.4%) |
| Mean age in years (range; SD) | 70.1 (30 - 96; 12.0) |
| DAPT before hospital admission | 58 (14.1%) |
| DAPT therapy | |
| ASA + clopidogrel | 258 (62.8%) |
| ASA + prasugrel | 2 (0.5%) |
| ASA + ticagrelor | 151 (36.7%) |
| Indication for DAPT | |
| Neurologic | 193 (47.0%) |
| Cardiovascular | 213 (51.8%) |
| Surgical | 3 (0.7%) |
| Multiple | 2 (0.5%) |
| SD: standard deviation; DAPT: dual antiplatelet therapy; ASA: acetylsalicylic acid | |

mentioned that the deviation from the guidelines had been intentional, the deviation was discussed, as mentioned before. After the intervention, the patient's medical record and prescribed medication were reviewed on the same day and on subsequent days during the admission, to verify whether the therapy was adjusted in line with the advice.

**Data collection**

The reviews and potential interventions were registered in the patient's medical record in Epic. Data acquisition was performed using Crystal Reports (Walldorf, Germany). The following patient data were collected from the patient's medical record to determine whether these risk factors contribute to failure to adhere to the DAPT guidelines without a valid reason: gender, age, DAPT combination, whether DAPT was used before admission and treating specialty. The use of DAPT before admission was defined as having the medicines in the list of pre-admission medication. These factors were chosen because automated selection by a hospital information system on these factors is possible.

**Outcome measure**

The primary outcome was the proportion of hospitalized patients treated with DAPT whose treatment deviated erroneously and unintentionally from the guidelines. The secondary outcomes were the risk factors associated with erroneous deviations from the guidelines and the proportion of advice in the interventions that was accepted by the physician.

**Data analysis**

Descriptive statistics were used to describe the proportion of patients using DAPT therapy with an erroneous deviation from the guidelines. With a univariate logistic regression analysis, the association of potential risk factors (gender, age, whether DAPT was used before admission, DAPT combination and indication) for erroneous deviation from the guideline was analyzed. Analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp. Armonk, NY).

**Ethics**

The intervention was part of regular pharmaceutical care in the hospital and was discussed with the Anticoagulation Committee of the hospital before implementation. Members of all relevant medical specialties are involved in this committee. The study was reviewed by the institutional review board of the Spaarne Gasthuis.

## RESULTS

During the study period, 411 patients were included, of whom 353 (85.9%) started with DAPT during the admission (Table 2). For 390 of the 411 patients (94.9%), the DAPT treatment did not deviate from the guidelines, while for 21 of the 411 patients (5.1%), the treatment deviated from the guidelines. For 10 of the 21 patients (48%) whose treatment deviated from the guidelines, the deviation was intentional. These 10 patients were treated for a longer duration than recommended in the guidelines. The reasons that were given for these deviations were stent thrombosis or occlusion (five patients), multiple events for which DAPT is indicated (four patients) and thrombocytosis in addition to a history of PCI and cerebrovascular accident (one patient). For 11 patients (52%), the deviation was unintended and erroneous. Five of the 11 patients had their DAPT treatment continued after the intended treatment period, two patients for less than a month, two patients for between one month and one year, and one patient for more than a year. Six of the 11 patients with unintended and erroneous deviations never had an indication for DAPT.

The pharmacist contacted the physician to discuss the treatment for 8 of the 11 patients with unintended and erroneous deviations. The DAPT treatment was changed following the intervention for these eight patients. The pharmacist did not contact the prescriber for three patients because one patient had passed away before intervention was possible and for two patients the physician had changed the DAPT treatment in line with the guidelines before the pharmacist could contact the prescriber.

Various covariates were analyzed as potential risk factors (Table 3). In the univariate analysis, whether DAPT was prescribed before hospital admission was statistically significantly associated with an erroneous deviation from the guidelines (OR 18.7; 95%CI 4.79-72.7). In 8 of the 58 patients (14%) who were hospitalized and used DAPT before admission, the deviation was erroneous, while in 3 of the 353 patients (0.8%) who started DAPT treatment during hospitalization, the deviation was erroneous. Of the eight patients with erroneous DAPT before admission, five were a result of DAPT treatment continuing after the intended stop date, and three patients never had an indication for DAPT. The three patients who started DAPT during admission had no indication for DAPT. Ten of the 58 patients using DAPT before admission had an intended deviation from the guidelines.

## DISCUSSION

Around 1 in 20 hospitalized patients treated with DAPT was not treated according to the guidelines, nor was there an intentional deviation due to patient-specific characteristics. In the eight cases with an erroneous deviation from the guidelines for which the pharmacist contacted the prescriber and gave advice to adjust the therapy, the DAPT was adjusted in line with the guidelines. The use of DAPT before admission was a potential risk factor for erroneous deviations.

Table 3. Risk factors for erroneous and unintentional deviations from the guidelines in inpatients using dual antiplatelet therapy

| Risk factor | n/N (%) in erroneous deviation from guidelines | | Univariate logistic regression | | |
|---|---|---|---|---|---|
| | | | OR | 95% CI | p-value |
| Gender | | | | | |
| Male | 9/244 | 3.7 % | Ref. | | |
| Female | 2/167 | 1.2 % | 0.32 | 0.07-1.48 | 0.14 |
| Age | | | 1.06 | 1.00-1.12 | 0.06 |
| DAPT before admission | | | | | |
| No | 3/353 | 0.8 % | Ref. | | |
| Yes | 8/58 | 13.8 % | 18.7 | 4.79-72.7 | <0.0001 |
| DAPT | | | | | |
| ASA + clopidogrel | 10/258 | 3.9 % | Ref. | | |
| ASA + prasugrel | 0/2 | N/A | 0.16 [a] | 0.02-1.29 | 0.09 |
| ASA + ticagrelor | 1 / 151 | 0.7 % | | | |
| Indication | | | | | |
| Cardiovascular | 6/213 | 2.8 % | Ref. | | |
| Neurologic | 4/193 | 2.1 % | 0.73 | 0.20-2.63 | 0.63 |
| Surgical | 0/3 | N/A | 8.63 [a] | 0.83-89.3 | 0.07 |
| Multiple | 1/2 | 50 % | | | |

[a] the DAPT therapies ASA + prasugrel and ASA + ticagrelor and the indications surgical and multiple were analyzed as one group in the regression analyses due to low numbers.
DAPT: dual antiplatelet therapy; ASA: acetylsalicylic acid; N/A: not applicable; OR: odds ratio; CI: confidence interval

The majority of patients who used DAPT in this study had started this treatment during the current hospitalization, and adherence to the guidelines mentioned in Table 1 was high in this patient group. Guideline adherence levels of 84% and above in hospitalized patients have also been reported by other studies analyzing adherence to guidelines recommending antithrombotic therapy.[18-20]

Regarding patients who used DAPT before admission, 18 out of 58 (31%) cases deviated from the guidelines; of these deviations 8 (14%) were erroneous. These results are in line with the findings of Warlé-van Herwaarden *et al*., who stated that 24% of patients from a community pharmacy who used DAPT had a deviation from the guidelines.[16] In the study by Warlé-van Herwaarden *et al*., the prescriber was not contacted, and it was therefore unknown whether the deviations were intentional or erroneous. In the present study, three of the eight patients with an erroneous deviation from the guidelines never had an indication for DAPT, while in five patients one of the two agents should have been stopped in the past. The guidelines recommend the use of DAPT for a limited period of between three weeks and 30 months, depending on the indication. These recommendations involve the risk of the patient or healthcare providers overlooking that one of the TARs should be stopped. Our results suggest that erroneous DAPT continuation contributes substantially to guideline non-adherence in primary care, a conclusion that supports the findings of Warlé-van Herwaarden *et al*.[16]

DAPT is most frequently initiated in the hospital, for example, after a myocardial infarction or a cerebrovascular accident. This treatment is continued after discharge and should be stopped in the outpatient setting. Errors occur if the neurologist, cardiologist or surgeon communicate to the patient that one of the TARs should be stopped without effect or if there are no follow-up visits at the time the DAPT should be stopped. The intended stop date is often mentioned in the discharge letter sent to the primary care physician, but this is often archived. A notification to the prescriber is needed at the time the DAPT therapy should be stopped, during either prescribing or dispensing. Improved collaboration between physicians and pharmacists is needed to avoid the continuation of DAPT after the intended stop date. Treating patients for a longer period results in a 1.4 to 1.6 times greater risk of bleeding.[10-13] Pharmacists have an important role in reducing medication errors. Since the proportion of errors was higher in patients who were admitted with DAPT versus patients who started DAPT during admission, the focus should be on patients in primary care. Better cooperation between pharmacists in the hospital and community pharmacists, along with communication on the intended DAPT stop date after discharge from the hospital, is an intervention of interest to improve guideline adherence and reduce preventable bleedings.

Our study has several potential strengths and limitations. First, due to the prospective design, we were able to discuss the indication for the antiplatelet therapy with the prescriber in case there was doubt about it, and we could analyze the effect of a pharmacist intervention. Second, we collected various potential risk factors for analysis, including the indication and whether the patients used DAPT before admission. By analyzing potential risk factors, we could identify patients using DAPT before admission as a group to whom extra attention should be given to avoid erroneous prescribing of DAPT. A potential limitation of this study is the single-center setting, which potentially limits the generalizability of the results. However, the results were in line with a previous study performed in a community pharmacy in another region of the Netherlands. Since the guidelines for the prescription of DAPT are similar between countries, we expect this problem to also exist in other countries. Third, we used the information from the patient's medical record, information that may not be complete or correct. For example, we may have missed patients who used DAPT before admission if the pre-admission medication list was incomplete, or we may have missed patients who had temporarily stopped DAPT during admission due, for example, to surgery. Fourth, we performed this study without a control group, and we do not know whether erroneous deviations would have been corrected without intervention by a pharmacist. Fifth, only a limited number of variables were assessed as potential risk factors. Finally, the number of patients with erroneous

deviations from the guidelines was limited, making the power for statistical analyses low.

## CONCLUSIONS

To conclude, adherence to guidelines that recommend the prescription of DAPT is high within the hospital. The use of DAPT before admission is a potential risk factor for erroneous deviations from the guidelines, which suggests that the intended stop date after discharge needs to be better communicated to improve guideline adherence in primary care. Intervention by a pharmacist increased adherence to the guidelines in patients using DAPT and may thus reduce the number of preventable bleeding cases.

## CONFLICT OF INTEREST

None of the authors has any conflict of interest.

## FUNDING

No sources of funding or support were received for performing this study.

## References

1. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM; HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008;168(17):1890-1896. https://doi.org/10.1001/archinternmed.2008.3
2. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344-e418. https://doi.org/10.1161/str.0000000000000211
3. Federatie Medisch Specialisten. [Guideline database: Cerebral infarction and cerebral hemorrhage]. Available at: https://richtlijnendatabase.nl/richtlijn/herseninfarct_en_hersenbloeding/startpagina_herseninfarct_-bloeding.html (accessed Aug 18, 2019).
4. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39(3):213-260. https://doi.org/10.1093/eurheartj/ehx419
5. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-2791. https://doi.org/10.1093/eurheartj/ehx391
6. Aboyans V, et al. Editor's Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2018;55(3):305-368. https://doi.org/10.1016/j.ejvs.2017.07.018
7. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Röther J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I; ESC Scientific Document Group. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Eur Heart J. 2018;39(9):763-816. https://doi.org/10.1093/eurheartj/ehx095
8. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK; Society for Vascular Surgery. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease: executive summary [published correction appears in J Vasc Surg. 2012 Mar;55(3):894]. J Vasc Surg. 2011;54(3):832-836. https://doi.org/10.1016/j.jvs.2011.07.004
9. Federatie Medisch Specialisten. [Guideline database: Peripheral arterial disease]. Available at: https://richtlijnendatabase.nl/richtlijn/perifeer_arterieel_vaatlijden_pav/pav_-_startpagina.html (accessed Aug 18, 2019).
10. Sørensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jørgensen C, Madsen JK, Hansen PR, Køber L, Torp-Pedersen C, Gislason GH. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet. 2009;374(9706):1967-1974. https://doi.org/10.1016/s0140-6736(09)61751-7
11. Bhatt DL, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006;354(16):1706-1717. https://doi.org/10.1056/nejmoa060989
12. Donadini MP, Bellesini M, Squizzato A. Aspirin Plus Clopidogrel vs Aspirin Alone for Preventing Cardiovascular Events Among Patients at High Risk for Cardiovascular Events. JAMA. 2018;320(6):593-594. https://doi.org/10.1001/jama.2018.9641
13. van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major Bleeding Rates in Atrial Fibrillation Patients on Single, Dual, or Triple Antithrombotic Therapy. Circulation. 2019;139(6):775-786. https://doi.org/10.1161/circulationaha.118.036248
14. Costa F, Valgimigli M. The optimal duration of dual antiplatelet therapy after coronary stent implantation: to go too far is as bad as to fall short. Cardiovasc Diagn Ther. 2018;8(5):630-646. https://doi.org/10.21037/cdt.2018.10.01

15. Ferrante G, Condorelli G, Pagnotta P, Reimers B. Dual Antiplatelet Therapy Continuation Beyond 1 Year After Drug-Eluting Stents: A Meta-Analysis of Randomized Trials. Circ Cardiovasc Interv. 2017;10(5):e004139. https://doi.org/10.1161/circinterventions.116.004139
16. Warlé-Van Herwaarden MF, Roukens M, Pop GA, Lamfers EJ, De Smet PA, Kramers C. Adherence to guidelines for the prescribing of double and triple combinations of antithrombotic agents. Eur J Prev Cardiol. 2014;21(2):231-243. https://doi.org/10.1177/2047487312451253
17. Breuckmann F, Hochadel M, Darius H, Giannitsis E, Münzel T, Maier LS, Schmitt C, Schumacher B, Heusch G, Voigtländer T, Mudra H, Senges J. Guideline-adherence and perspectives in the acute management of unstable angina - Initial results from the German chest pain unit registry. J Cardiol. 2015;66(2):108-113. https://doi.org/10.1016/j.jjcc.2014.11.003
18. Nelson Worel J. Venous thromboembolism: what is preventing achievement of performance measures and consensus guidelines?. J Cardiovasc Nurs. 2009;24(6 Suppl):S14-S19. https://doi.org/10.1097/jcn.0b013e3181b85c7b
19. Lisowska A, Makarewicz-Wujec M, Dworakowska AM, Kozłowska-Wojciechowska M. Adherence to guidelines for pharmacological treatment of young adults with myocardial infarction in Poland: Data from Polish Registry of Acute Coronary Syndromes (PL-ACS). J Clin Pharm Ther. 2019;44(3):471-478. https://doi.org/10.1111/jcpt.12813
20. Engel J, Damen NL, van der Wulp I, de Bruijne MC, Wagner C. Adherence to Cardiac Practice Guidelines in the Management of Non-ST-Elevation Acute Coronary Syndromes: A Systematic Literature Review. Curr Cardiol Rev. 2017;13(1):3-27. https://doi.org/10.2174/1573403x12666160504100025