Management of combined oral antithrombotic therapy by an antithrombotic stewardship program: a prospective study

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Abstract

Aims: Given the complexity of antithrombotic therapy guidelines especially in patients with combined antithrombotic therapy, there is a risk of inappropriate prescribing and medication errors. In order to prevent this, a multidisciplinary antithrombotic stewardship (ASP) is implemented in our hospital. The primary aim of this study is to determine the efficacy of this ASP by assessing the number of patients on combined antithrombotic therapy for whom one or more interventions are needed. Methods: A prospective cohort study in a large teaching hospital is conducted. Hospitalized patients who received combined antithrombotic therapy in which an oral anticoagulant was combined with one (double therapy) or two (triple therapy) platelet aggregation inhibitors were included. The ASP proactively evaluated the appropriateness of this combined antithrombotic therapy. If needed, ASP improved the concerned therapy. Each improvement measurement by ASP was counted as one intervention. Results: A total of 460 patients were included over a period of 12 months. 251 (54.6%) patients required at least one intervention from the ASP. The most common intervention was to define and document a maximum duration of the combined antithrombotic therapy (65.5%) instead of lifetime use of the combination, to discontinue antithrombotic therapy (19.4%) as the proper indication was lacking and to adjust the dosage (8.1%). Conclusion: As intervention was needed in more than half of the patients on combined antithrombotic therapy, it seems essential to implement an ASP that dedicated evaluates antithrombotic therapy to improve and ensure optimal use and medication safety.

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Principal investigator

The interventions performed in this study were part of the daily patient care. There is no principal investigator.

Keywords

Anticoagulation, antithrombotic, platelet aggregation inhibitors, antithrombotic stewardship program, guideline adherence

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Methods: A prospective cohort study in a large teaching hospital is conducted. Hospitalized patients who received combined antithrombotic therapy in which an oral anticoagulant was combined with one (double therapy) or two (triple therapy) platelet aggregation inhibitors were included. The ASP proactively evaluated the appropriateness of this combined antithrombotic therapy. If needed, ASP improved the concerned therapy. Each improvement measurement by ASP was counted as one intervention.

Results: A total of 460 patients were included over a period of 12 months. 251 (54.6%) patients required at least one intervention from the ASP. The most common intervention was to define and document a maximum duration of the combined antithrombotic therapy (65.5%) instead of lifetime use of the combination, to discontinue antithrombotic therapy (19.4%) as the proper indication was lacking and to adjust the dosage (8.1%).

Conclusion : As intervention was needed in more than half of the patients on combined antithrombotic therapy, it seems essential to implement an ASP that dedicated evaluates antithrombotic therapy to improve and ensure optimal use and medication safety.

What is already known about this subject?

- Antithrombotic treatment guidelines are complex, especially in patients with combined therapy.
- Given this complexity, antithrombotic care is susceptible for prescribing and medication errors.
- It is essential to determine the indication for combined antithrombotic therapy correctly and not to use the combination longer than appropriate, which increases the risk of bleeding.

What this study adds?

- 54.6% of patients with combined antithrombotic therapy required minimal one intervention from the multidisciplinary antithrombotic stewardship (ASP).
- The most common intervention was to determine the maximum duration of the combined antithrombotic therapy (65.5%) to prevent overuse and bleeding complications
- Implementation of a dedicated ASP is important to improve patient safety.

1. Introduction

Antithrombotic therapy such as antiplatelet drugs and oral anticoagulation (OAC) are used extensively to treat and prevent thromboembolic events by inhibiting platelet aggregation and coagulation. OAC (vitamin K-antagonist (VKA, coumarines) and direct oral anticoagulation (DOAC) therapy) is recommended for the prevention of stroke in patients with atrial fibrillation (AF) and systemic embolism, while antiplatelet therapy

(platelet aggregation inhibitors (PAI) such as acetylsalicylic acid and P2Y12 inhibitors) is recommended for the prevention of (recurrent) myocardial infarction and stent thrombosis.

The patient population on antithrombotic therapy is growing and the antithrombotic landscape is complex. In clinical practice, a subgroup of patients have an indication for both OAC and antiplatelet therapy.[1-4] However, combining OAC with other antithrombotic agents is associated with a high risk of bleeding complications.[5,6] In addition, the complexity of guidelines and schedules for combined antithrombotic therapy could cause unnecessarily prolonged continuation of this combined therapy. Due to this complexity, medication errors may occur. [7-11] In fact, antithrombotics are the most common cause of potentially avoidable adverse events that result in a prolonged hospitalisation compared to other medications. [12-14] For these reasons, combined antithrombotic therapy should be monitored closely to prevent unintentional longer use than indicated, avoidable bleeding complications and unnecessary (re)hospitalizations. Therefore, our hospital has implemented a multidisciplinary antithrombotic stewardship (ASP) to proactively monitor the in-patients safety and efficacy of daily antithrombotic therapy use.

The main objective of this study is to determine the efficacy of the ASP by assessing the number of patients on combined antithrombotic therapy for whom one or more interventions are needed by ASP to optimize the antithrombotic therapy. Secondarily, reasons for intervention are explored. Furthermore, we aim to describe the safety outcomes such as bleeding and thromboembolic complications in patients on combined antithrombotic therapy.

2. Methods

2.1 Study design and setting

A prospective cohort study was conducted in a large teaching hospital in the Netherlands, Amsterdam (OLVG). Consecutive patients on combined antithrombotic therapy who were hospitalized for any reason, were included. Subsequently, a member of the multidisciplinary ASP proactively evaluated the appropriateness of this combined antithrombotic therapy by assessing proper indication according to local hospital guideline, proper prescription and length of use. In case of doubt, the combined antithrombotic therapy was discussed in the ASP. If needed, an intervention was proposed to the treating physician to ensure efficacy and safe use during and after hospitalization. The multidisciplinary ASP consisted of an internist (vascular), a cardiologist, a (cardiothoracic) surgeon, a hospital pharmacist, a pharmacist technician and a nurse specialist. When needed, a surgeon (vascular) and neurologist could were consulted by ASP.

This study protocol was approved by the local ethics committee " Advies Commissie Wetenschappelijk Onderzoek-Medisch Ethische Commissie (ACWO-MEC) OLVG hospital. As ASP was implemented for improvement of daily clinical care, no written informed consent was required for the interventions described in this study.

2.2 Study population

Consecutive patients who were admitted between March 2019 and March 2020 and were treated with a combined antithrombotic therapy enrolled in this study. Inclusion criteria were that the combined therapy existed of one OAC (VKA and/or DOAC) combined with one (double antithrombotic therapy, DAT) or two PAI's (triple antithrombotic therapy, TAT).

Exclusion criteria were if the combination existed of only PAI's (dual antiplatelet therapy (DAPT)) without OAC. Exclusion also occurred if admission was less than 24 hours.

2.3 Data collection

Patient characteristics were extracted from the electronic medical record of the hospital information system and each record was reviewed manually. Data were collected from the day of hospitalization or time starting the DAT or TAT. All data were stored in Castor Electronic Data Capture (EDC) version 12.51.

2.4 Outcome measures

The primary outcome was the proportion of patients with one or more interventions suggested by the ASP. An intervention was defined as an advice from a member of the ASP which was given to the treating physician to optimize the antithrombotic therapy. Secondarily, reasons for intervention were explored and detailed information of the intervention were also collected (

For the safety outcome, we described the proportion of bleeding events, thromboembolic complications and death. Bleeding and thromboembolic complications were defined as an event that occurred at admission, a new event during hospitalization or within 30 days after discharge. Moreover, mortality was defined if it occurred during hospitalization or within 30 days after discharge.

2.5 Analysis

All data were analyzed using IBM SPSS Statistics 22 (IBM, New York, USA). Descriptive statistics were used to describe patient characteristics and outcomes. All normally distributed continuous variables were expressed as mean ± standard deviation (SD). Non-normal variables were expressed as medians and interquartile ranges (IQR) and tested for statistical significance between groups using the Mann-Whitney *U* test. Categorical variables were displayed as frequencies and percentages per category and were tested for differences between groups with the Chi-square test. A p-value of <0.05 was considered to be statistically significant.

In total three subgroup analyses were performed. The first subgroup analysis compared the type of antithrombotic therapy (DAT *versus*TAT). Also, results are separately assessed for the subgroup of patients based on the initiation of antithrombotic therapy (initiation during current hospitalization *versus* initiation before current hospitalization). Lastly, a subgroup analysis was performed by using a combination of type of antithrombotic therapy and initiation of antithrombotic therapy. The last subgroup analysis was used to identify the group of patients who had the most complications.

3. Results

3.1 Study Population

In total, 460 patients were included in the study. Patient characteristics are shown in Table 1. The majority of the patients had DAT (n= 386, 83.9%) and antithrombotic therapy was initiated during current admission (n= 360, 78.3%). Most of the patients included in this study were admitted to the cardiac ward.

3.2 Primary outcome

A total of 251 (54.6%) patients required at least one ASP intervention and 59 patients needed two interventions (Table 2).

3.3 Secondary outcomes

A total of 310 interventions were carried out (table 3) in 251 patients. The most common intervention (n=203 out of 310, 65.5%) was when the maximum duration of the combined therapy was not defined nor documented. The second reason for intervention counted for 19.4% of cases in which there was no (more) indication for the combined therapy and therefore ASP intervened to discontinue either antiplatelet drugs or oral anticoagulant therapy. Interventions due to dose adjustment counted for 8.1% of the total interventions. Lastly, seven interventions (2.3%) were to switch between OAC's and the reason for switching was due to interaction, reduced kidney function or wrong indication.

3.4 Interventions in patients with DAT versus TAT

Of the 460 patients who were included, a total of 386 patients were treated with DAT. Of these patients, 203 (52.6%) required at least one ASP intervention and a total of 233 interventions were carried out.

A total of 74 patients had TAT. Of these patients, 48 (64.9%) needed at least one intervention and a total of 77 interventions were carried out.

In figure 1, the type of intervention per subgroup is shown.

In patients who were treated with DAT, we observed that 138 out of the total 233 ASP interventions (59.2%) were to define and document the maximum duration of therapy. However, this type of intervention was significantly more observed in the TAT group (84.4%; 65 out of the 77 ASP interventions) compared to the DAT group ($p<0.001$). Moreover, in the DAT group 53 interventions (22.7%) were suggested by the ASP to discontinue antithrombotic therapy, while the TAT group required this type of intervention significantly less (9.1%; $p=0.009$).

3.5 Interventions in patients who initiated combined therapy during versus prior to hospitalization

A combined antithrombotic therapy was initiated during hospitalization in 360 patients (78% of 460 included patients) while 100 patients entered the hospital already using a combination of antithrombotics (22% of 460 included patients).

Out of the 360 patients for whom the combined antithrombotic therapy was initiated during the hospitalisation, 198 (55%) required at least one ASP intervention and a total of 251 interventions were carried out.

Out of the total of 100 patients who entered the hospital already using a combination of antithrombotic therapy 53 (53%) required at least one ASP intervention and 59 interventions were carried out in total.

In figure 2 the reason of intervention per subgroup is depicted. the intervention to discontinue antithrombotic therapy due to a lack of indication was more seen in patients who initiated combined therapy prior to hospitalization compared to those who initiated during hospitalization (17.5% versus 27.1%, $p = 0.09$). This result was non-significant. In addition, although not statistically significant, the intervention to define the maximum duration of therapy was more frequently observed in patients whose combined therapy was initiated during current hospitalization compared to the group who initiated therapy prior to hospitalization (67.3% vs 57.6%, $p= 0.16$).

3.6 Safety outcomes

Bleeding complications occurred in 11.7% (n= 54) of all patients (table 4). Patients who had a bleeding at admission were more likely to be those who were already using a combined antithrombotic therapy prior to admission, whereas bleeding during hospitalisation was more likely to occur among patients who started the combined antithrombotic therapy during hospitalisation. Although the total of

patients are small per subgroup, the overall bleeding rate seems to be the highest in the subgroup of patients who were using TAT prior to hospitalisation.

The overall rate of thromboembolism in this study population was 5.4% (n=25) (table 4). This rate seems to be higher among patients at admission who therefore initiated a combined antithrombotic therapy during hospitalisation. However, two patients (2.1%) still had a thromboembolism at admission despite that DAT was initiated prior to hospitalization. A thromboembolism during hospitalization was seen in 1.3% (n= 6) of all patients and these patients all had initiated their combined therapy (DAT) after the thromboembolism.

The overall mortality rate was 4.3% (table 4).

4. Discussion

This prospective cohort study showed that 251 out of 460 patients (54.6 %) with combined antithrombotic therapy needed at least one intervention from the multidisciplinary ASP to optimize their antithrombotic therapy. The most common interventions were to define and document the maximum duration of the combined therapy (65.5%), to discontinue the combined antithrombotic therapy (19.4%) and to adjust the dosage

(8.1%). More patients with TAT required at least one intervention compared to DAT patients. Complications in terms of bleeding, thromboembolism and death were seen in 54 patients (11.7%), 25 patients (5.4%), 20 patients (4.3%), respectively. Bleeding complications were seen more frequently at admission and among patients who already used a combined antithrombotic therapy before admission.

Previous studies have shown that 20% to 52% of patients on combined antithrombotic therapy had inappropriate prescribing which is confirmed with our results. [15-20] Studies have demonstrated that introducing ASP or a structured daily review has led to a significantly higher overall adherence to guidelines among prescribers.[11,20] A learning effect develops over time, because the prescriber will be contacted with every intervention. Our results also underlined the complexity of combined antithrombotic therapy and addressed the importance of implementing an ASP. Considering our primary outcome of this research, we showed that a dedicated ASP is able to capture these inappropriateness and intervene effectively during hospitalisation.

The majority of interventions (65.5%) observed in the current study was to define and document the maximum duration of the combined antithrombotic therapy. This intervention prevents prospectively unnecessarily prolonged use of combined anticoagulant therapy. Also, bleeding complications (n=17) at admission among patients already using combined antithrombotic therapy could be lowered when over-use is avoided by proper definition of the required duration of use.

It is noteworthy that we assessed an expired indication for the combined therapy in one of the five interventions (19.1%). We can therefore assume that inappropriate documentation of the maximum duration will eventually lead to an unnecessarily longer use and avoidable bleeding complications. Therefore, this intervention is appealingly simple, yet very important to assure effectiveness and safety of this therapy.

In our subgroup analyses, we observed that patients with TAT frequently needed more interventions compared to DAT (64.9% vs 52.6%). This can be explained due to the fact that the TAT therapy guidelines may be more complex than DAT. For instance, guidelines advice a very short duration of use of triple therapy (2 weeks up to a maximum of one month) due to a high risk of bleeding which does not weigh against its capacity to prevent thromboembolic events. Besides documenting the duration of use of the triple therapy, also maximum duration for the remaining combination of two antithrombotics should be assessed. Again, due to higher bleeding risk outweighing the prevention of thromboembolic complications, it is advised not to use double antithrombotic combination longer than 6 to 12 months. So, two maximum durations of use should be documented in TAT. This is reflected by our results as we saw ASP that interventions to define the maximum duration of use was significantly more required in the TAT group compared to the DAT group (84.4% vs 59.2%). However, the intervention to discontinue antiplatelet therapy or OAC due to the lack of a valid indication was more seen in patients with DAT compared to patients with TAT (22.7% vs 9.1%). This could be explained by the fact that DAT can generally be used for a longer period of time (e.g. 12 months) and documenting the required duration of use is often postponed (e.g. to outpatient clinic) and lost due to time and more transition moments.

Regarding the safety outcomes, we have observed an overall bleeding rate of 11.7% in patients with combined anticoagulation therapy and an overall thromboembolism rate of 1.3%. Compared to previous studies, our bleeding rate is similar (7.3% - 44.4%). [21-23] The overall bleeding rate seems to be highest in the subgroup of patients who were using TAT prior to hospitalisation. Dreijer et al demonstrated that implementing an antithrombotic stewardship could significantly reduce bleeding and thrombotic events in patients with anticoagulant therapy. Although, the study design and ASP in this specific study differed from our ASP. Their study design was a before-and-after intervention study in which their ASP mainly focused on education, medication reviews by pharmacist, patient counselling and implementation of local anticoagulant guidelines. They also showed that implementation of an antithrombotic team was accompanied by a cost reduction of implementing a multidisciplinary ASP that daily evaluates every combined anticoagulant therapy, avoidable complications and hospitalisation may be prevented. Future studies should focus whether an ASP can effectively reduce bleeding complications in patients with combined antithrombotic therapy.

Strengths and limitations:

To the best of our knowledge this is the first study that evaluates the effect of antithrombotic stewardship in which a prospective daily monitoring of all hospitalized patients on combined antithrombotic therapy is part of daily clinical practice. Therefore, the results of this study reflect the daily clinical practice. Additionally, agreements were made in advance within the ASP with regard to guidelines, responsibilities, tasks and communication and therefore we had a good basis that resulted in a dedicated and committed ASP team. Other strengths are the prospective study design and the follow up after post-discharge to evaluate medication safety. However, the present study should be viewed in the context of several limitations. Firstly, not all the interventions were recorded by the members of the antithrombotic stewardship. This implicated that the real number of interventions is in fact higher than reported. Secondly, for the safety outcomes we only relied on data in the medical record in our hospital, which can result in an underestimation of complications. Thirdly, due to COVID-19 pandemic we had fewer admissions in the last month of the study. Lastly, the external validity is limited due to the single-centre study design. Despite these limitations, with our results, we showed that implementing a multidisciplinary ASP is effective in improving antithrombotic care in patients with combined therapy.

Conclusion:

This study illustrates that inappropriate combined antithrombotic therapy is observed frequently among hospitalized patients, which could result in an altered benefit-risk ratio for these patients. Optimal and safe antithrombotic use can be stimulated by implementing an antithrombotic stewardship that evaluates patients using combined antithrombotic therapy, prevents overuse of the combined therapy by adequate documentation of duration of therapy when combined therapy is initiated and a structured validation of the indication for the combined antithrombotic therapy when patients are already using combined antithrombotic therapy.

Future studies are needed to conclude whether these interventions will lead to a decrease of patients entering the hospital with a major bleeding using combined antithrombotic therapy without increasing the number of thromboembolic events among these patients.

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Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions

ZZ and NK conceived of and designed the study. ZZ collected the data and ZZ and NK analyzed the data. ZZ, NK, JS, WS and SW interpreted data. ZZ drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript version.

Availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval

The protocol was evaluated and approved by the Institutional Review Board of OLVG Hospital. No written informed consent was required since only previously collected information was analysed. Individual patient data were documented anonymously.

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Tables

Table 1. Baseline characteristics.

Table 2. Interventions by the antithrombotic stewardship.

Table 3. Type of interventions initiated by the antithrombotic stewardship.

Table 4. Bleeding-, thromboembolism complications and mortality

Figures

Figure 1. Type of interventions in patients using double therapy or triple therapy. OAC, oral anticoagulation.

Figure 2. Type of interventions in patients who initiated double or triple therapy during or prior to hospitalization. OAC, oral anticoagulation.

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