Real-life management of dual antiplatelet therapy interruption: the REGINA survey

Registre gestion de la l’interruption de la bithérapie antiagrégante plaquettaire orale dans la vraie vie : le registre Regina

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Summary
Background. — Concern about procedure-related bleeding is a major reason for premature discontinuation of dual oral antiplatelet therapy (APT); treatment cessation is detrimental in patients with coronary artery disease (CAD), especially after drug-eluting stent (DES) placement. The nationwide REGINA survey was designed to evaluate how the interruption of dual APT is managed in the ‘real world’.

Methods. — Physicians (2700/4581) were randomly selected to participate in a computer-assisted telephone interview. Knowledge about DES and APT was appraised by multiple-choice questions. Strategies for temporary interruption of dual APT before an invasive or surgical procedure were evaluated using 21 scenarios, including high-risk (30 days after DES) and low-risk (18 months after DES) periods.

REGINA: registre sur la gestion de l’interruption des antiagrégants plaquettaires oraux chez le coronarien.

The results of this study were presented in part at the Congress of the European Society of Cardiology, September 2007.

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Results. — Out of 2700 practitioners, 2515 completed the interview. Rates of correct answers to basic knowledge questions ranged from 0% (dentists) to 52% (cardiologists). Unjustified total interruption of dual APT was much more frequent than expected (22.0% vs. 11.8%). A strategy of total interruption was less frequently chosen in the period of high ischemic risk compared to the low-risk period (13.7% vs. 31.1%, \( p < 0.0001 \)). Dual APT interruption in patients who require additional invasive cardiac or surgical procedures depended on type of physician consulted (more frequent in specialists than general practitioners or dentists), and on the physician's age and practice type (rural/private vs. urban/hospital). Correct answers were more frequently given in situations bearing a major risk, either ischemic or bleeding risk, than in those with no risk (49.2% vs. 30.2%, \( p < 0.0001 \)). Low-molecular-weight heparin was the substitution therapy in over two-thirds of scenarios and was associated with longer periods of APT interruption.

Interpretation. — Adequate management of APT in patients with intracoronary stents who undergo potentially haemorrhagic invasive procedures depends mainly on the type of physician involved and their practice rather than on a carefully weighted assessment of ischemic/bleeding risk. Our findings suggest a lack of scientific evidence, insufficient knowledge of guidelines, and poor communication between physicians managing these patients.

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Introduction

Discontinuation of antiplatelet therapy in patients with established coronary artery disease (CAD) has become an increasingly important concern. Evidence has arisen that stopping aspirin in patients with stable CAD treated with aspirin alone leads to an increased risk of acute coronary syndrome (ACS) and death [1,2]. This potential hazard is amplified by the large numbers of patients treated with bare-metal stents (BMS) and drug-eluting stents (DES) [3].
who are receiving long-term dual oral antiplatelet therapy (APT). The risk of APT interruption in these patients is even higher, especially when DES have been used [4—9]. Recent recommendations from the European Society of Cardiology and the American Heart Association [10—12] have warned against premature and unjustified interruption of APT. The bleeding hazard often does not justify the interruption of APT. Recommendations from different scientific societies, including gastroenterologists, anaesthesiologists, lung specialists and dentists, have provided some important practical guidelines [13—16]. However, exaggerated concern about increased procedure-related bleeding remains the major factor for premature discontinuation of APT. The ischaemic hazard related to discontinuation of APT depends on many factors, of which the context of recent stent implantation in ACS is certainly the most critical. This is why a recent advisory committee/consensus group stressed the importance of 12 months of dual APT after DES implantation and of educating patients and healthcare providers about the hazards of premature discontinuation [10,12]. Educating physicians and healthcare providers has become a critical aspect of good clinical practice. Temporary discontinuation (<15 days) of APT because of planned invasive procedure is handled mainly by noncardiologists; these practitioners are very sensitive to recommendations from their national societies. In addition, a real-life situation clearly lacks prospective and scientific evaluation, and physicians are often unsure how to approach this dilemma. The registre sur la gestion de l’interruption des antithrombotiques plaquettaires oraux chez le coronarien (REGINA) survey was designed to evaluate how interruption of dual APT is handled in the real world by different categories of practitioner. Our major aim was to evaluate the rate of complete interruption of dual APT according to the period at risk of stent thrombosis for each category of physician and as to whether complete interruption was justified or not.

Methods

Evaluation of basic knowledge

Evaluation of basic knowledge was performed by determining the rate of correct answers to three multiple-choice questions (Appendix A). For each question, there were five possible responses. The first question referred to the definition of a DES. The other two related to the minimum duration of dual APT following BMS and DES placement. A scientific advisory board was created to validate the questionnaires and to determine the expected correct answers, based on the recommendations in all currently available guidelines [13—15]. Correct answers are highlighted in bold and italics in the Appendix B.

Evaluation of interruption strategies

Interruption strategies following DES were evaluated for periods of high risk (30 days after DES implantation) and low risk (18 months after DES implantation). In the high-risk situation, discontinuation was considered (by the scientific committee) as detrimental because of the high risk of ischaemic events whereas the bleeding risk was acceptable. In the low-risk situation, discontinuation was considered (by the scientific committee) to be mandatory because of the low risk of ischaemic events and the high bleeding risk.

Both situations were evaluated by one or two simple multiple-choice questions (Appendix B). All questions were constructed using a unique pattern of six possibilities, delivered in the same order to facilitate the interview. The first choice was postponing the procedure. The second was continuation of both aspirin and clopidogrel during the procedure. The third and the fourth choices were partial discontinuation of dual APT, either aspirin or clopidogrel. The fifth was temporary complete interruption of dual APT. The last choice was ‘Don’t know’, but this response was discouraged.

Each situation was tailored according to the category of physician. Concordance was assessed systematically by an additional question in which the physician had to consider themselves as the patient. Management of APT interruption, either complete or partial, was carefully evaluated when it was the chosen strategy. In particular, the time delay of interruption before the procedure and substitution therapy with either low-molecular-weight heparin or a non-steroidal anti-inflammatory drug (NSAID) were carefully assessed (Appendix C).

Study population and computed-assisted telephone interview technique

National scientific societies for each category of physician were contacted and asked to participate in the study. Their tasks were to nominate a member of the scientific board and to provide a list of physicians recognised as members who could potentially participate in the study. Exclusion criteria were retirement and absence of clinical practice. A specialised consulting agency (IPSOS Insight Santé, Paris, France) was responsible for undertaking the interviews. The computed-assisted telephone interview method was chosen to avoid selection bias and to give each potential physician the same probability of being interviewed. This approach allowed direct quoting of the answers and automatic and random delivery of the questionnaire. In addition, each choice of question was randomly delivered. The rate of refusal and of abandon was monitored, as well as real-time follow-up of the overall study sample.

To expedite the telephone interviews and to prevent a high rate of refusal, all members of staff who performed the interviews participated in a training session on APT and on scientific interview techniques. A letter outlining the objectives of the REGINA study and the methodological approach was sent on behalf of the advisory board to all potential participants five days before random selection.

Statistical analyses

The frequency of different answers was compared using the Chi² test. Multivariable stepwise logistic regression analysis was carried out to identify independent correlates of correct answers, both in the whole sample of practitioners and in each category. Concordance between the answers from each practitioner to high-risk situations in which ‘the doctor was the patient’ and ‘the doctor was not the patient’ was estimated by the Kappa coefficient. The two-sided sig-

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significance level was fixed at 5%. All analyses were performed using SAS 9.1.3 (SAS Institute).

**Role of the funding source**

The study sponsors had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

**Results**

**Study population**

Six different categories of practitioner were selected: general practitioners (GPs), dentists, lung specialists, gastroenterologists, anaesthetists and cardiologists. Of the original database, 88% of practitioners were successfully contacted; 525 were excluded because they did not match the inclusion criteria (Fig. 1). After the first telephone contact, 608 practitioners declined for reasons including lack of time or interest, refusal to participate in telephone interviews or surveys of public opinion as a general principle, and the secretary’s refusal. For the majority of physicians, no reason was given.

Of the 2700 practitioners who participated in the interview, 2515 completed it. The overall rate of participation was 82% (Fig. 1). The main reason for failure to complete the questionnaire was lack of time. The participation rate varied widely, ranging from 65% for GPs to 97% for anaesthetists.

Practitioners were more often male and there was a heterogeneous distribution in age across specialties (Table 1).

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**Figure 1.** Study population flowchart.
There was broad variation in terms of practice location, with 3% of dentists working exclusively in hospitals compared with 48% of anaesthetists. The average length of interview was 8 mins. The study was undertaken between June and September 2006.

**Basic knowledge and recommendations**

There was a dramatic heterogeneity in the rate of correct answers to all basic questions ranging from 0% for dentists to 52% for cardiologists; 95% of cardiologists could correctly define a DES vs. only 7% of dentists (Fig. 2). Among other categories of practitioner, the correct answer was given by 39% of GPs, 40% of lung specialists, 43% of gastroenterologists and 56% of anaesthetists. Overall, the minimum duration of dual APT was better known for DES than for BMS (Fig. 3).

Again, there was a large difference between cardiologists and other categories of physician: less than 10% of dentists gave the expected appropriate answers; however, only 54% of cardiologists knew how to handle dual APT following BMS placement.

After multivariable logistic regression analysis, independent correlates of correct answers to all basic questions were ‘being a cardiologist’ vs. ‘other practitioner’ (odds ratio [OR] 19.0, 95% confidence interval [CI] 14.4–25.2; \( p < 0.0001 \)), young age (\( \leq 45 \) vs > 60 years, OR 3.5, 95% CI 1.9–6.4, \( p < 0.0001 \); \( \leq 45 \) vs 50 to \( \leq 60 \) years, OR 1.9, 95% CI 1.3–2.6, \( p < 0.001 \)), and male sex (OR 1.8, 95% CI 1.2–2.7, \( p < 0.01 \)).

**Total or partial interruption of dual APT**

A total of 21 scenarios were proposed, including 14 with high ischemic risk and seven with low ischemic risk features. They are listed in the appendix with correct answers, as defined by the expert committee, in bold italics. Partial (one of the two oral antiplatelet agents) or total (both aspirin and clopidogrel) interruption was the strategy chosen by 72% of practitioners about to perform an invasive or...
surgical procedure, although continuation of dual APT was mandatory in 47% of all situations (10 of 21). Total interruption was a particularly frequent strategy (22.0%), although it was justified and expected in only 11.8% (4 of 21) of clinical situations given the high risk of bleeding (Fig. 4). Unjustified total interruption was more frequently chosen by specialists compared with dentists or GPs (Fig. 4). A strategy of total interruption was more frequently chosen in the period of low ischemic risk (Q4–5, Q10–11, 15, Q18–19, 21, Q25–26, 30) compared to the high-risk period (31.1% vs. 13.7%, \( p < 0.0001 \)); this trend was observed only among specialists, whereas similar rates were reported among dentists and GPs (Fig. 5).

The choice of postponing surgery or the invasive procedure varied according to category of practitioner. Dentists (78%) and GPs (56%) displayed the highest rates compared to lung specialists (27%), gastroenterologists (20%), anaesthetists (12%) and cardiologists (35%) (\( p < 0.0001 \) for all).

Independent correlates of total interruption after multivariable regression analysis, conducted separately for each category of practitioner, were age for cardiologists (> 60 vs ≤ 45 years, OR 2.26, 95% CI 1.13–4.50, \( p = 0.02 \); and > 50 to ≤ 60 vs ≤ 45 years, OR 1.76, 95% CI 1.12–2.79, \( p = 0.015 \)).

Management of interruption and of reintroduction of APT

Interruption of APT was usually planned for more than five days; 17% of the population who chose the interruption strategy planned to interrupt for less than five days, 30% from 6–9 days, and 25% more than 10 days prior to planned intervention. There was no significant difference with respect to category of physician. Low-molecular-weight heparin was chosen as the substitution therapy in more than two-thirds of situations.

Large discrepancies were observed between categories of practitioner as to whether reintroduction of APT was systematically advised. Only 51% of dentists and 67% of gastroenterologists systematically recommended rapid reintroduction, compared to 77% of anaesthetists, 84% of GPs, 88% of lung specialists and 92% of cardiologists.

Total interruption could be chosen either by the practitioner alone or after requesting expert advice. Cardiologists and anaesthetists requested expert advice from gastroenterologists and surgeons, when indicated, in 73% and 72%, of the situations, respectively, whereas lung specialists, anaesthetists and gastroenterologists requested expert advice from cardiologists in only 42, 32 and 54% of the situations, respectively.

Concordance between answers from each practitioner to high-risk situations in which they themselves were the patient and they were not the patient was high. The Kappa coefficient ranged from 0.73 (0.67–0.79) for GPs, 0.79 (0.73–0.85) for lung specialists and cardiologists, 0.80 (0.75–0.86) for gastroenterologists, to 0.84 (0.78–0.89) for anaesthetists.

Correct answer according to the period at risk of stent thrombosis and to the bleeding risk

The high-risk situations were much better managed than the low-risk one (Fig. 6). There was a trend for under treat-
The REGINA survey is the first prospective evaluation of dual APT discontinuation among a wide variety of French practitioners who regularly deliver medical care to patients with established CAD who require invasive cardiac or surgical procedures. Both ischemic and bleeding risks were carefully weighted in selected and common real-life situations. Knowledge of recommendations regarding use of dual APT after stent placement was poor overall, although there were large discrepancies according to category of practitioner. Misguided concerns about excessive procedure-related bleeding led to a dramatic and inappropriate rate of complete interruption of dual APT. As a consequence, excessive use of substitution therapies that have not been properly evaluated in randomised studies, leading to prolonged discontinuation of APT, was observed. Reassuringly, scenarios of high risk were better managed than low-risk ones (Fig. 6). Taken together, the findings suggest that adequate management of dual APT interruption in patients who require additional invasive cardiac or surgical procedures depends greatly on the type of physician consulted, and often on the physician’s age and type of practice (rural or private vs. urban or hospital), suggesting a frequent lack of information and probably also lack of communication between the different physicians concerned with the care of an individual patient. Scientific recommendations on the use of APT in patients with DES clearly need further development and dissemination to avoid adverse outcomes in coronary patients at temporary risk of bleeding.

With the increasing use of DES and recent data on the long-term benefit of dual APT [17], discontinuation of APT has become a great concern not only for cardiologists but for all practitioners in charge of patients with atherothrombosis. Interruption of APT is mainly driven by the potential risk of bleeding complications in the context of planned surgery or any other intervention that incurs an additional bleeding risk. However, the lack of prospective and scientific evaluation in the real world may account for the notable discrepancies between physicians on how to approach this dilemma. Consistent data are available demonstrating the detrimental effect of complete APT discontinuation [1,2,18–20], although some clinical situations require further clarification, namely partial interruption of dual APT [21–24]. For example, discontinuation of clopidogrel after the recommended duration, while maintaining aspirin, is a real challenge given the suspected increase of late DES thrombosis but the lack of scientific evidence [4,21,25–27].

There are clearly situations for which discontinuation of antiplatelet therapy is indicated, and careful assessment of the relative risks of ischaemic and bleeding events is necessary to determine whether antiplatelet therapy continuation or withdrawal is most appropriate. In the present investigation, high- and low-risk ischaemic situations were carefully chosen to avoid misunderstanding. In particular, the high-risk situation corresponded to surgery soon after DES implantation, a scenario with a well-established mortality risk [21,23]. As a consequence, complete interruption was rarely mandatory according to prespecified recommendations from the advisory board. However, the rate of complete interruption was very high overall. Reassuringly, situations with a high ischaemic risk were better managed than low-risk ones, although they are far less frequent in the real world. Indeed, patients with recent stent placement who require immediate invasive care with potential bleeding are much fewer in number than those who had a stent implanted more than a year earlier.

Not surprisingly, significant differences in approach were observed with respect to the type of practitioner. With the exception of dentists, practitioners who usually carry out invasive or diagnostic procedures with potential bleeding risk were more likely to discontinue dual APT compared with GPs. Although the very low rate among dentists is striking, it should be noted that there are 10 to 40 times more dentists than any other type of practitioner in France; there are also 40 000 dentists for every 100 lung specialists and every 100 interventional lung specialists. In addition, considering that most dental procedures do not require discontinuation of dual APT, it is reasonable to assume that the absolute number of inappropriate complete interruptions of dual APT is probably higher among dentists than for any other type of practitioner. Significant differences between rates of complete interruption between low- and high-ischaemic risk situations were observed for all types of practitioner except for dentists. This intriguing finding suggests an additional risk—that dentists are unlikely to make a decision to discontinue based on the patient’s clinical situation and rather refer the patients to specialists. The low rate of discontinuation of dual APT reported among GPs is because they are less likely to perform invasive procedures compared to other practitioners, but also because they do not make the decision themselves, instead referring the patient to a specialist. This last option was not evaluated in the present investigation.
One of the major consequences of complete interruption of dual APT is the use of ‘substitution therapies’, which are sought to prevent acute coronary events in patients with stable CAD. Two different types of antithrombotic regimen were chosen in the present investigation, given previous recommendations—low-molecular-weight heparins and NSAIDs [28]. Neither of these treatments has been evaluated in a stable situation, nor has either proven efficacy in preventing stent thrombosis. Our study provides clear evidence that substitution is a frequent strategy after the decision to interrupt dual APT has been made. It also shows that when substitution therapy is the preferred strategy, discontinuation continues for longer, leading to a prolonged time without any effective antiplatelet agents to prevent acute stent thrombosis. Overall, these results highlight the lack of clear guidance available for APT interruption during invasive procedures in patients with coronary stents [29].

Our investigation provides clear evidence that discontinuation of dual APT in patients undergoing additional non-cardiac invasive or surgical procedures depends greatly on the category of physician concerned and on whether scientific recommendations have been developed for their specialty. However, despite the availability of recommendations, inappropriate decisions about APT discontinuation remain frequent. The most dramatic finding is the low rate of correct answers to the ‘basic knowledge’ questions: only 7% of dentists could correctly define a DES and 5% of cardiologists could not. Given the recent controversy on the long-term safety of DES, continuing medical education remains an urgent priority; education of patients may also help to improve physicians’ understanding and clinical practice! Specifically, knowledge of recommendations on the use of APT in patients with stents requires improvement. It appears likely that guidelines are effective in identifying situations of high ischaemic risk but we also need to determine the bleeding risk associated with the type of procedure, particularly for planned surgery. Bleeding is an independent correlate of mortality, especially in patients with CAD who are treated with antithrombotic therapies [11] and premature discontinuation of antiplatelet therapies has been suggested as one of the potential mechanisms of death in patients who bleed [30]. The situation of high bleeding risk was not clearly identified by all practitioners who tended to continue dual APT in patients with high-risk bleeding features and who would have required interruption of dual APT.

Limitations

Although we interviewed 1% of all active practitioners in France, no surgeons, rheumatologists or other specialists who perform invasive procedures requiring discontinuation of APT were interviewed. However, there were no available recommendations for these specialties. Moreover, for some of the categories of physician interviewed, guidelines on APT interruption have been only recently available, and dissemination of these recommendations was not optimal at the time of the interview [13,16]. In addition, we did not quote whether practitioners were aware of available recommendations. The risk of stent thrombosis and the debate on DES is still ongoing, with new information released during and after this survey that may have an impact on how physicians weigh the risk/benefit of APT interruption in their patients [21,31–33]. All of these limitations may contribute to the discrepancies we observed in responses to our questions. Nevertheless, we believe that the question of APT interruption remains poorly understood, with limited scientific knowledge, and uncertainty persists regarding the optimal strategies for the multiple presenting clinical situations [29]. Our survey provides a worrying but worthwhile picture of the situation and should help further in bringing attention to this public healthcare issue. Our results apply specifically to French physicians and one may have expected a different pattern in other countries.

Conclusions

Our data highlight an urgent need to improve not only guidelines but also practitioners’ basic knowledge to avoid unnecessary risk for patients and communication between physicians and between patient and physicians. Although perception of ischaemic risk is reasonably well established, there is also a need to improve guidelines on identification of bleeding risk. In that respect, the results of the ongoing STRATAGEM trial, [34] which randomly selects patients with established atherothrombosis to continue or discontinue chronic aspirin therapy in the context of planned non-cardiac surgery, should be very helpful. Finally, we also need additional prospective large-scale trial randomising clopidogrel discontinuation after one year of treatment following DES implantation.

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Appendix A.

A.1. Basic knowledge questions

Q1: What is a drug-eluting stent (DES)?
1. An endovascular prosthesis coated with a controlled-release polymer containing antiproliferative drugs
2. An endovascular prosthesis cAPTed with a controlled-release polymer containing antithrombotic drugs
3. An endovascular prosthesis with progressive resorption after placement
4. An autoexpandable endovascular prosthesis
5. Do not know

Q2: What is the minimum duration of dual oral antiplatelet therapy after bare-metal stent (BMS) placement?
Q3: What is the minimum duration of dual oral antiplatelet therapy after DES placement?
1. 8 days
2. 1 month
3. Between 2 months and up to 1 year
4. Life long
5. Do not know

Appendix B.

B.1. Questions for lung specialists Q4—Q9

Q4: A heavy smoker is referred to you for a bronchoscopy to investigate haemoptysis. He has recently undergone DES placement (< 1 month) and is currently being treated with a combination of 75 mg/d aspirin and 75 mg/d clopidogrel. What do you do? (Single answer)
1. You refuse to perform diagnostic bronchoscopy
2. You agree to perform diagnostic bronchoscopy while the patient continues to take dual APT
3. You agree to perform diagnostic bronchoscopy after the patient temporarily stops taking aspirin
4. You agree to perform diagnostic bronchoscopy after the patient temporarily stops taking clopidogrel
5. You agree to perform diagnostic bronchoscopy after the patient temporarily stops taking aspirin and clopidogrel
6. You do not know

Q5: A bronchus narrowing is found with a suspect mass (non-haemorrhagic). A biopsy is required given the suspicion of an underlying cancer. What do you do? (Single answer)
1. You recommend postponing the biopsy
2. You agree to perform the biopsy while the patient continues to take dual APT
3. You agree to perform the biopsy after the patient temporarily stops taking aspirin
4. You agree to perform the biopsy after the patient temporarily stops taking clopidogrel
5. You agree to perform the biopsy after the patient temporarily stops taking both aspirin and clopidogrel
6. You do not know

Q6: A patient is referred to you for bronchoalveolar lavage because of a suspected pulmonary fibrosis. They underwent DES placement 18 months ago and are currently being treated with a combination of 75 mg/d aspirin and 75 mg/d clopidogrel. What do you do? (Single answer)
1. You refuse to perform BAL
2. You agree to perform BAL while the patient continues to take dual APT
3. You agree to perform BAL after the patient temporarily stops taking aspirin
4. You agree to perform BAL after the patient temporarily stops taking clopidogrel
5. You agree to perform the BAL after the patient temporarily stops taking both aspirin and clopidogrel
6. You do not know

Q7: A transbronchus biopsy is necessary for diagnostic confirmation. What do you do? (Single answer)
1. You recommend postponing the biopsy
2. You perform the biopsy while the patient continues to take dual APT
3. You perform the biopsy after the patient temporarily stops taking aspirin
4. You perform the biopsy after the patient temporarily stops taking clopidogrel
5. You perform the biopsy after the patient temporarily stops taking both aspirin and clopidogrel
6. You do not know

Q8: Same question as Q7 but you are the patient. (Single answer)
1. You recommend postponing the biopsy
2. You undergo the biopsy while continuing to take dual APT
3. You undergo the biopsy after temporarily stopping taking aspirin
4. You undergo the biopsy after temporarily stopping taking clopidogrel
5. You undergo the biopsy after temporarily stopping taking both aspirin and clopidogrel
6. You do not know

[B.2. Questions for anaesthetists Q10—Q14]

Q10: A patient with a recent DES placement (< 1 month) is referred to you for a diagnostic colonoscopy to explore a mild anaemia associated with black stools. They are currently being treated with a combination of 75 mg/d aspirin and 75 mg/d clopidogrel. The patient has been informed of the risk. What do you do? (Single answer)
1. You refuse to administer anaesthesia while the patient continues to take aspirin and clopidogrel
2. You agree to administer anaesthesia while the patient continues to take aspirin and clopidogrel
3. You agree to administer anaesthesia after the patient temporarily stops taking aspirin but continues to take clopidogrel
4. You agree to administer anaesthesia after the patient temporarily stops taking aspirin
5. You agree to administer anaesthesia after the patient temporarily stops taking both aspirin and clopidogrel
6. You do not know

Q11: A malignant tumour of the right angle of the colon is diagnosed and surgery is planned. The anaesthetist asks you what should be done regarding APT. (Single answer)
1. You refuse to administer anaesthesia while the patient continues to take aspirin and clopidogrel
2. You agree to administer anaesthesia while the patient continues to take aspirin and clopidogrel
3. You agree to administer anaesthesia after the patient temporarily stops taking aspirin
4. You agree to administer anaesthesia after the patient temporarily stops taking both aspirin and clopidogrel
5. You agree to administer anaesthesia after the patient temporarily stops taking both aspirin and clopidogrel
6. You do not know

Q12: A transbronchus biopsy is necessary for diagnostic confirmation. What do you do? (Single answer)
1. You recommend postponing the biopsy
2. You perform the biopsy while the patient continues to take dual APT
3. You perform the biopsy after the patient temporarily stops taking aspirin
4. You perform the biopsy after the patient temporarily stops taking clopidogrel
5. You perform the biopsy after the patient temporarily stops taking both aspirin and clopidogrel
6. You do not know

Q13: Same question as Q12 but you are the patient. (Single answer)
1. You recommend postponing the biopsy
2. You undergo the biopsy while continuing to take dual APT
3. You undergo the biopsy after temporarily stopping taking aspirin
4. You undergo the biopsy after temporarily stopping taking clopidogrel
5. You undergo the biopsy after temporarily stopping taking both aspirin and clopidogrel
6. You do not know

Q14: A transbronchus biopsy is necessary for diagnostic confirmation. What do you do? (Single answer)
1. You recommend postponing the biopsy
2. You perform the biopsy while the patient continues to take dual APT
3. You perform the biopsy after the patient temporarily stops taking aspirin
4. You perform the biopsy after the patient temporarily stops taking clopidogrel
5. You perform the biopsy after the patient temporarily stops taking both aspirin and clopidogrel
6. You do not know

Q15: A heavy smoker is referred to you for a bronchoscopy to investigate haemoptysis. He has recently undergone DES placement (< 1 month) and is currently being treated with a combination of 75 mg/d aspirin and 75 mg/d clopidogrel. What do you do? (Single answer)
1. You refuse to perform diagnostic bronchoscopy
2. You agree to perform diagnostic bronchoscopy while the patient continues to take dual APT
3. You agree to perform diagnostic bronchoscopy after the patient temporarily stops taking aspirin
4. You agree to perform diagnostic bronchoscopy after the patient temporarily stops taking clopidogrel
5. You agree to perform diagnostic bronchoscopy after the patient temporarily stops taking aspirin and clopidogrel
6. You do not know
B.3. Questions for cardiologists Q15—Q20

Q15: A patient who has recently undergone DES placement (< 1 month) needs to have a tooth extraction. They are currently being treated with a combination of 75 mg/d aspirin and 75 mg/d clopidogrel. What do you recommend? (Single answer)

Q16: Same question as Q15 but you are the patient. (Single answer)

Q17: A patient needs to have impacted back teeth extracted. They have undergone DES placement 18 months ago and are currently being treated with a combination of 75 mg/d aspirin and 75 mg/d clopidogrel. What do you recommend? (Single answer)

Q18: An anaesthetist asks for your expert opinion because they have been asked to take care of a patient who needs a diagnostic colonoscopy (mild anaemia with black stools). The is patient has recently undergone DES placement (< 1 month) and is currently being treated by a combination of 75 mg/d aspirin and 75 mg/d clopidogrel. What do you recommend? (Single answer)
Q19: A cancer of the right angle of the colon is diagnosed and surgery is planned. The anaesthetist asks for your expert opinion. *(Single answer)*
1. You recommend that the surgery goes ahead while the patient continues to take both aspirin and clopidogrel
2. **You recommend that the surgery is postponed**
3. You recommend that the surgery is performed after the patient temporarily stops taking aspirin but continues to take clopidogrel
4. You recommend that the surgery is performed after the patient temporarily stops taking clopidogrel but continues to take aspirin
5. You recommend that the surgery is performed after the patient temporarily stops taking both aspirin and clopidogrel
6. You do not know

Q20: What would you have recommended to the anaesthetist if the time delay from DES placement to colonoscopy had been > 18 months and the patient was stable? *(Single answer)*
1. You recommend administering anaesthesia and performing the colonoscopy while the patient continues to take aspirin and clopidogrel
2. You recommend postponing the colonoscopy
3. You recommend administering anaesthesia and performing the colonoscopy after the patient temporarily stops taking aspirin but continues to take clopidogrel
4. **You recommend administering anaesthesia and performing the colonoscopy after the patient temporarily stops taking clopidogrel but continues to take aspirin**
5. You recommend administering anaesthesia and performing the colonoscopy after the patient temporarily stops taking both aspirin and clopidogrel
6. You do not know

B.4. Questions for dentists Q21—Q24

Q21: A patient with a recent DES placement (< 1 month) needs to have a simple tooth extraction (not impacted). They are being treated with a combination of 75 mg/d aspirin and of 75 mg/d clopidogrel. What do you do? *(One possible answer)*
1. You ask the patient to temporarily stop taking both aspirin and clopidogrel before the tooth extraction
2. You ask the patient to temporarily stop taking both aspirin and clopidogrel before the tooth extraction
3. **You perform the tooth extraction with careful haemostasis and without interruption of APT**
4. You refuse to perform the tooth extraction and you refer the patient to their GP or cardiologist for expert advice
5. You ask the patient to temporarily stop taking aspirin before the tooth extraction
6. You don’t know

Q22: Same as question Q21 but the time delay from stent placement to extraction is > 18 months and there are two impacted back teeth to be extracted. What do you do? *(One possible answer)*
1. You ask the patient to temporarily stop taking both aspirin and clopidogrel before the tooth extraction
2. **You ask the patient to temporarily stop taking clopidogrel before the tooth extraction**
3. You perform the tooth extraction with careful haemostasis and without interruption of APT
4. You refuse to perform the tooth extraction and you refer the patient to their GP or cardiologist for expert advice
5. You ask the patient to temporarily stop taking aspirin before the tooth extraction
6. You do not know

Q23: Same as Q21, but you are the patient. What do you do? *(One possible answer)*
1. You would temporarily stop taking both aspirin and clopidogrel before the tooth extraction
2. You would temporarily stop taking clopidogrel before the tooth extraction
3. You would continue to take both aspirin and clopidogrel before the tooth extraction
4. You would ask your cardiologist for advice
5. You would temporarily stop taking aspirin before the tooth extraction
6. You do not know

Q24: Same as Q22, but you are the patient. What do you do? *(One possible answer)*
1. You would temporarily stop taking both aspirin and clopidogrel before the tooth extraction
2. You would temporarily stop taking clopidogrel before the tooth extraction
3. You would continue to take both aspirin and clopidogrel before the tooth extraction
4. You would ask your cardiologist for advice
5. You would temporarily stop taking aspirin before the tooth extraction
6. You do not know

B.5. Questions for gastroenterologists Q25—Q29

Q25: A patient with a recent DES stent placement (< 1 month) is referred to you for diagnostic gastroscopy to investigate why they are producing black stools. They are being treated with a combination of 75 mg/d aspirin and 75 mg/d clopidogrel. What would you do? *(Single answer)*
1. You refuse to perform the gastroscopy and you start the patient on proton pump inhibitor (PPI) treatment
2. **You agree to perform the gastroscopy while the patient continues with dual APT and you start the patient on PPI treatment**
3. You agree to perform the gastroscopy after the patient temporarily stops taking aspirin and you start the patient on PPI treatment
4. You agree to perform the gastroscopy after the patient temporarily stops taking clopidogrel and you start the patient on PPI treatment
5. You agree to perform the gastroscopy after the patient temporarily stops taking dual APT and you start the patient on PPI treatment
6. You do not know
Q26: A non-bleeding ulcer is discovered. You are asked to perform a biopsy to investigate a possible underlying cancer. What do you do? (Single answer)
1. You refuse and you recommend postponing the biopsy
2. You agree to perform the biopsy while the patient continues with dual APT and you start the patient on PPI treatment
3. You perform the biopsy after the patient temporarily stops taking aspirin
4. You perform the biopsy after the patient temporarily stops taking clopidogrel
5. You perform the biopsy after the patient temporarily stops taking both aspirin and clopidogrel
You do not know

Q27: Same question as Q26 but you are the patient. What would you do? (Single answer)
1. You refuse to have the biopsy and advise that it be postponed
2. You have the biopsy while continuing to take dual APT and you start PPI treatment
3. You have the biopsy after temporarily stopping taking aspirin
4. You have the biopsy after temporarily stopping taking clopidogrel
5. You have the biopsy after temporarily stopping taking both aspirin and clopidogrel
6. You do not know

Q28: A patient is referred to you for diagnostic colonoscopy because of the presence of blood in their stools. This patient has undergone DES placement 18 months before and is currently being treated with a combination of 75 mg/d aspirin and 75 mg/d clopidogrel. What do you recommend? (Single answer)
1. You refuse to perform the colonoscopy while the patient continues to take dual APT
2. You agree to perform the colonoscopy while the patient continues to take dual APT
3. You agree to perform the colonoscopy after the patient temporarily stops taking aspirin
4. You agree to perform the colonoscopy after the patient temporarily stops taking clopidogrel
5. You agree to perform the colonoscopy after the patient temporarily stops taking both aspirin and clopidogrel
6. You do not know

Q29: A pedicle polyp (< 1 cm) is discovered in the transverse colon. The decision to perform a polypectomy is made. What do you do? (Single answer)
1. You refuse to perform the polypectomy while the patient continues to take dual APT
2. You agree to perform the polypectomy while the patient continues to take dual APT
3. You agree to perform the polypectomy after the patient temporarily stops taking aspirin
4. You agree to perform the polypectomy after the patient temporarily stops taking clopidogrel
5. You agree to perform the polypectomy after the patient temporarily stops taking both aspirin and clopidogrel
6. You do not know

B.6. Questions for GPs Q30–Q32

Q30: A patient with a recent DES placement (< 1 month) needs to have a simple tooth extraction (not impacted). They are being treated with a combination of 75 mg/d aspirin and 75 mg/d clopidogrel. What do you recommend? (Single answer)
1. You agree to the tooth extraction after the patient temporarily stops taking dual APT
2. You ask the patient to temporarily stop taking clopidogrel before the tooth extraction
3. You request that the patient continues to take dual APT before the tooth extraction
4. You ask for the expert advice of a cardiologist
5. You recommend the patient temporarily stops taking aspirin before the tooth extraction but keeps taking clopidogrel
6. You do not know

Q31: Same question as Q30 but you are the patient. What would you do? (Single answer)
1. You agree to the tooth extraction after stopping taking dual APT
2. You agree to temporarily stop taking clopidogrel before the tooth extraction
3. You continue taking dual APT before the tooth extraction
4. You ask for the expert advice of a cardiologist
5. You suggest temporarily stopping taking aspirin before the tooth extraction but keep taking clopidogrel
6. You do not know

Q32: Same as question Q30 but the time delay from DES placement to extraction is > 18 months and there are two impacted back teeth to be extracted. What do you do? (Single answer)
1. You agree to the tooth extraction after the patient temporarily stops taking dual APT
2. You ask the patient to temporarily stop taking clopidogrel before the tooth extraction
3. You ask the patient to continue with dual APT during the tooth extraction
4. You ask for the expert advice of a cardiologist
5. You recommend the patient temporarily stops taking aspirin before the tooth extraction but keeps taking clopidogrel
6. You do not know

Appendix C.

C.1. Questions related to complete interruption of dual APT

For lung specialists

If the answers to Q4 or Q5 or Q6 or Q7 or Q8 = 3 or 4 or 5, then ask Q33 to Q36 and Q38

For anaesthetists

If the answers to Q10 or Q11 or Q12 or Q13 or Q14 = 3 or 4 or 5, then ask Q33 to Q38

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### The REGINA survey

**Q33:** Do you regularly inform the patient about the potential thrombotic risk after they stop taking APT?

1. Yes
2. No
3. Do not know

**Q34:** For how long should the patient stop taking dual APT before surgical intervention?

- 1...1...1 days

**Q35:** Do you use substitution therapy?

1. Yes
   - i. Low-molecular-weight heparin
   - ii. Non-steroidal anti-inflammatory drug (Cébutid®)
2. No
3. Do not know

**Q36:** Would you ask your patient to resume taking dual APT after surgical intervention?

1. Yes
2. No
3. Do not know

**Q37:** Would you ask for expert advice from a dentist or gastroenterologist?

1. Yes
2. No
3. Do not know

**Q38:** Would you ask for expert advice from a cardiologist?

1. Always
2. Depends on the situation
3. Never
4. Do not know

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**References**


dogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-


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