Management of antithrombotics in situations with a gap in evidence: A national French survey focusing on patients with coronary artery disease and atrial fibrillation

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Running title: Antithrombotic management in CAD and AF

List of Authors

Gilles Lemesle*, Christophe Bauters†, Laurent Bonello‡, Laurent Fauchier§, Guillaume Cayla‖, Eloi Marijon¶, Maxime Guenoun#, Guillaume Schurtz**, Sandro Ninni*, Marjorie Richardson**, Franck Albert††, Serge Cohen‡‡, Nicolas Lamblin†, Nicolas Danchin§§

Institutions

* Heart and Lung Institute, University hospital of Lille, F-59000 Lille, France. Univ. Lille, F-59000, France. Institut Pasteur of Lille, Inserm U1011, F-59000 Lille, France. FACT (French Alliance for Cardiovascular Trials), F-75000 Paris, France

† Heart and Lung Institute, University hospital of Lille, F-59000 Lille, France. Univ. Lille, F-59000, France. Institut Pasteur of Lille, Inserm U1167, F-59000 Lille, France

‡ Aix-Marseille Univ, Intensive care unit, Department of Cardiology, Assistance Publique-Hôpitaux de Marseille, Hôpital Nord, Marseille, France ; Mediterranean Association for Research and Studies in Cardiology (MARS Cardio), Marseille, France ; Centre for CardioVascular and Nutrition research (C2VN), INSERM 1263, INRA 1260, Marseille, France

§ Department of Cardiology, CHU de Trousseau, University François-Rabelais, 37170 Chambray-lès-Tours, France

‖ Department of Cardiology, University Hospital of Nîmes, 30000 Nîmes, France

¶ Department of Cardiology, Hôpital Européen Georges Pompidou, AP-HP, University of Paris, Paris, France

Department of Cardiology, Hôpital Européen de Marseille, 13003 Marseille, France

** Heart and Lung Institute, University hospital of Lille, F-59000 Lille, France

†† Department of Cardiology, Hospital of Chartres, 28000 Chartres, France

‡‡ Department of Cardiology, Hôpital St Antoine, APHP, Paris, France

§§ Department of Cardiology, Hôpital Européen Georges Pompidou, AP-HP, University of Paris, and FACT (French Alliance for Cardiovascular Trials), Paris, France

All these authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Address for correspondence
Pr Gilles Lemesle
Service USIC et Centre Hémodynamique
Institut Cœur Poumon
CHU de Lille
59037 Lille Cedex, France
gilles_lemesle@yahoo.fr
Phone +33 320445330
Fax +33 320444898

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‡ Aix-Marseille Univ, Intensive care unit, Department of Cardiology, Assistance Publique-Hôpitaux de Marseille, Hôpital Nord, Marseille, France ; Mediterranean Association for Research and Studies in Cardiology (MARS Cardio), Marseille, France ; Centre for CardioVascular and Nutrition research (C2VN), INSERM 1263, INRA 1260, Marseille, France

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Address for correspondence
Pr Gilles Lemesle
Service USIC et Centre Hémodynamique
Institut Cœur Poumon
CHU de Lille
59037 Lille Cedex, France
gilles_lemesle@yahoo.fr
Phone +33 320445330
Fax +33 320444898

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ABSTRACT (n=249)

Background. If several randomized studies allowed to better apprehend what should be the best antithrombotic strategy in patients with concomitant coronary artery disease (CAD) and atrial fibrillation (AF), there are still several clinical situations with a gap of evidence.

Methods. We conducted a national French survey in September-October 2020 among cardiologists in order to assess what are daily practices regarding the antithrombotic management in several specific clinical settings where no or little scientific evidence is available. The questionnaires were built by a committee of 6 cardiologists routinely involved in the field of CAD and/or AF.

Results. Among the 6388 French cardiologists, 483 (7.6%) cardiologists participated to the survey. The rate of participation was rather homogeneous across the country. The mean age of participants was 48 +/- 12.7. There were 134 women (27.7%) and 349 men. Altogether, 181 (37.5%) cardiologists worked in private, 153 (31.7%) in non-universitary public and 83 (17.2%) in universitary public centers. The remaining had shared activity. Among the participants, 150 were interventional (coronary) cardiologists (31.1%). Others were general cardiologists (n=229), specialists in the field of rhythmology (n=43), heart failure (n=17) or imaging (n=44). The survey consisted of 10 questions pertaining to 2 virtual clinical scenarios.

Conclusions. The present survey is an illustration of how therapeutic decisions may vary in such situations with little or no scientific evidence. Such surveys may help experts to build consensus (answers with little variability) and to target the need for future trials and more research (answers with a lot of variability).

INTRODUCTION

In patients with coronary artery disease (CAD), the need for long-term oral anticoagulation (OAC), especially for atrial fibrillation (AF) is rather frequent and affects 10% to 15% of the cases [1-3].

Importantly, such patients with concomitant CAD and AF have been shown to be at very high risk of both: thrombotic/ischemic and bleeding events [1-3]. The management of antithrombotics in these patients is therefore critical in daily practice. In theory, these patients may require a combination of OAC (to avoid systemic embolism and stroke on one side) and antiplatelet therapies (APT) (to avoid recurrent coronary events on the other side). By contrast, combination of treatments may unnecessarily increase the risk of bleeding [1-6].

The benefit/risk ratio of each antithrombotic strategy is sometimes difficult to assess in daily practice in this context. If several randomized studies allowed to progress and to better apprehend what should be the best strategy in some specific contexts [7-11], there is still to date several clinical situations with either a complete gap or a low level of evidence.

In the present study, we therefore conducted a national French survey among cardiologists in order to assess what are daily practices regarding the antithrombotic management in several specific clinical settings where no or little scientific evidence is available. Such surveys may identify, on one side, clinical situations with little variability in answers and therefore help to build future consensus, and by contrast, to the other side, some other clinical situations with a lot of variability in answers and therefore target the need for future trials.

METHODS

The survey

The national survey was conducted in France between the 1st September and the 15th October 2020. The survey was disseminated by e-mail 6 times during the period (each week) to all French active cardiologists using a mailing list that pooled databases from the "collège national des cardiologues Français", the "collège national des cardiologues des hôpitaux", and the French Cardiology Journal "Cordiam". Among the 6388 French cardiologists, 483 (7.6%) cardiologists participated to the survey.

The questionnaire

The clinical vignettes and questionnaires were built by a committee of 6 cardiologists (GL, CB, LB, SN, NL, ND) routinely involved and experts in the field of coronary artery disease (CAD) and/or atrial fibrillation (AF) in order to specifically and exclusively cover some of the situations with a lack of evidence. The committee paid attention that none of the answers could be either absolutely true or absolutely wrong.

Information about participants was collected: age, sex, region where they work, sub-specialty (general cardiology, interventional cardiology, rhythmology, heart failure or imaging), and type of activity (private, public non-university, public university or mixed). The survey consisted of 10 questions pertaining to 2 clinical scenarios focusing on the problematic of the antithrombotic management in patients with concomitant CAD and AF (Supplemental Figures S1 and S2). Answers were collected electronically and strictly anonymously. Answers to the previous question had to be completely validated before accessing the following question.

Statistical analysis

Continuous variables are presented as means ± standard deviation (SD). Categorical variables are presented as absolute numbers and/or percentages. Univariate analysis using the

χ^2 test was performed to search for associations between answers and the different clinical scenarios. Statistical significance was assumed at P-value < 0.05.

RESULTS

The Survey

This survey was conducted in France between the 1st September and the 15th October 2020. Among the 6388 French cardiologists, 483 (7.6%) cardiologists participated to the survey. The participation rate in the country was rather homogeneous across the regions of France although the region "Nord" and the region "Paris" were overrepresented (Supplemental Figure S3). The mean age of participants was 48 year-old +/- 12.7. There were 134 women (27.7%) and 349 men. Of note, 181 cardiologists worked in private (37.5%), 153 (31.7%) in non-universitary public and 83 (17.2%) in universitary public centers. The remaining cardiologists had shared activity (private and public) (Supplemental Figure S4). Among the 483 participants, 150 were interventional (coronary) cardiologists (31.1%). Others were either general cardiologists (n=229), specialists in the field of rhythmology (n=43), heart failure (n=17) or imaging (n=44) (Supplemental Figure S5).

Case 1

The clinical vignette is detailed in Supplemental Figure S1. This case concerned a young man presenting with non ST-elevation acute coronary syndrome (ACS) and who experienced a short period of atrial fibrillation (AF) (30 min) with spontaneous restoration in sinus rhythm at the acute phase. He underwent percutaneous coronary intervention (PCI) with drug-eluting stents.

Questions 1 and 2

To the question, what initial antithrombotic strategy do you prefer in the event that the patient had a CHADS-VASc score at 1 (only 1 point related to the CAD itself), the most frequent answer was dual APT (47.2%) followed by triple therapy (35.4%) (Figure 1). In case of triple therapy, half of the cardiologists suggested to use low-dose direct oral anticoagulants

(DOAC) and the other half high-dose DOAC. Very few proposed a dual therapy combining DOAC and single APT with either aspirin or clopidogrel at discharge (10.2%).

When the vignette was modified as follow: the CHADS-VASc score is now at 2 (same case with history of hypertension), the most frequent preferred strategy was then triple therapy (66.4%) with half of low-dose and half of high-dose DOAC (Figure 1). This choice was significantly different from the previous question ($p<0.0001$). Dual APT was preferred for only 13.5% of the participants in this setting. The use of dual therapy was still low and at 13.9%.

It is interesting to note that, in case of a CHADS-VASc score equal to 1 (only 1 point related to the underlying CAD), dual APT was the most frequent initial strategy chosen despite the absence of any strong evidence and/or recommendations for such a strategy [12-14]. Importantly, in case of a CHADS-VASc score equal to 2, this rate sharply decreased to only 13.5% in favor of triple therapy. Such a strategy may be explained by several reasons. First, although dual APT (using clopidogrel) has shown to be inferior to OAC alone to prevent the risk of systemic embolism in case of AF [15], it has also shown to be beneficial as compared to aspirin alone in the ACTIVE-A trial [16]. In addition, in the THALES study (patient with history of AF excluded), dual APT (using ticagrelor) has also shown to be superior to aspirin alone to prevent recurrent stroke [17]. Such a strategy has therefore shown a certain efficiency in preventing stroke occurrence. Second, the annual risk of systemic embolism is very low in patients with a CHADS-VASc equal to 1 (1% per year); and in the past, previous guidelines have suggested that, in patients with a CHADS score equal to 0-1, the absence of any antithrombotics or a treatment by aspirin alone could be considered [18]. The risk of stroke and/or systemic embolism looked to be a critical parameter that has been taken into account by participants as illustrated by the sharp decrease in the rate of dual APT prescription (if favor of triple therapy) when the case has been modified to increase the CHADS-VASc score.

Importantly, when a triple therapy was chosen, participants were equally divided between the high- and the low-dose of OAC suggesting that the answer to what is the best strategy in this context is really unclear. In the AUGUSTUS and ENTRUST-AF trials, most patients (close to 90%) were treated using the high-dose of DOAC in the dual therapy groups [9,10]. In the PIONEER-AF trial, the low-dose of rivaroxaban was used in the dual therapy group [8]. Finally, in the RE-DUAL-PCI trial, both doses of dabigatran were tested with rather similar results [7]. However, it is important to note that the power of each trial, taken individually, is rather limited and that the dose of DOAC used (except in AUGUSTUS) was the one used in case of dual therapy and not triple therapy. Finally, it should be highlighted that the low-dose in not "equivalent" for all drugs: half the dose for apixaban and edoxaban, 2/3 of the dose for dabigatran, and 3/4 of the dose for rivaroxaban. Although, guidelines recommend to use the high-dose of DOAC in the context of dual therapy [12], it should be acknowledged that the level of evidence is low since no study (except RE-DUAL-PCI) has specifically tested this question. Whether the high- or the low-dose of DOAC should be preferred in case of triple therapy is still unknown and has never been tested in a randomized trial.

Questions 3 and 4

To the question, what duration of triple therapy do you prefer in the event you would do an initial triple therapy, the most frequent answer was 4 weeks (44.9%) (Figure 2). Of note, almost one third (32.1%) of the cardiologists suggested to pursue the triple therapy for 3 months or more and only 14.1% suggested to stop triple therapy after 1 week.

To the question, what criteria would suggest you to pursue longer the triple therapy in a patient with AF who requires PCI, the most frequent answer was the need for multiple stent implantation (76.4%) followed by the context of ACS (56.5%) (Figure 2).

In case of triple therapy, only 15% suggested a very short triple therapy of 1 week. Importantly, the survey was conducted immediately after the publication of the last European

guidelines on the management of NSTE-ACS, which suggest that a 1-week triple therapy should be considered as the default strategy in such a context [12]. In addition, the context of ACS and the need for multiple stent implantation may have largely influenced the answers here as highlighted by the question 4. The risk of stent thrombosis looked something prevalent in the mind of participants at the early phase. The results of recent meta-analyses suggesting that dual therapy is associated with a higher risk of stent thrombosis as compared to triple therapy may have influenced the answers [19,20].

Case 2

The clinical vignette is detailed in Supplemental Figure S2. This case concerned an elderly woman with history of AF and under long-term high-dose DOAC. She was referred to the catheter laboratory for angina and documented ischemia. She had mild anemia (10.7 g/dL). The patient required PCI and implantation of 1 drug-eluting stent.

Questions 1, 2 and 3

To the question, how would you manage OAC in such a patient requiring coronary angiogram through radial approach, the most frequent answer was to pursue OAC unchanged (Figure 3). This answer was significantly more frequent in case of treatment by vitamin-K antagonist (VKA) (73.9%) as compared to DOAC (44.5% and 39.5% for once-daily and twice daily DOAC respectively, $p<0.0001$). In case of DOAC, a significant proportion (around 40-45%) of the participants preferred to avoid the last dose (in case of once-daily DOAC) or the two last doses of treatment (in case of twice daily DOAC) before the coronary angiogram. Bridging therapy by heparin was almost never suggested (0% in case of DOAC and less than 5% in case of VKA use).

The management of long-term OAC to perform a coronary angiogram (or any other minimally invasive procedure at low risk of bleeding) has been poorly studied (no randomized

trial). Of note, a coronary angiogram may lead to PCI within the same procedure which, beyond the risk of bleeding, is something important to take into account since a dedicated management of antithrombotics may be required. In case of VKA use, OAC discontinuation for several days without bridging has shown to increase the risk of thrombotic events [21,22]. But, bridging by heparin has shown to be a period at high risk of both: bleeding and thrombotic events [21,22]. Therefore, guidelines currently recommend to pursue OAC without bridging for such minimally invasive procedures (with target INR between 2 and 3 in case of VKA use) but the level of evidence is low and based on registries published at time of VKA use [21,22]. In our study, the vast majority (3/4) of the participants preferred to pursue OAC without bridging in case of VKA use. By contrast, in case of DOAC use, only 40% of the participants preferred to pursue OAC unchanged and around 45% of the cardiologists suggested to avoid the last (or the 2 last) treatment dose. There is an evidence gap regarding the management of DOAC in this context but it should be acknowledged that they are much easier to manage than VKA. These are some points to consider in case of DOAC use that may explain the variability in answers. First, avoiding a single dose (or 2 doses) in patients with AF and without history of stroke may not increase that much the risk of thrombotic events as compared to a discontinuation of several days in case of VKA use. Second, there is therefore no need of bridging in such a situation. Third, there is no INR destabilization and therefore no increased risk of bleeding with such a strategy. And fourth, there is no need to repeat blood tests when OAC is restarted.

Questions 4 and 5

The patient had PCI. If then, 15 months later, the patient is stable with still a mild anemia (without history of overt bleeding). To the question, what would you choose as the best antithrombotic regimen, the vast majority (70.8%) preferred OAC alone using high-dose DOAC (Figure 4). Around 25% of the cardiologists preferred a dual therapy combining DOAC

and single APT (equally divided between low- vs. high-dose DOAC and aspirin vs. clopidogrel).

When the vignette was modified as follow: same case but with a history of overt bleeding (melena) 4 months earlier requiring a 6-day long hospitalization and transfusions of 3 blood units. Explorations revealed a gastric ulcer, which was treated with success. For now, the situation is completely stabilized and the hemoglobin value is strictly normal. To the same question, answers were significantly modified (Figure 4). If the OAC alone using DOAC was more pregnant (87.5%), a significant proportion (26.5%) of the participants preferred low-dose DOAC ($p<0.0001$ as compared to the previous situation). Dual therapy was preferred in only 12.5% of the cases in this context.

As stated in the guidelines, OAC alone should be the default strategy in patients with AF and stabilized chronic CAD [14]. Such a strategy emanates from analyses derived from registries and randomized trials [1-3,5,6,11], that all showed no benefit and a higher risk of bleeding of a dual therapy in chronic CAD patients under long-term OAC for AF. Here, participants largely preferred to pursue OAC alone (close to 3/4 of them) as suggested by guidelines. However, the question of what dose of DOAC (low vs. high) should be pursued is still not settled in a patient with CAD and AF and at high risk of bleeding as illustrated here. Outside the context of CAD, registries have shown that the lowest dose of DOAC is often overused in daily practice [23,24]. Interestingly, in our analysis, most participants preferred to pursue unchanged long-term high-dose DOAC in case of chronic and stable mild anemia (even with no clear explanation for anemia). By contrast, when the case was modified to introduce a clear explanation for anemia but a recent history of major gastro-intestinal bleeding (although completely cured), a significant proportion (1/4) of the participants made the choice to decrease the dose to the lowest dose of DOAC. It is uncertain whether this modification has rather been

influenced by the presence of a recent acute bleeding event, the location of the bleeding (since some DOAC have shown to increase the risk of gastro-intestinal bleeding [25]) or both.

Question 6

If then, 24 months later, the patient is under OAC alone using high-dose DOAC and requires non-urgent invasive surgery (total hip prosthesis). To the question, how would you manage antithrombotics before surgery, between the following 3 different strategies: stop DOAC for several days without bridging, stop DOAC with bridging by heparin or stop DOAC with bridging by low-dose aspirin, participants were equally divided (close to 1/3) between the 3 strategies even if bridging by heparin was a bit less preferred (26.9%) (Supplemental Figure S6).

In daily practice, as suggested by guidelines [13,14], many patients with stable chronic CAD and AF are treated using OAC alone especially those at high risk of bleeding as in the present case (anemia, history of bleeding …). But it is also often needed to stop OAC during follow-up in these patients for many reasons (invasive surgery, major bleeding …). In these clinical situations at high risk of bleeding, it is recommended to stop OAC for several days surrounding the invasive procedure [21,22]. The discontinuation may even be longer in case of major bleeding occurrence. However, it is unknown whether a bridging therapy should be prescribed pending OAC discontinuation in this context, especially in patients with history of coronary stent implantation. On a theorical point of view, the absence of any antithrombotics for several days for CAD prevention on one side (risk of stent thrombosis, risk of recurrent myocardial infraction) and AF prevention on the other side (risk of systemic embolism and stroke) may be highly deleterious in these patients. In our analysis, we perfectly illustrated the absence of guidelines or data in this specific situation since participants were almost equally divided between the 3 options: discontinuation without bridging (relatively long period without any antithrombotics), bridging using aspirin (often accepted for invasive procedure) or bridging

using heparin (that lead to a very short period without any antithrombotics). A consensus of experts and further studies are therefore critical to help cardiologists, surgeons and anesthetists in daily practice.

DISCUSSION

In medicine, the place of scientific proofs and international guidelines is constantly growing. However, in many cases (and cardiology is not an exception), the level of evidence is still low and the physician decisions are more influenced by expert consensus and/or personal experience or convictions. The present survey is a clear illustration of how therapeutic decisions may vary in such situations with little or no scientific evidence.

In CAD patients, the need for long-term OAC (especially for AF) is frequent and around 10% of the cases [1-3]. Of main importance, such patients have been shown to be at higher risk of both: thrombotic/ischemic and bleeding events [1-3]. The management of antithrombotic therapies in these patients with AF and CAD is therefore critical. If several studies allowed to progress and to better apprehend what should be the best strategy in some specific contexts, there is still to date several clinical situations with a gap of evidence. In the present study, we therefore conducted a national French survey in order to assess what are daily practices regarding the antithrombotic management in several specific clinical settings. The clinical vignettes were built by a committee in order to cover some of the situations with a lack of evidence. The committee paid attention that none of the answers could be either absolutely true or wrong. Only questions with a low level of evidence were selected. Besides the results of the survey and the interpretation of each answer by itself, we strongly believe that conducting such surveys may carry relevant information to help physicians in their daily practice, but also to help experts to build consensus and to design future trials. Indeed, such surveys may provide different information from those provided by patient-based registries on what is the daily practice in a specific domain. It may highlight that, in a dedicated situation, practices are rather homogeneous even if the level of evidence is low. In the present analysis, the question 1 of the case 1 is a good illustration. At the end, this may help experts to build consensus. It also allows to highlight that in some other specific situations, physicians do absolutely not know what they

should do (lot of variability in answers). In the present survey, the question 6 of the case 2 is a perfect illustration as answers were equally divided between all possibilities. Such targeted questions may then lead to initiate future dedicated studies in order to fill the gap of evidence.

Strengths and Limitations

The present survey was conducted on a nationwide basis and the participation rate was rather homogeneous across the country. Cardiologists who participated represent the whole spectrum of cardiology sub-specialties although interventional cardiologists were a bit overrepresented as compared to others. As well, all types (private, public and universitary) of workers were represented. Therefore, even if the sample size is modest (7.6% of the French cardiologist community), we feel that it perfectly represents the population of the French cardiologists. Finally, it should be acknowledged that answers to virtual case-vignettes were declarative and may differ from actual practices when physicians are confronted with similar real-life clinical cases. The survey was however strictly anonymous, which have allowed to not influence participant answers. The results of this survey study are not meant for practice changing.

CONCLUSION

Gaps of evidence persist in medicine and in cardiology as illustrated by the present study. Surveys, as we performed here, allow to collect relevant information on actual practices and the dissemination of the results may help them in daily care. Importantly, it also carries relevant information to help experts in building consensus and future trials to fill the evidence gaps in the near future.

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FIGURE LEGENDS

Figure 1. Answers to questions 1 (in blue) and 2 (in red) of the virtual case number 1

DOAC = direct oral anticoagulant

Figure 2. Answers to questions 3 and 4 of the virtual case number 1

ACS = acute coronary syndrome, PPI = proton pump inhibitors, DOAC = direct oral anticoagulant, VKA = vitamin-K antagonist

Figure 3. Answers to questions 1 (panel A), 2 (panel B) and 3 (panel C) of the virtual case number 2

Figure 4. Answers to questions 4 (in blue) and 5 (in red) of the virtual case number 2

OAC = oral anticoagulant, DOAC = direct oral anticoagulant

Supplemental Figure S1. Virtual case number 1

Supplemental Figure S2. Virtual case number 2

Supplemental Figure S3. Repartition of the participants to the survey across the country

Supplemental Figure S4. Repartition of the participants to the survey according to the location of their professional activity (private, non-universitary public, universitary public or shared activity)

Supplemental Figure S5. Repartition of the participants to the survey according to their sub-specialty (general cardiology, interventional (coronary) cardiology, rhythmology, heart failure, imaging)

Supplemental Figure S6. Answers to question 6 of the virtual case number 2

Case 1 - Questions 1 and 2

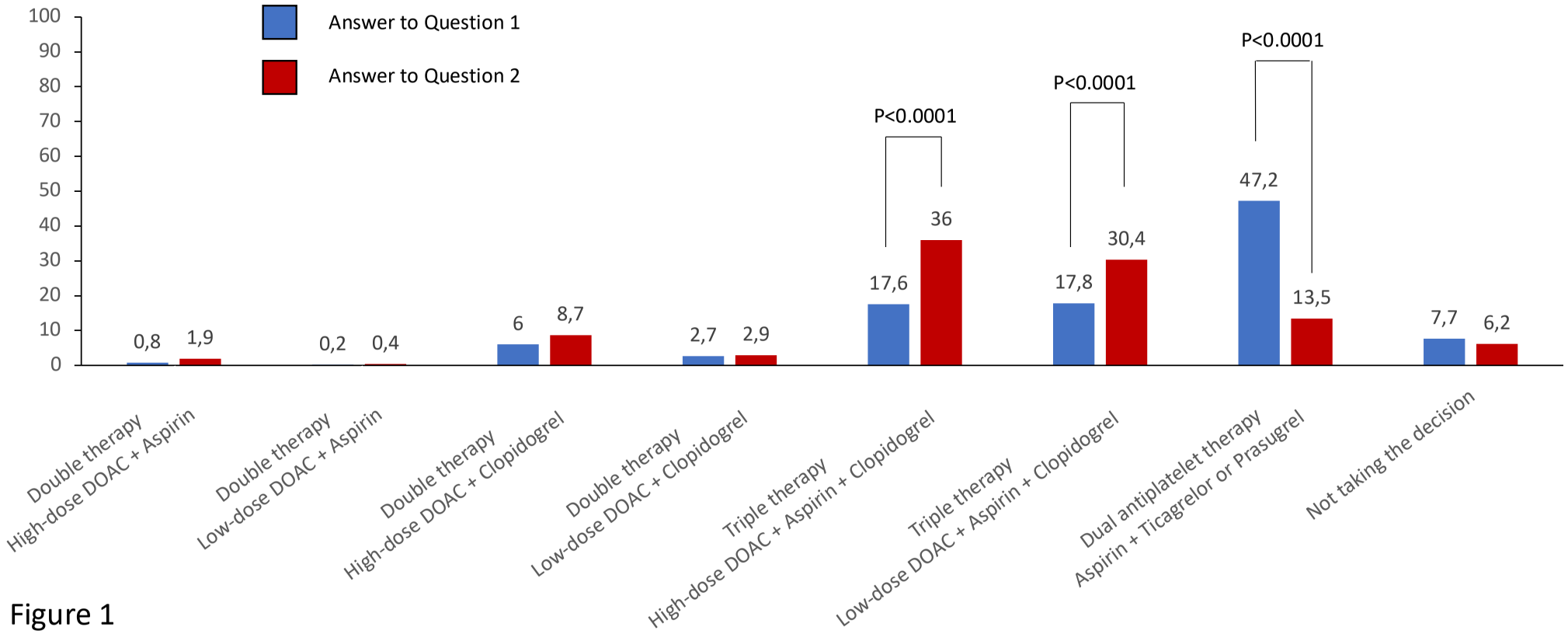
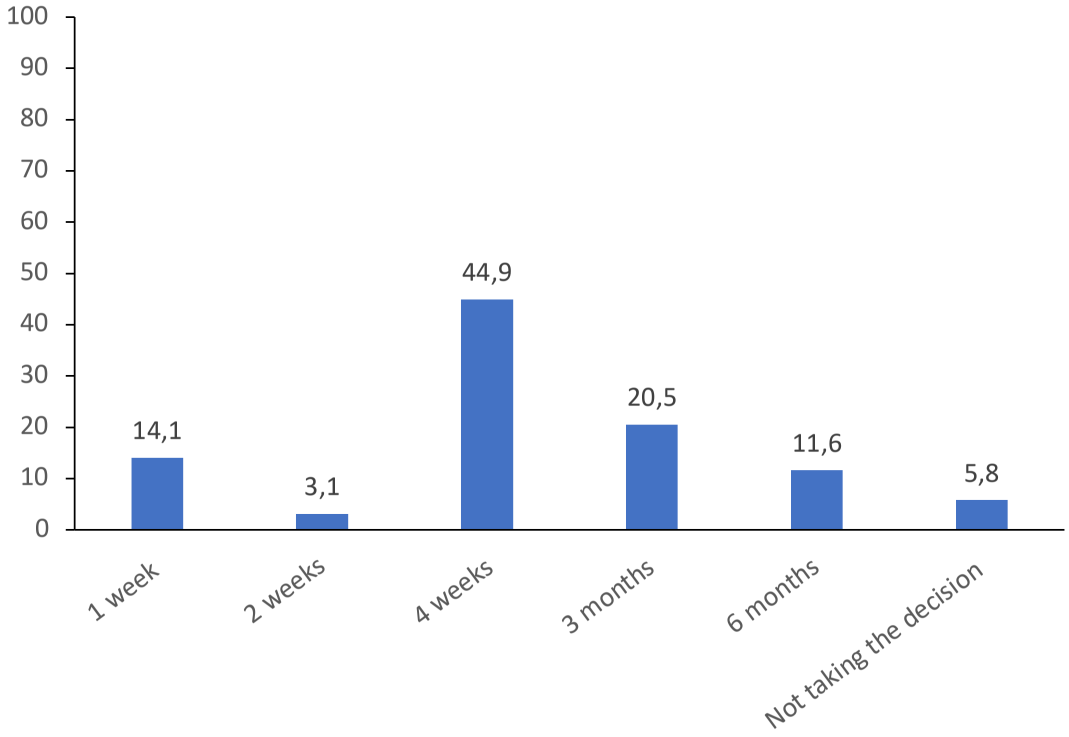


Figure 1

Case 1 - Question 3



Case 1 - Question 4

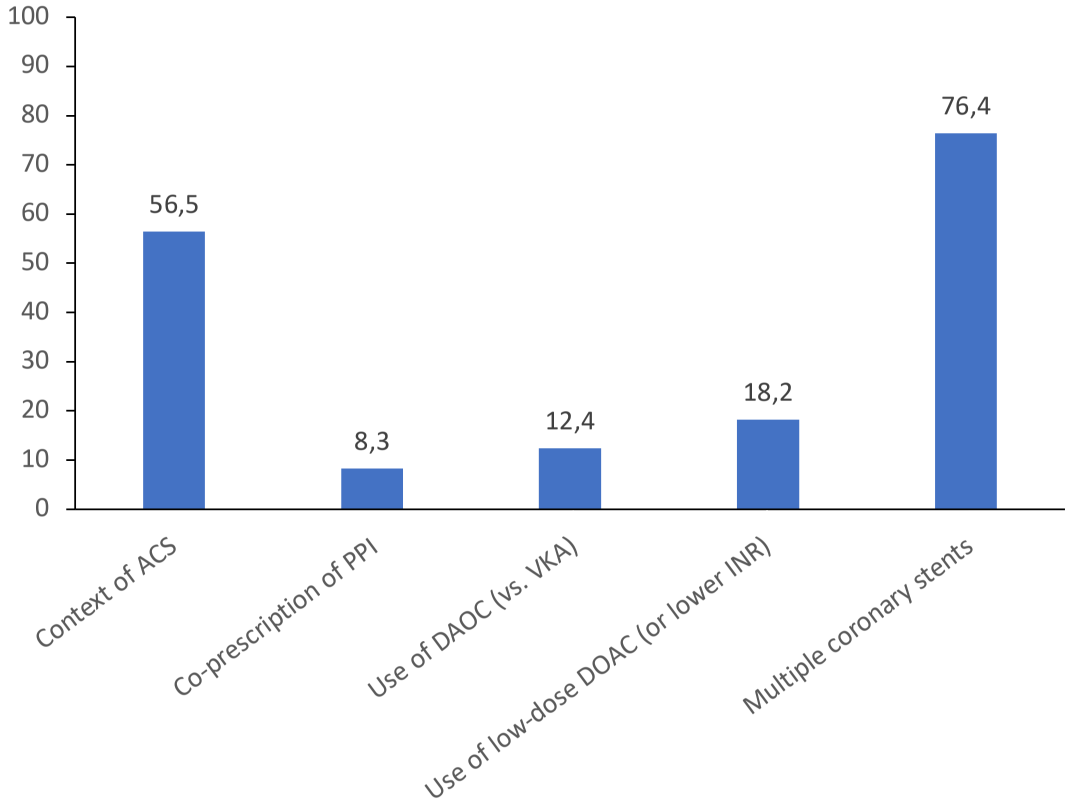
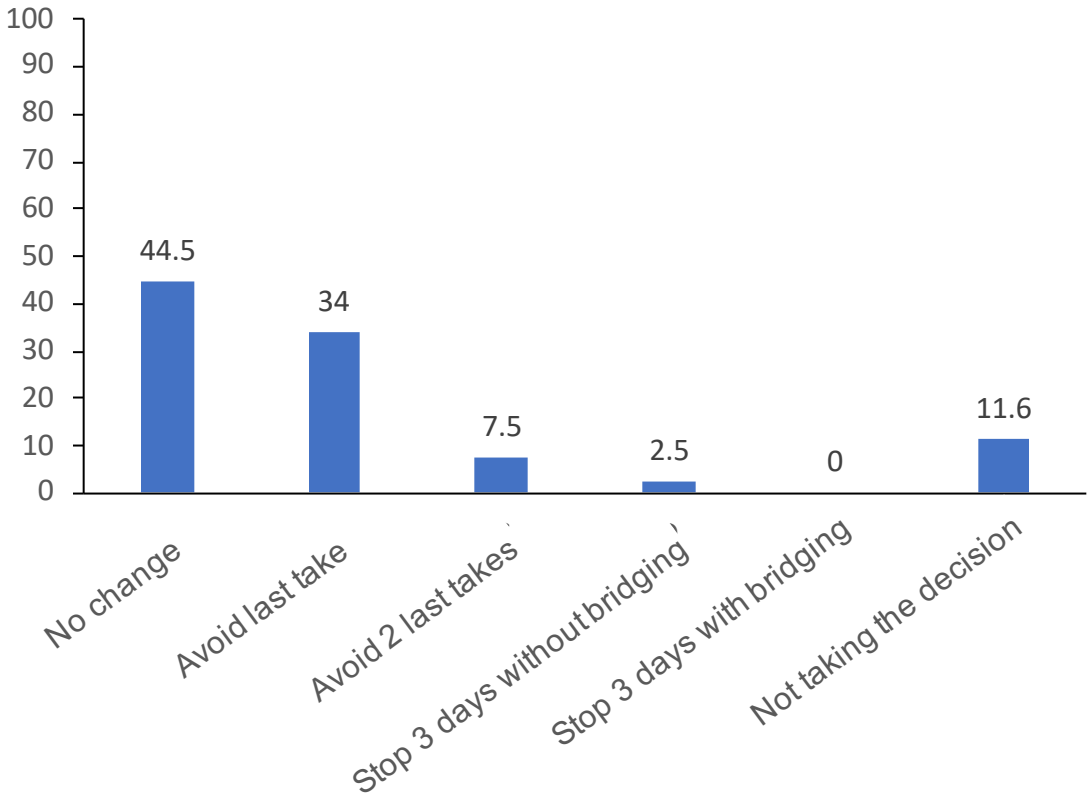
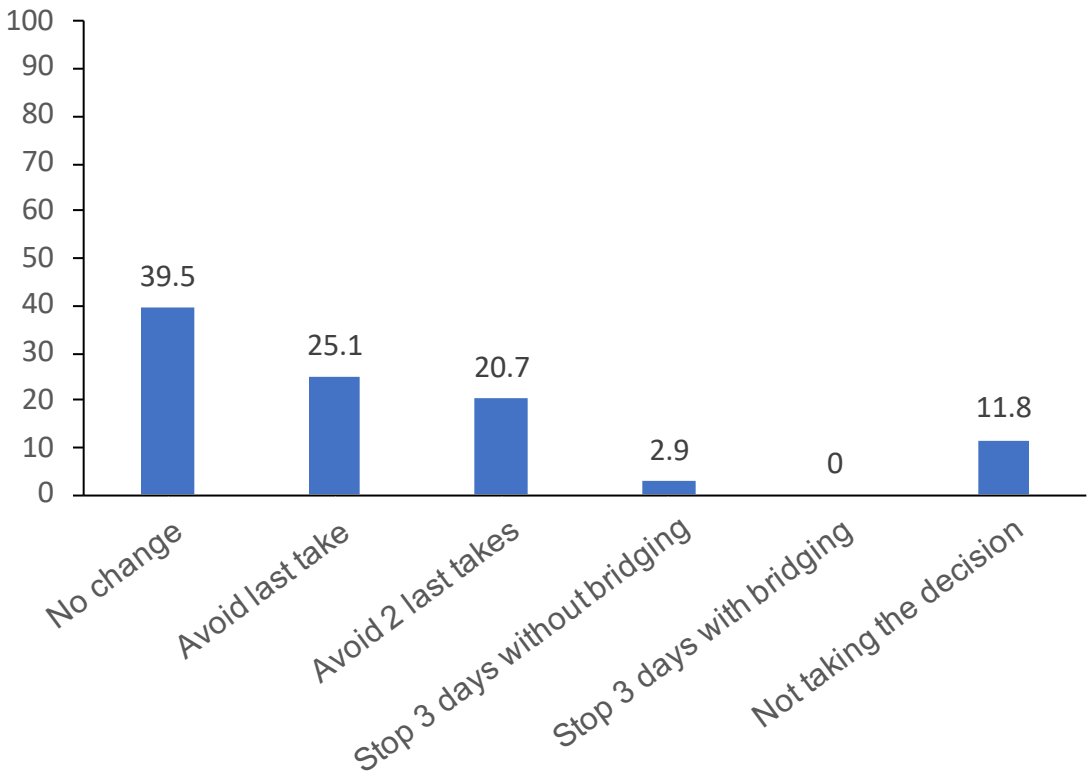


Figure 2

A - Case 2 - Question 1



B - Case 2 - Question 2



C - Case 2 - Question 3

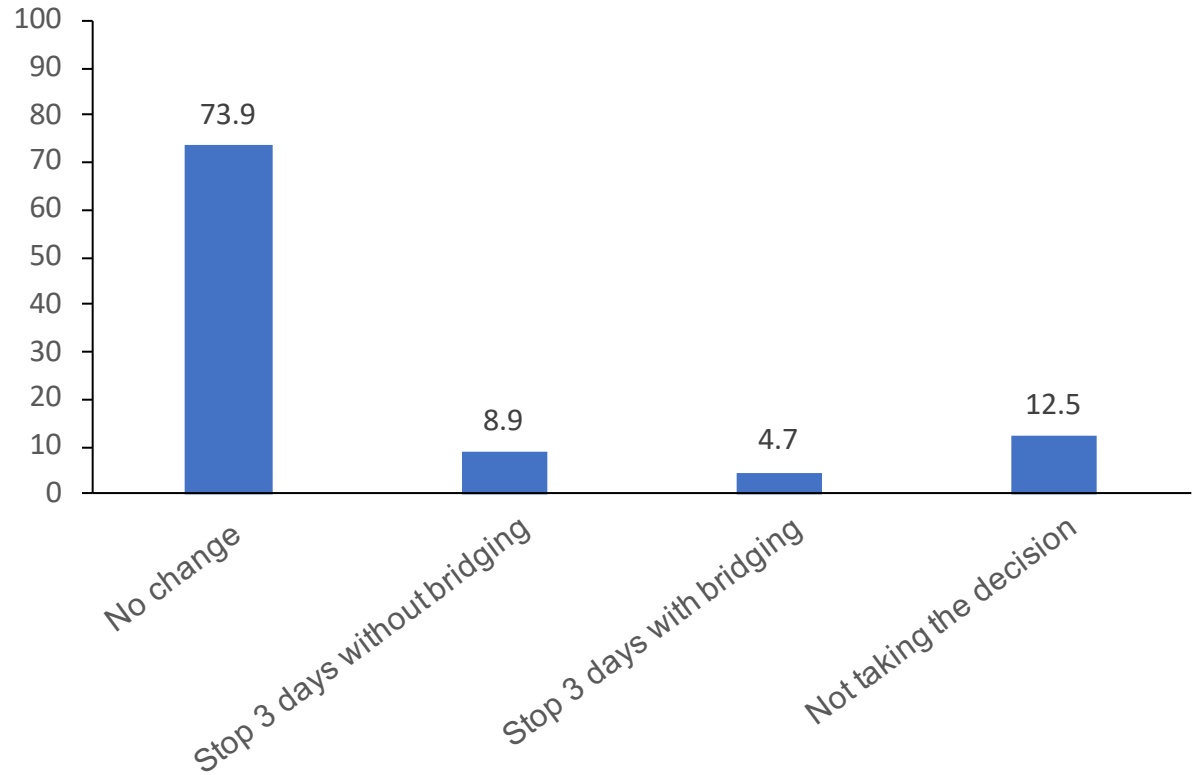


Figure 6

Case 2 - Questions 4 and 5

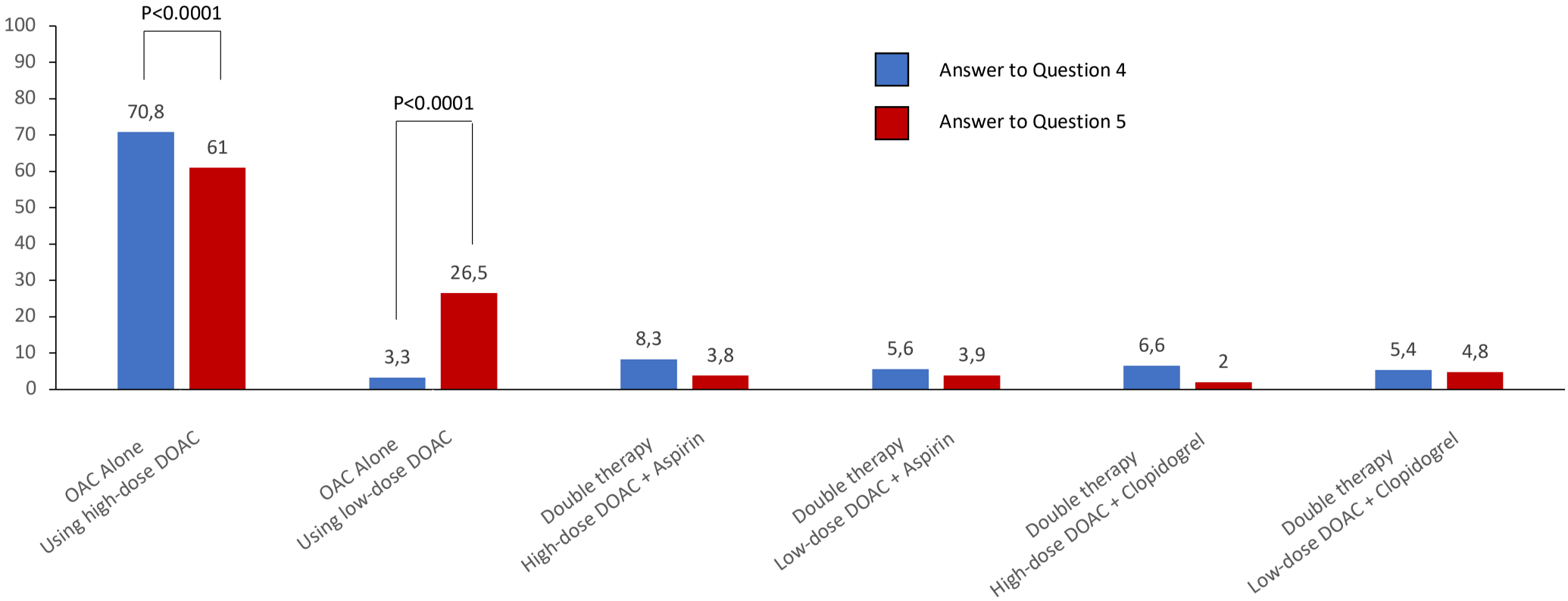


Figure 4