Ticagrelor Use and Practice Patterns among Canadian Cardiac Surgeons

Running Title: Ticagrelor in Cardiac Surgery

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Keywords: Ticagrelor, CABG, ACS, Survey

Word count: 2830

Conflict of Interest: Dr. Verma holds a Tier 1 Canada Research Chair in Cardiovascular Surgery; and reports receiving research grants and/or speaking honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, EOCI Pharmacomm Ltd, HLS Therapeutics, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, Phase Bio, Sanofi, Sun Pharmaceuticals, and the Toronto Knowledge Translation Working Group. He is the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. Dr. Yau reports consulting relationships with Abbott, Medtronic, Gore and BlueRock Therapeutics.

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Abstract

Background and Aim: The P2Y12 platelet receptor inhibitor ticagrelor is widely used in patients following acute coronary syndromes or in those who have received coronary stents. Bentracimab is a monoclonal antibody-based reversal agent that is being formally evaluated in a Phase 3 clinical trial. Here, we probe the knowledge, attitudes, and practice patterns of cardiac surgeons regarding their perioperative management of ticagrelor and potential application of a ticagrelor reversal agent.

Methods: A questionnaire was developed by a working group of cardiac surgeons to inquire into participants' practices and beliefs regarding ticagrelor and disseminated to practicing Canadian cardiac surgeons.

Results: A total of 70 Canadian cardiac surgeons participated. Bleeding risk was identified as the most significant consideration when surgically revascularizing ticagrelor-treated patients (90%). There is variability in the duration of withholding ticagrelor prior to coronary artery bypass graft procedure in a stable patient; 44.3% wait 3 days and 32.9% wait 4 days or longer. Currently, 14.3% of cardiac surgeons prophylactically give platelet transfusions and/or fresh frozen plasma intraoperatively following protamine infusion in patients who have recently received ticagrelor. Interestingly, 47.1% of surveyed surgeons were aware of a reversal agent for ticagrelor, 91.4% of cardiac surgeons would consider utilizing a ticagrelor reversal agent if available, and 51.4% acknowledged that the introduction of such an agent would be a major advance in clinical practice.

Conclusions: The present survey identified ticagrelor-related bleeding as a major concern for cardiac surgeons. Surgeons recognized the significant unmet need that a ticagrelor reversal agent would address.

Introduction

Dual-antiplatelet therapy (DAPT) remains a cornerstone of acute coronary syndrome (ACS) management, irrespective of whether medical, percutaneous, or surgical methods are employed as treatment strategies. The benefits of this therapy in reducing adverse cardiovascular outcomes have been established by multiple large-scale randomized controlled trials.[1-3] Ticagrelor, a competitive and direct antagonist of the P2Y12- platelet receptor,[4] has emerged as a mainstay of DAPT and has notably demonstrated superior efficacy to clopidogrel in the setting of ACS.[2] Beyond its use in ACS, ticagrelor has also demonstrated efficacy in secondary protection amongst patients with a history of myocardial infarction,[5] cardioprotective benefits in patients with coronary artery disease, type II diabetes mellitus, and a history of percutaneous coronary intervention,[6] and potential use in preventing recurrent stroke or death within 30 days following an acute noncardioembolic ischemic stroke or transient ischemic attack in select patients.[7]

Due to its potency, there is a fine balance between ischemic and bleeding risks when patients require surgical intervention, most often coronary artery bypass grafting (CABG), following ticagrelor administration. Surgically, ticagrelor use is associated with higher risk of bleeding and blood or platelet transfusion,[8-11] the former being an independent risk factor for mortality.[12,13] To address this clinically unmet need, a novel monoclonal antibody ticagrelor reversal agent, bentracimab (PB2452), has been developed. Phase 1 and Phase 2a clinical studies have demonstrated the rapid and potent ticagrelor reversal properties of bentracimab.[14,15] These results led to an ongoing randomized controlled trial (REVERSE-IT) that is currently evaluating the efficacy of bentracimab (PB2452) for patients presenting with major bleeding events or requiring urgent interventions (*clinical trial identifier: NCT04286438)*.

In order to better understand the potential impact of a ticagrelor reversal agent on clinical practice, we probed the knowledge, attitudes, and practice patterns of cardiac surgeons as it pertains to their management of ticagrelor in patients with ACS undergoing CABG.

Materials and Methods

Survey Development and Population

A prospective survey of Canadian cardiac surgeons was conducted with the purpose of assessing their current knowledge, attitudes, and practice patterns regarding ticagrelor use in ACS patients requiring coronary bypass surgery. The 15-question survey was developed by a working group of cardiac surgeons prior to dissemination. The individual questions, detailed in **Appendix 1**, were created to address key unresolved issues in each of the aforementioned three domains being examined. Specifically, the questions were designed to evaluate current concerns with ticagrelor use, methods for managing intraoperative bleeding in patients treated with this antiplatelet agent and the potential application of a ticagrelor reversal agent if available. To validate and confirm that the length and wording of the survey was conducive to its comprehensibility and clarity, four cardiac surgery fellows pilot tested the survey prior to widespread distribution. Each surgeon was contacted personally, and an automatic email confirmation was generated upon their completion of the survey. We obtained a unique confirmation from each participant to ensure that each surgeon completed the anonymous survey once.

Between December, 2020 and January, 2021, 70 cardiac surgeons were invited to participate through a web-based platform (*SurveyMonkey.com*), with up to 3 reminders regarding the survey sent via email. All responses were anonymous to preserve confidentiality of responses and surgeons were informed that their participation was completely voluntary. Consent from all subjects was obtained as part of the survey prior to their participation and the subsequent analysis of received data. Ethics approval for this investigation was obtained by the research ethics board through ADVARRA (IRB #00000971).

Statistical Analysis

We used descriptive statistics to summarize demographic characteristics of survey participants and their responses to individual questions. Where appropriate, counts with percentages are presented for interpretation of the data. Proportions and summary statistics were generated using Microsoft Excel 2016 (Microsoft, Redmond, WA).

Results

Surgeon Demographics

Of the 70 Canadian cardiac surgeons that were sent the survey, all 70 participated in the survey (**Appendix 2**). The results of the present survey are broadly outlined in the conceptual summary slide (**Figure 1**). The demographics of participating surgeons are summarized in **Table 1**; all surgeons are currently practicing in Canada with 50% practicing in the province of Ontario. There was a bimodal distribution across participants with respect to years in practice, with 30% having more than 20 years in practice and 24.3% having five years or less. Almost half (44.3%) of the surgeons that completed the survey perform between 100-150 CABG cases per year, while 58.6% of the surgeons performed more than 100 per year. Participating surgeons predominantly practiced in academic centres (94.3%).

Ticagrelor Utilization and Management of Intraoperative Bleeding

The majority of cardiac surgeons surveyed in the present investigation (98.6%) identified bleeding risk as one of their primary concerns when operating on patients recently administered ticagrelor in the setting of ACS, with 90% reporting bleeding as the sole principal issue. Importantly, there was variability amongst surgeons on the ticagrelor withholding period prior to performing bypass surgery in a stable patient (**Figure 2**). The most common response was to utilize a washout period of three days (44.3%), but a substantial population of cardiac surgeons (32.9%) use a longer waiting period than this. The minimum length of washout period identified amongst participating cardiac surgeons was 1 day, and the maximum was 6 days.

When probed on the management of ticagrelor-related intraoperative bleeding during CABG, 84.3% of participants reported that blood product transfusion would be employed if bleeding was persistent following protamine administration. Interestingly, 14.3% of cardiac surgeons prophylactically administer platelet transfusions and fresh frozen plasma (FFP) following protamine titration in patients on ticagrelor. No cardiac surgeons participating in this survey use recombinant factor VIIa nor cryoprecipitate as the first-line therapy to minimize to minimize ticagrelor-related bleeding complications. The management options used by surgeons, and their respective frequency of utilization amongst participants, are presented in **Figure 3**.

Ticagrelor Reversal

Overall, 47.1% of cardiac surgeons surveyed in the present investigation were aware of a reversal agent for ticagrelor. Unsurprisingly, 91.4% of participants identified that a ticagrelor reversal agent, if available, would have a place in their practice. In fact, a substantial majority (90%) noted that a ticagrelor reversal agent would be an advance in clinical practice, with 51.4% highlighting it as a potentially major advance (**Table 2**). At a more granular level, 94.3% of participants identified that they would use a ticagrelor reversal agent with unstable patients requiring urgent surgery, and at least 50% of participants noted that they would additionally use the agent in the setting of critical left main disease or ST-elevation myocardial infarction (STEMI) needing urgent surgery (**Figure 4**).

Discussion

To our knowledge, this is the first surgeon survey to examine the practice patterns and beliefs as it pertained to their management of ticagrelor in patients requiring surgery. The major findings were as follows: 1) The majority of cardiac surgeons (90%) reported bleeding risk as the issue of paramount concern when operating on ticagrelor-treated patients; 2) 77% of cardiac surgeons use a waiting period of at least three days between most recent ticagrelor administration and CABG in a stable patient, with 33% waiting longer than three days; 3) 91% of cardiac surgeons would consider using a ticagrelor reversal agent in appropriate patients and 51% believe the development of a ticagrelor reversal agent to be a major advance in clinical practice.

Bleeding is the major concern amongst cardiac surgeons operating on patients recently administered ticagrelor. Ticagrelor has been demonstrated to have a more rapid onset and to be a more potent inhibitor of platelet aggregation compared with clopidogrel.[4,16] Notably, ticagrelor also has a faster offset than clopidogrel and therefore allows for a quicker restoration of platelet function upon its discontinuation.[16] Two unique characteristics separate ticagrelor from its thienopyridine counterparts clopidogrel and prasugrel: first, ticagrelor is immediately active once it reaches circulation and does not require metabolism, and second, ticagrelor binds reversibly to the P2Y12 platelet receptor.[4] This latter property provides the opportunity for an agent to reverse the effects of ticagrelor by removing it from circulation or blocking its receptor-activity.

There is currently no reversal agent for ticagrelor presently approved for clinical use. The only current active option for neutralizing the effects of ticagrelor is to provide platelet transfusion when the last ticagrelor intake was greater than 24 hours ago, and the efficacy of this approach remains unclear. When ticagrelor administration was within 24 hours, no effective strategy exists for ticagrelor reversal, although providing recombinant factor VIIa has been theorized as a potentially viable option.[17] Although prophylactic platelet transfusion is employed as a ticagrelor neutralization strategy by 14.3% of cardiac surgeons surveyed in the present study, it should be highlighted that platelet transfusion may only partially counteract ticagrelor's effects given that the transfused platelets can still be bound by free ticagrelor.[18,19] Given the lack of a completely efficacious mechanism by which ticagrelor's effects can be reversed, current guidelines recommend a washout period of 3-5 days between last ticagrelor administration and elective

CABG;[20-22] in the context of urgent or semi-urgent surgery, this period can be shortened to 24 or 48-72 hours, respectively.[21,22] In the present analysis, 75.7% of surveyed cardiac surgeons reported their adherence to these recommendations through utilization of a waiting period between 3-5 days between ticagrelor administration and CABG in a stable patient. However, there was a meaningful proportion of cardiac surgeons (22.9%) who use a shorter waiting period than 3 days, presumably with the goal of minimizing the risk for myocardial ischemia in urgent or emergent situations.

The mechanism of bentracimab (a monoclonal antibody fragment) involves binding ticagrelor and its active metabolite with high affinity and specificity, thereby preventing ticagrelor from interacting with the P2Y12 receptor and allowing for normal platelet function to resume within minutes of administration.[15,23] Investigation of the safety and efficacy of bentracimab in reversing ticagrelor's effects was conducted through a Phase 1 randomized controlled trial.[15] Through the analysis of healthy volunteers pre-treated with ticagrelor using light transmission aggregometry, the study reported that increases in platelet aggregation were significantly greater at all time points from 5 minutes to 20 hours in those that received an initial bolus of bentracimab followed by a prolonged infusion compared to placebo. Corroboration of these findings was provided by a point-of-care P2Y12 platelet-reactivity test and a vasodilator-stimulated phosphoprotein (VASP) immunoassay. Indeed, findings from these tests correlated significantly with the results from the light transmission aggregometry assessment, and, within specific dose cohorts, demonstrated normalization of platelet reactivity and signalling following bentracimab provision.[15] With drug-related adverse events limited to those related to the infusion site amongst healthy participants,[15] these promising initial results prompted investigators to initiate Phase 2B and Phase 3 trials. The Phase 3 trial (REVERSE-IT; *clinical trial identifier: NCT04286438*), through analyzing the outcomes of bentracimab use in 200 patients will be particularly important in clarifying the potential impacts of this agent on clinical practice. The study, using an open label single arm design, is evaluating the efficacy of bentracimab in patients with uncontrolled major bleeding or in those at high risk of bleeding (such as those requiring cardiac surgery).

Much like the identification of pharmacological options for reversing the effects of direct oral anticoagulants catalyzed material evolution in cardiovascular care,[24,25] a ticagrelor-reversing

agent similarly has the capacity to advance antiplatelet therapy. The fact that 16.5% of patients in the CURE trial and 10% of patients in the PLATO trial required CABG during the study,[1,2] and may therefore benefit from an active platelet reversal option, serves as evidence of the widespread impact this agent may have on cardiac surgical practice. As expected, this potential was reflected in at least 90% of respondents in the present study indicating that they would utilize such an agent and recognizing it as an advance in clinical practice. In considering these cardiac surgical uses within the broader context of the various applications of bentracimab including ticagrelor-treated patients with uncontrolled major bleeding or requiring urgent non-cardiac surgery, it is clear that there is an unmet clinical need for such a reversal agent.

This study has some limitations. First, these results have been derived from voluntary Canadian participants and may not be generalizable to all cardiac surgeons. Second, reporting bias could have been introduced given that surgeons may have had a tendency to report practices and beliefs closer to a preconceived norm rather than report their actual practice. The lack of verification mechanisms used in this investigation to ensure accuracy of answers may also have contributed to this potential bias. Third, the surgical scenarios and questions presented in this investigation were simple and required categorical responses; in reality, these situations usually demand more complex and nuanced decision making. Nevertheless, this study does have several strengths including its 100% response rate and its targeting of general cardiac surgeons that perform CABG regularly.

Conclusion

In conclusion, we herein report the results of a survey administered to 70 Canadian cardiac surgeons inquiring into their knowledge, attitudes, and practice patterns regarding management of patients who have received ticagrelor. While there was consensus that bleeding represents the most important concern in patients on ticagrelor undergoing CABG, there was relative variability in the exact strategy cardiac surgeons utilize to manage ticagrelor-treated patients requiring surgical intervention. Ultimately, through demonstrating that the overwhelming majority of cardiac surgeons would not only utilize a ticagrelor reversal agent, but see it is an advance in clinical practice, the present findings also point towards an important unmet clinical need and the potential widespread impact that the approval of such an agent would have.

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Figure Legends

Figure 1. Conceptual summary slide outlining the general findings of the present survey.

Figure 2. Length of waiting period employed by cardiac surgeons between ticagrelor administration and coronary artery bypass grafting (CABG) in a stable ACS patient.

Figure 3. Management of ticagrelor-related intraoperative bleeding during CABG.

Figure 4. Patients in which a ticagrelor reversal agent could be applicable.

Tables

	Total Participants (n = 70)
Region/Country, n (%)	
Ontario	35 (50.0)
Quebec	7 (10.0)
Nova Scotia	6 (8.57)
British Columbia	1 (1.43)
Alberta	10 (14.3)
Saskatchewan	1 (1.43)
Manitoba	6 (8.57)
New Brunswick	1 (1.43)
Newfoundland	1 (1.43)
United States	1 (1.43)
Saudi Arabia	1 (1.43)
Years in Practice, n (%)	
0-5	17 (24.3%)
5-10	10 (14.3%)
10-15	12 (17.1%)
15-20	10 (14.3%)
>20	21 (30.0%)
Practice Setting, n (%)	
Academic	66 (94.3)
Community	4 (5.71)
Number of CABG cases performed each year, n (%)	
0-50	9 (12.9)
50-100	20 (28.6)
100-150	31 (44.3)
150-200	6 (8.57)
>200	3 (4.29)
Skipped	1 (1.43)

Table 1. Demographics of surveyed cardiac surgeons.

	Total Participants (n = 70)
Awareness of a ticagrelor reversal agent, n (%)	
Yes	33 (47.1)
No	37 (52.9)
Consideration for use of a ticagrelor reversal agent, n (%)	
Yes	64 (91.4)
No	6 (8.57)
Impact of a ticagrelor reversal agent, n (%)	
Major advance	36 (51.4)
Minor advance	27 (38.6)
No difference	7 (10.0)

Table 2. Potential use of a ticagrelor reversal agent.

Appendix 1. Ticagrelor Use and Practice Patterns among Cardiac Surgeons survey questions.

1) In what province/country is your practice? (Check one)

- ◊ Ontario
- ◊ Quebec
- ◊ Nova Scotia
- ◊ British Columbia
- ◊ Alberta
- ◊ Saskatchewan
- ◊ Manitoba
- ◊ New Brunswick
- ◊ Newfoundland
- ◊ United States

2) How would you describe your cardiac surgical practice? (Check one)

- ◊ Academic setting
- ◊ Community setting

3) How many years have you been in practice as a staff cardiac surgeon in years? (Check one)

- ◊ 0-5
- ◊ 5-10
- ◊ 10-15
- ◊ 15-20
- ◊ >20

4) How many CABG cases do you perform per year?

- ◊ 0-50
- ◊ 50-100
- ◊ 100-150

◊ 150-200

◊ >200

5) In your hospital, how often is Ticagrelor used in the management of ACS patients? (Check oene)

◊ 0-25%

◊ 25-50%

◊ 50-75%

◊ 75-100%

6) Which of the following statements about Ticagrelor is correct? (Check one)

◊ Ticagrelor is a directly acting agent that does not require hepatic transformation

◊ Ticagrelor bioavailability is variable and can be influenced by loss of function mutations in cytochrome 3A4/5

◊ Ticagrelor is equally efficacious to Clopidogrel and Prasugrel with respect to antiplatelet activity

◊ Ticagrelor has been shown to be superior to Clopidogrel in the treatment of patients with ACS

7) In patients on ticagrelor requiring CABG after ACS, what most concerns you? (Check one)

◊ Bleeding risk

◊ Ischemic risk

◊ Both

8) Patient with critical coronary artery disease on Ticagrelor needs a CABG. The patient is stable, how many days would you wait to follow the last dose of Ticagrelor? (Check one)

◊ 1

◊ 2

◊ 3

◊ 4

◊ 5

◊ 6

◊ 7

9) How do you manage intraoperative bleeding when patients are on Ticagrelor? (Check one)

◊ Prophylactically give platelets transfusion and FFP after protamine has been administered

◊ Reserve blood product transfusion only if patients have excessive bleeding after protamine has been given

◊ Use of recombinant factor VIIa to reduce bleeding

◊ Prophylactically give platelets and FFP after protamine has been administered

◊ Use of Cryoprecipitate to reverse the bleeding

10) In patients with ACS loaded with Ticagrelor and have undergone uncomplicated CABG, do you reinitiate Ticagrelor postoperatively? (Check one)

◊ Yes

◊ No

11) If you were to consider using Ticagrelor post – CABG, who would most likely be responsible for initiating this therapy? (Check one)

◊ Cardiac surgeon, in hospital

◊ Cardiac surgeon, at follow up outpatient visit (Usually 4-6 weeks after)

◊ Cardiologist, in hospital

◊ Cardiologist, at follow up outpatient visit

◊ Nurse practitioner, in hospital

12) Are you aware of a reversal agent that immediately reverse Ticagrelor?

◊ Yes

◊ No

13) Would you consider using a Ticagrelor reversal agent?

◊ Yes

◊ No

14) If you were to use a Ticagrelor reversal agent, which patients would you consider using the agent with?

- ◊ Critical left main disease
- ◊ Unstable patients requiring urgent surgery
- ◊ STEMI
- ◊ All of the above

15) How would you describe this agent in your clinical practice?

- ◊ Major advance
- ◊ Minor advance
- ◊ No difference

Appendix 2. Ticagrelor Use and Practice Patterns among Cardiac Surgeons survey responses.

1) In what province/country is your practice? (Check one)

Ontario	35 (50.0%)
Quebec	7 (10.0%)
Nova Scotia	6 (8.57%)
British Columbia	1 (1.43%)
Alberta	10 (14.3%)
Saskatchewan	1 (1.43%)
Manitoba	6 (8.57%)
New Brunswick	1 (1.43%)
Newfoundland	1 (1.43%)
United States	1 (1.43%)
Skipped	1 (1.43%)
Total	**70 (100%)**

2) How would you describe your cardiac surgical practice? (Check one)

Academic setting	66 (94.3%)
Community setting	4 (5.71%)
Skipped	0 (0.00%)
Total	**70 (100%)**

3) How many years have you been in practice as a staff cardiac surgeon in years? (Check one)

0-5	17 (24.3%)
5-10	10 (14.3%)
10-15	12 (17.1%)
15-20	10 (14.3%)
>20	21 (30.0%)
Skipped	0 (0.00%)
Total	**70 (100%)**

4) How many CABG cases do you perform per year?

0-50	9 (12.9%)
50-100	20 (28.6%)
100-150	31 (44.3%)
150-200	6 (8.57%)
>200	3 (4.29%)
Skipped	1 (1.43%)
Total	**70 (100%)**

5) In your hospital, how often is Ticagrelor used in the management of ACS patients? (Check one)

0-25%	11 (15.7%)
25-50%	20 (28.6%)
50-75%	19 (27.1%)
75-100%	20 (28.6%)
Skipped	0.00 (0%)
Total	**70 (100%)**

6) Which of the following statements about Ticagrelor is correct? (Check one)

Ticagrelor is a directly acting agent that does not require hepatic transformation	12 (17.1%)
Ticagrelor bioavailability is variable and can be influenced by loss of function mutations in cytochrome 3A4/5	0 (0.00%)
Ticagrelor is equally efficacious to Clopidogrel and Prasugrel with respect to antiplatelet activity	0 (0.00%)
Ticagrelor has been shown to be superior to Clopidogrel in the treatment of patients with ACS	57 (81.4%)
Skipped	1 (1.43%)

Total	**70 (100%)**

7) In patients on ticagrelor requiring CABG after ACS, what most concerns you? (Check one)

Bleeding risk	63 (90.0%)
Ischemic risk	1 (1.43%)
Both	6 (8.57%)
Skipped	0 (0.00%)
Total	**70 (100%)**

8) Patient with critical coronary artery disease on Ticagrelor needs a CABG. The patient is stable, how many days would you wait to follow the last dose of Ticagrelor? (Check one)

1	3 (4.29%)
2	13 (18.6%)
3	31 (44.3%)
4	8 (11.4%)
5	14 (20.0%)
6	1 (1.43%)
7	0 (0.00%)
Skipped	0 (0.00%)
Total	**70 (100%)**

9) How do you manage intraoperative bleeding when patients are on Ticagrelor? (Check one)

Prophylactically give platelets transfusion and FFP after protamine has been administered	10 (14.3%)
Reserve blood product transfusion only if patients have excessive bleeding after protamine has been given	59 (84.3%)

Use of recombinant factor VIIa to reduce bleeding	0 (0.00%)
Prophylactically give platelets and FFP after protamine has been administered	1 (1.43%)
Use of Cryoprecipitate to reverse the bleeding	0 (0.00%)
Skipped	0 (0.00%)
Total	**70 (100%)**

10) In patients with ACS loaded with Ticagrelor and have undergone uncomplicated CABG, do you reinitiate Ticagrelor postoperatively? (Check one)

Yes	49 (70.0%)
No	21 (30.0%)
Skipped	0 (0.00%)
Total	**70 (100%)**

11) If you were to consider using Ticagrelor post – CABG, who would most likely be responsible for initiating this therapy? (Check one)

Cardiac surgeon, in hospital	52 (74.3%)
Cardiac surgeon, at follow up outpatient visit (Usually 4-6 weeks after)	5 (7.14%)
Cardiologist, in hospital	2 (2.86%)
Cardiologist, at follow up outpatient visit	2 (2.86%)
Nurse practitioner, in hospital	9 (12.86%)
Skipped	0 (0.00%)
Total	**70 (100%)**

12) Are you aware of a reversal agent that immediately reverse Ticagrelor?

Yes	33 (47.1%)
No	37 (52.9%)
Skipped	0 (0.00%)
Total	**70 (100%)**

13) Would you consider using a Ticagrelor reversal agent?

Yes	64 (91.4%)
No	6 (8.57%)
Skipped	0 (0.00%)
Total	**70 (100%)**

14) If you were to use a Ticagrelor reversal agent, which patients would you consider using the agent with?

Critical left main disease	0 (0.00%)
Unstable patients requiring urgent surgery	31 (44.3%)
STEMI	2 (2.86%)
All of the above	35 (50.0%)
Skipped	2 (2.86%)
Total	**70 (100%)**

15) How would you describe this agent in your clinical practice?

Major advance	36 (51.4%)
Minor advance	27 (38.6%)
No difference	7 (10.0%)
Skipped	0 (0.00%)
Total	**70 (100%)**