Accuracy of physicians to differentiate type 1 and type 2 myocardial infarction based on clinical information

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Short title: Accuracy of myocardial infarction etiology

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BRIEF SUMMARY

We performed a survey using real cases to determine the accuracy of physician's judgment in the etiology of myocardial infarction (MI) using intracoronary optical coherence tomography (OCT) as the gold standard. Among 308 physicians, overall accuracy to classify MI as type 1 versus type 2 was 60%. Overall chance-corrected agreement between physicians' assessment and intracoronary OCT was poor (kappa=0.05). Physicians' ability to differentiate type 1 versus type 2 MI based on clinical information is limited.

ABSTRACT

Background: Physicians commonly judge whether a myocardial infarction (MI) is type 1 (thrombotic) versus type 2 (supply/demand mismatch) based on clinical information. Little is known about the accuracy of physicians' clinical judgement. We aimed to determine the accuracy of physician's judgment in the classification of type 1 versus type 2 MI in perioperative and non-operative settings.

Methods: We performed an online survey using cases from the OPTIMUS Study, which investigated the prevalence of a culprit lesion thrombus based on intracoronary optical coherence tomography (OCT) in patients experiencing MI. Four MI cases, 2 perioperative and 2 non-operative, were selected randomly, stratified by etiology. Physicians were provided with the patient's medical history, laboratory parameters, and electrocardiograms. Physicians did not have access to intracoronary OCT results. Primary outcome was the accuracy of physicians' judgement of MI etiology as raw agreement between physicians and intracoronary OCT findings. Fleiss' kappa and Gwet's AC1 were calculated to correct for chance.

Results: The response rate was 57% (308/536). Respondents were 62% male, median age was 45 years (SD±11), 45% had been in practice for >15 years. Respondents' overall accuracy for MI etiology was 60% (95% confidence interval [CI] 57%-63%), including 63% (95% CI 60%-68%) for non-operative cases, and 56% (95% CI 52%-60%) for perioperative cases. Overall chance-corrected agreement was poor (kappa=0.05), consistent across specialties and clinical scenarios.

Conclusion: Physicians' accuracy to determine MI etiology based on clinical information is poor. Physicians should consider results from other testing, such as invasive coronary angiography, when determining MI etiology.

INTRODUCTION

Myocardial infarction (MI) is one of the leading causes of mortality worldwide.[1,2] In the perioperative setting, MI is one of the most common clinical complications after noncardiac surgery.[3,4] There is debate regarding the pathophysiology of perioperative MI. Patients undergoing noncardiac surgery are susceptible to sympathetic nervous system activation, tachycardia, bleeding, hypertension, and hypotension, which can lead to cardiac oxygen supply-demand mismatch. Surgery also causes hypercoagulability and inflammation, which can trigger platelet activation, plaque destabilization, erosion or rupture, leading to thrombus formation. These mechanisms fall within different categories of the Universal Definition of MI, type 1 (thrombotic), or type 2 (supply-demand mismatch).[5]

In the perioperative and non-operative setting, it is unclear how accurate physicians are at determining whether a non-ST segment elevation MI (NSTEMI) is type 1 versus 2 based only on clinical information. Physician's judgment about MI etiology often has implications for patient's management and may influence whether physicians opt for a conservative versus an invasive treatment strategy.[5]

We previously conducted the OPtical coherence Tomographic IMaging of thrombUS (OPTIMUS) Study to determine the prevalence of a culprit lesion thrombus in patients experiencing a perioperative NSTEMI as compared to a matched cohort of patients experiencing a non-operative NSTEMI, using intracoronary optical coherence tomography (OCT).[6] OCT is an

accurate intravascular imaging technique for the detection of thrombus, and thus classification of MI etiology.[7-9] The main objective of this current study was to determine the accuracy of physicians' judgment in the classification of NSTEMI etiology (i.e., type 1 versus 2) in patients diagnosed with NSTEMI in both perioperative and non-operative scenarios using cases from the OPTIMUS Study.

MATERIAL AND METHODS

Study Design

We undertook a cross sectional online survey study that evaluated physicians' accuracy for judgment of MI etiology using real cases from the OPTIMUS Study database.

Participants

From July 2017 to January 2018, we recruited anesthesiologists, non-invasive and invasive cardiologist, and general internists (i.e., the specialists most commonly involved with perioperative MIs) from 7 centres in Brazil, Canada, and Italy (Supplemental Table S1). We excluded investigators involved in the design of the survey, physicians originally involved in the cases, physicians whose scope of practice did not include management of MI and physicians on leave (i.e., out-of-office message for more than 6 months). Representatives of each specialty were contacted by email and invited to participate in the survey. Individuals were sent electronic reminders every two weeks. To maximize the response rate we used a short questionnaire, emphasized the relevance of the topic, offered to provide the survey results, and assured confidentiality.[10,11] Local leaders directly contacted non-respondents to encourage participation.

Data source

We developed cases for the survey from the OPTIMUS Study. The OPTIMUS Study was a prospective cohort study of 60 patients (i.e., 30 patients who had a perioperative MI and 30 patients who had a non-operative MI) that used OCT imaging to determine the presence of intracoronary thrombus. Full methods of the OPTIMUS Study are published elsewhere.[6] In brief, eligible patients were >18 years of age, experienced an MI after noncardiac surgery or non-operative MI that fulfilled the Universal Definition of MI[5] and underwent cardiac angiography within 3 days of the event. For each included perioperative MI patient, a non-operative MI patient was matched based on gender, age, and ECG ischemic changes. Patients were excluded if they had an ST segment elevation myocardial infarction (STEMI), cardiac revascularization in the prior 6 months, cardiogenic shock, or estimated glomerular filtration rate <35 mL/min.

After angiography, the culprit artery was identified for OCT imaging. OCT images were evaluated by a core laboratory (Cardiovascular Imaging Core Laboratory, case Western Reserve University, Canada). Two independent interventional cardiologists, blinded to whether patients had suffered a perioperative or non-operative MI, reviewed all images and decided on the presence or absence of intracoronary thrombus.

We randomly selected four cases from the OPTIMUS Study that underwent successful OCT imaging and for which we had all the clinical progress notes and consults, ECGs and troponin results. We divided the OPTIMUS cases into four groups according to clinical scenario (perioperative and non-operative MI) and according to the final MI etiology based on OCT results (type 1 and type 2 MI). We defined type 1 MI cases as the presence of thrombus at the culprit lesion based on OCT, and type 2 MI cases as the absence of thrombus or plaque rupture in the culprit artery based on OCT. Then, we randomly selected one case from each group. We pre-specified that in the event the selected case did not had complete clinical information, serial

troponin measurements, or an ECG, we would randomly select another case in that specific subgroup. All four cases selected were considered complete. Case details are provided in the supplement material.

Primary outcome

The primary outcome was the accuracy of physicians' judgement of MI etiology (type 1 versus type 2) based on the clinical information without knowledge of the OCT results. The OCT findings were used as the gold standard.

Case assessment

Invited physicians received a login linked to a unique token to access the survey with full documentation for all cases. Each token could be used only once. We used lime survey (https://surveys.mcmaster.ca/limesurvey), which is a free access internet-based survey platform. Each physician was invited to evaluate the cases which were presented in a random order unique to each token. Respondents were blinded to cardiac angiography and OCT results. For each case, physicians were provided with the original consulting physicians' progress and consultation notes, ECG images and laboratory results, including troponins, until the day of cardiac angiography. Physicians were invited to indicate whether they believed the case was a type 1 or type 2 MI. They were also asked to provide data on their demographics including their clinical practice. Details on consent form and questionnaire are presented in the Supplemental Material.

Survey development and testing

The questionnaire was developed by a multi-disciplinary group of physicians who planned, discussed, and built the final questionnaire based on the results of survey testing. Feedback was collected to evaluate the content and time to complete the questionnaire. Fourteen

out of seventeen invited physicians (including anesthesiologists, cardiologists, and internists) participated in the survey development. All survey questions were presented and the group was asked to judge the adequacy of documentation provided for the sample cases. Based on the information obtained through the development process, we expected respondents could complete a case within 5 minutes.

Statistical Analysis

We report number of physicians invited, reasons for exclusion and response rate (number of respondents/total invited who were eligible). Respondents' characteristics are presented as proportions for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables and median and interquartile ranges (IQRs) for non-normally distributed variables. We report overall clinical judgment accuracy as proportion of physicians' answers that were concordant with OCT findings, and its 95% confidence interval (CI). A priori we specified that we would report accuracy according to clinical scenarios (i.e., perioperative and non-operative), and the following physician characteristics: specialty (anesthesia; internal medicine; and cardiology); years of clinical work after completing training (<5; 5-15; >15); and proportion of time dedicated to clinical practice (<20%, 21-50%, >50%). To estimate overall accuracy and the accuracy by subgroup, and corresponding 95% CI, we used log-binomial generalized estimating equations (GEEs) to account for repeated measures per respondent. We report the accuracy by single clinical scenario with 95% CI using generalized linear models based on log-binomial distribution. We also explored if physician and scenario characteristics independently predicted the accuracy of clinical judgement in univariate and multivariable GEE models. Variables included in the model defined a priori were the following: clinical scenario, clinical specialty, years of clinical experience, and time dedicated to clinical practice. We

performed a post-hoc multivariate analysis including the number of MI cases per year managed by physicians in the last 12 months. Additionally, we reported clinical judgment accuracy by type 1 and type 2 MI.

Fleiss' kappa (κ) statistic was calculated for overall chance-correct agreement between physicians and OCT findings on the determination of MI etiology.[12] Fleiss' k is the chance-correct agreement measure for multiple raters, where values close to zero indicate agreement no better than by chance, and values close to one are considered perfect agreement. Fleiss' k values were interpreted as follows: values greater than 0.75, strong agreement; between 0.40 and 0.75 fair to good agreement; values less than 0.40, poor agreement; and less than 0, no agreement.[13] We determined Kappa by specialty and by clinical scenario (perioperative and non-operative). We report κ value and 95% CI.

To overcome the kappa paradox, when high raters' agreement can be translated into misleading smaller kappa values, we also determined Gwet's AC1 analysis.[14-16] We interpreted Gwet's AC1 analysis using the same parameters as Fleiss' k.[15]

Analyses were completed using SPSS version 17.0 and STATA version 12. We considered a two-tailed p-value <0.05 statistically significant.

Ethical Considerations

The study protocol was approved by the Hamilton Integrated Research Ethics Board and all participants signed an electronic informed consent form. All patient information was kept confidential and all patient identifiers were removed from the source documents provided to physicians. Physicians were not linked to their responses. All information was obtained using a secure web-based system, and stored in anonymous, aggregate form.

RESULTS

Survey respondents' characteristics

Among 592 potential participants, 56 (9.5%) were not eligible. Figure 1 shows reasons for exclusion. Response rate was 308 (57%). The proportion of respondents by country and by clinical specialty are presented in Supplemental Table S2. There were 1144 assessed cases, with an average of 3.7 cases (minimum 1; maximum 4) per respondent. Most physicians completed all cases (88%). Respondents were 62% male, had a median age of 45 years (SD±11). With respect to specialty, 44% were anesthesiologists, 35% were internists, and 21% were cardiologists. Respondents' characteristics are presented in Table 1.

Accuracy of clinical assessment of MI etiology

Figure 2 presents distribution of physicians' responses by OCT-based MI etiology and physicians' level of confidence in their judgement for each case. Overall accuracy of clinical judgement (i.e., agreement between physicians and OCT) across 1144 cases was 60% (95% CI 57%-63%). Accuracy was 63% (95% CI 59.5%-67.5%) for non-operative MI and 56% (95% CI 52%-60%) for perioperative MI. The majority of respondents were confident about their assessments. Table 2 presents overall accuracy and accuracy according to MI type by training level and specialty. Overall MI accuracy was similar according to physician's experience. Details are provided in the supplemental material. In the univariate analysis to predict physicians' accuracy, only clinical setting (perioperative versus non-operative) was statistically significant [Risk Ratio (RR) 0.88; 95% CI 0.80-0.97; p=0.013]. None of the physician characteristics (i.e., clinical specialty, years of clinical experience, and time dedicated to clinical practice) were associated with the level of accuracy, either in the univariate or in the multivariable model. The

post-hoc analysis including the number of MIs managed by physicians in the last 12 months did not demonstrated different results. Details of the multivariate analysis are presented in the Supplemental material.

Fleiss' κ statistic was 0.05 for overall chance-correct agreement between physicians and OCT findings on the determination of MI etiology. Fleiss' k agreement was consistently poor by clinical specialty, and by clinical scenario. Gwet's AC1 values confirmed low chance-adjusted agreement (Table 3).

DISCUSSION

This multicenter international survey demonstrates poor physicians' overall accuracy (i.e., 60%) for judging type 1 versus type 2 MI based on clinical data compared to OCT. Although physicians' accuracy to determine MI etiology was lower in the setting of perioperative MI as compared to non-operative MI (RR 0.88; 95% CI 0.80-0.97), accuracy for non-operative MI was also poor (accuracy 63%). Our study demonstrates that accuracy to classify type 2 MI is lower than for type 1 MI (51% vs. 69%; p<0.001). Overall chance-correct agreement between physicians and OCT findings on the determination of MI etiology (type 1 versus 2) was poor (k=0.05; Gwet's AC1 = 0.11), consistent across the non-operative and perioperative settings, and different clinical specialties. Despite the low accuracy and agreement beyond chance, most physicians were confident in their judgment.

Interpretation

These findings demonstrated that physicians were limited in their ability to predict beyond chance the underlying etiology of NSTEMI based on patients' clinical history, ECGs and troponin levels. Indeed, studies have shown that presence of ischemic features (e.g., ischemic

symptoms, ischemic ECG findings), and even troponin levels are not predictive of NSTEMI etiology.[6]

During the perioperative period, patients are exposed to sympathetic activation that can trigger hypertension, tachycardia, hyper-catabolism and subsequent increase in cardiac demand. Moreover, surgery is associated with bleeding, hypotension, and anemia resulting in a supply and demand imbalance.[5] However, surgery also leads to hypercoagulability, inflammation and endothelial dysfunction, predisposing patients to thrombotic events. Several studies have demonstrated the occurrence of type 1 MI, in 26% to 50% of patients with perioperative MI.[17-20] Yet, some of these studies are limited by the use of inadequate methods to detect intracoronary thrombus. The OPTIMUS Study used OCT and identified thrombus at the culprit lesion in 13% of patients who have experienced a perioperative MI as compared to 67% of those who experienced a non-operative MI.[6] Physicians should take into account prevalence of MI etiology in different clinical settings to guide diagnostic approachs and medical treatments. However, our study demonstrated that even among specialists from tertiary care academic hospitals, a significant proportion of patients suffering an MI were incorrectly classified without information from an invasive coronary assessment.

Physician's belief of whether an MI is type 1 versus 2 often has important therapeutic implications.[21] If an MI is thought to be type 1, the patient will more likely receive dual antiplatelet therapy and anticoagulation. Conversely, if an MI is deemed to be type 2, the patient is more likely to receive general treatment for anemia, hypotension or the triggers believed to be contributing to the ischemia process. In the perioperative setting in particular, mostly as a result of concerns for bleeding, patients with myocardial ischemia are discharged from hospital with limited cardiovascular secondary prevention treatment.[22] Moreover, if a physician assumes that a

perioperative MI has occurred as a result of supply-demand mismatch, patients may not be advanced for further risk stratification (i.e., angiography and possible detection of plaques required treatment).[23]

The Coronary CTA VISION Study demonstrated that among patients experiencing a perioperative MI, 72% had >50% coronary obstructive disease, and only 4% had normal coronaries on computed tomographic angiography imaging.[24] A perioperative MI, regardless of type 1 or type 2, might be an opportunity to identify at risk patients with asymptomatic coronary artery disease and offer medications with evidence for secondary cardiovascular prevention, such as aspirin, statins and ACE inhibitors. Recently, the MANAGE Trial[25,26] demonstrated that an intermediate-dose anticoagulation with dabigatran after a perioperative myocardial injury (including type 1 and type 2 MI) prevented major cardiovascular outcomes without increasing major bleedings at a mean of 16 months of follow-up.

Accuracy of diagnosing type 1 MI was significantly higher as compared to type 2 MI. These results suggest physicians should be even more careful when making the diagnosis of type 2 MI. Physicians should not underestimate the impact of type 2 MI on short and long term outcomes in both non-operative and perioperative settings. A recent systematic review and meta-analyses has shown that among 25,872 patients, type 2 MI patients had almost 3 times higher inpatient, 30-day and one year mortality, compared to those with type 1 MI. Operative stress was the most common trigger of type 2 MI. Patients labeled as type 2 MI were less likely referred to cardiac angiography as compared with type 1 MI.[27]

Strengths and Limitations

To our knowledge, this is the first study assessing the accuracy of physicians' judgment for MI etiology in non-operative and perioperative settings. The strength of this study is the use of real cases and the ability to compare physicians' judgement based on clinical information with OCT results. Physicians were exposed to scenarios similar to those to which they are exposed in daily clinical practice, where they commonly make decisions on MI etiology and determine next steps in investigation and treatment. This is a multicentre study, in 7 institutions, with a reasonable response rate, and most physicians completed all survey cases. We randomized the order of the cases to keep response rates similar across all cases.

This study has limitations. To minimize the length of the survey and increase the response rate, only 4 cases were included. It is possible that cases presented may not be representative of the variety of patients seen in practice causing a measurement effect; however, we selected random cases from the OPTIMUS Study. Also, in order to include perioperative and non-operative settings, and type 1 and 2 etiologies, the case prevalence in our sample (50% and 50%) was different from the actual prevalence of type 1 vs type 2 MI in the perioperative setting. Some physicians believe type 2 MI is more common than type 1 MI after noncardiac surgery.[28,29] Physicians were not aware of the stratification, but, given the low number of cases and the purpose of the survey, they may have guessed the even distribution of cases in the survey across settings and etiologies. This would have given them 50% probability to guess the etiology by chance, which is close to the accuracy we eventually found. The reported confidence in their responses, however, is a signal that they were not simply guessing, but based their responses on a believed knowledge. A substantial proportion of the physicians had not managed a considerable number of MIs in the preceding year before the survey. However, when our results were restricted to just cardiologists, or to physicians who had managed over than 30 MIs in the last

year, the overall accuracy of physicians' judgements compared to OCT did not improve compared to the overall cohort.

Non-response effect could be an issue; however, this study had a higher response rate than many survey studies. Although OCT is arguably the best objective assessment of the MI etiology, it is not 100% accurate. Thrombus could have already been dissolved in patients classified as having had a type 2 MI; in the OPTIMUS study the mean days from MI diagnosis to OCT was 1.9 (standard deviation [SD], ±1.1) days in the perioperative MI group and 1.5 (SD ±0.7) days in the non-operative MI group. Some readers may believe that the Universal Definition of MI angiography criteria for type 1 MI (i.e., identification of a coronary artery thrombus) is too restrictive and should be expanded to include identification of plaque rupture. Although the definition of type 1 MI used in this study was identification of coronary artery thrombus, none of the cases of type 2 MI used in this survey had evidence of plaque rupture.

Finally, we measured the chance-corrected agreement based on Fleiss' kappa that could underestimate the agreement when there is a high rate of agreement in one specific category. However, Gwet's AC1 should be a more stable measure of agreement, as it is less affected by prevalence and marginal probability.[16] Our survey demonstrated similar results with the two measures, as expected when the prevalence of categories (type 1 and 2 MI in our case) was 0.5.

CONCLUSIONS

Physicians' capacity to accurately determine type 1 versus type 2 MI based on clinical information is poor, consistent across different specialties, and for both perioperative and non-operative MI. Physicians should take this information into account when making treatment decisions based upon clinical assessment of type 1 versus 2 MI. There is a need for additional strategies to better define MI etiology and to guide clinical management.

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FIGURE LEGENDS

Figure 1. Participants flowchart.

Figure 2. Distribution of physicians' responses (Panel A) and level of confidence (Panel B) by case (%).

Table 1. Participants' characteristics

Respondent profile	Respondents (n=308)
Male (%)	190 (62)
Age - mean (SD)	45 (±11.1)
Specialty (%)	
Anesthesia	137 (44)
Cardiology	51 (17)
Interventional Cardiology	13 (4)
Internal Medicine	107 (35)
Years practicing specialty (%)	
<5	51 (17)
5-15	117 (38)
>15	140 (45)
Country practicing medicine (%)	
Brazil	84 (27)
Canada	148 (48)
Italy	76 (25)
Perioperative MIs managed in the last 12	

months (%)	
None	75 (24)
1 - 9	142 (46)
10- 30	63 (21)
>30	28 (9)
Non-operative MIs managed in the last 12 months (%)	
None	102 (33)
1 - 9	67 (22)
10- 30	65 (21)
>30	74 (24)
Time devoted to clinical practice (%)	
<20%	41 (13)
20- 50%	49 (16)
>50%	218 (71)

Abbreviations: MI – myocardial infarction

Table 2. Accuracy of physicians' judgement compared to intracoronary optical coherence tomography.

	Overall Accuracy % (95% CI)	Type I MI Accuracy % (95% CI)	Type II MI Accuracy % (95% CI)	p value
Overall cases	60 (57 - 63)	69 (65 – 73)	51 (47 – 55)	<0.001
By clinical scenario				
Non-operative	63 (60 - 68)	77 (73 - 82)	49 (43 – 55)	<0.001
Perioperative	56 (52 - 60)	60 (54 – 66)	52 (46 – 58)	0.057
By Specialty				
Anesthesia	63 (58 - 69)	84 (76 – 91)	42 (32 – 52)	<0.001
Cardiology	59 (55 - 63)	61 (55 – 67)	56 (50 – 62)	0.308
Internal Medicine	60 (55 - 65)	73 (67 – 79)	47 (40 – 54)	<0.001
By Years practicing specialty				
<5	58 (51 - 66)	63 (53 – 73)	53 (43 – 63)	0.161
5-15	60 (56 - 65)	75 (69 – 81)	45 (39 – 52)	<0.001
>15	60 (56 - 65)	66 (60 -72)	54 (48 – 61)	0.010
By Time devoted to clinical				

practice				
<20%	60 (51 - 70)	58 (47 – 65)	62 (51 – 73)	0.501
20- 50%	61 (55 - 68)	75 (66 – 84)	47 (37 – 58)	<0.001
>50%	60 (56 - 65)	69 (65 – 74)	49 (44 – 54)	<0.001

Abbreviations: CI, confidence interval.

Table 3. Fleiss‘ kappa (k) and Gwet’s AC1 agreement.

Group	K (95% CI)	Gwet’s AC1 (95% CI)
All	0.05 (-0.05, 0.16)	0.11 (-0.24, 0.46)
Specialty		
General Cardiology	0.11 (-0.18, 0.39)	0.37 (-0.43, 1.00)
Interventional Cardiology	0.01 (-0.12, 0.13)	0.13 (-0.31, 0.57)
Internal Medicine	0.05 (-0.05, 0.15)	0.16 (-0.26, 0.59)
Anesthesia	0.04 (-0.05, 0.12)	0.04 (-0.07, 0.14)
Clinical setting		
Perioperative cases	0.01 (0.01, 0.02)	0.02 (-0.47, 0.52)
Non-perioperative cases	0.07 (-0.09, 0.24)	0.21 (-1.00, 1.00)

Abbreviations: CI, confidence interval.

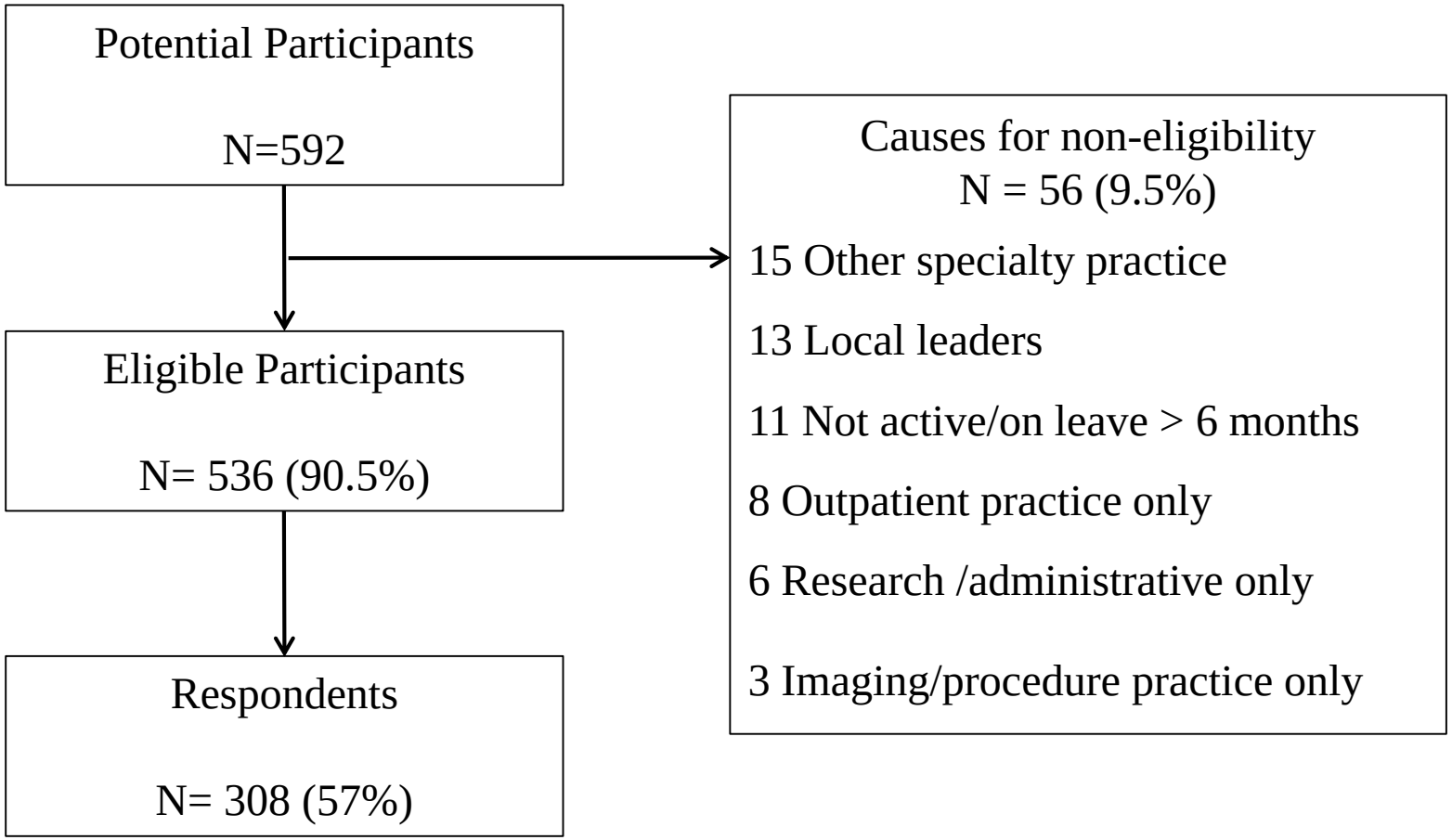
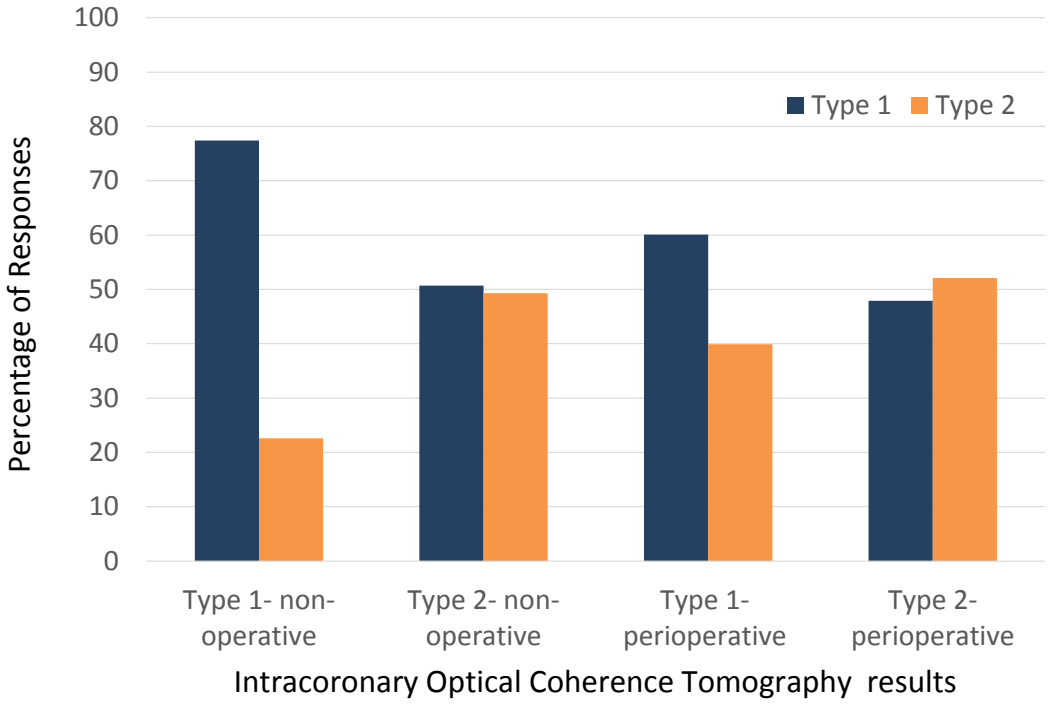
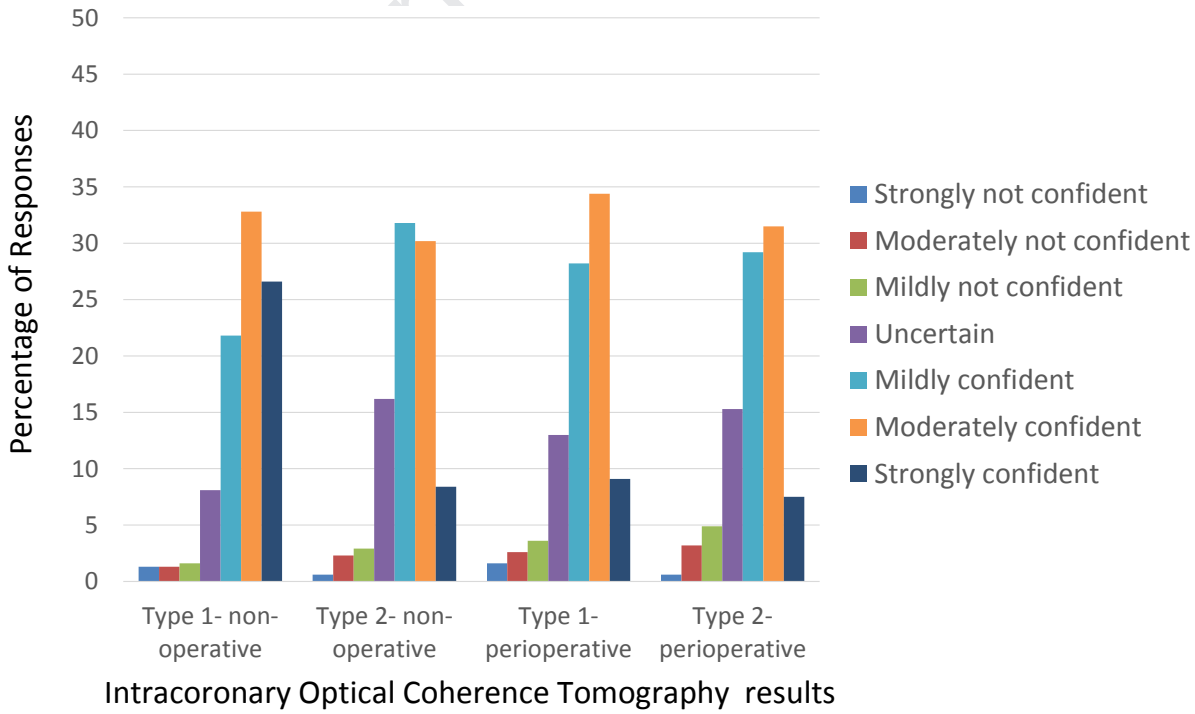

Potential Participants
N=592
Causes for non-eligibility
N = 56 (9.5%)
15 Other specialty practice
13 Local leaders
11 Not active/on leave > 6 months
8 Outpatient practice only
6 Research /administrative only
3 Imaging/procedure practice only
Eligible Participants
N= 536 (90.5%)
Respondents
N= 308 (57%)

Figure 2.

A


100
90
80
70
60
50
40
30
20
10
0
Percentage of Responses
Type 1
Type 2
Type 1- non-operative
Type 2- non-operative
Type 1- perioperative
Type 2- perioperative
Intracoronary Optical Coherence Tomography results

B


50
45
40
35
30
25
20
15
10
5
0
Percentage of Responses
Strongly not confident
Moderately not confident
Mildly not confident
Uncertain
Mildly confident
Moderately confident
Strongly confident
Type 1- non-operative
Type 2- non-operative
Type 1- perioperative
Type 2- perioperative
Intracoronary Optical Coherence Tomography results