INFORMED CONSENT IN ACUTE ST Elevation MYOCARDIAL INFARCTION

By

Rabia Kashur

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Department of Medicine
University of Alberta

Abstract

Research is crucial for the development of treatment guidelines. Informed consent is an essential component to ensure the ethical integrity of research. An ideal informed consent should meet three requirements; disclosure of adequate information about the study, subjects understand the information provided, and voluntariness to give consent.. The nature of acute myocardial infarction (AMI) presents special challenges to obtain ideal informed consent.

Literature suggest that most patients who consent to clinical trials remember the main information about the studies, however their degree of understanding and perceived comprehension was subjective and often questionable. Majority of patients prefer a summary of verbal information and do not read the written material provided to them prior to making decisions. However limited data is available in the literature addressing this issue with multiple remaining gaps of knowledge. The objective of *P*atients *A*cceptance and *C*omprehension to Written and *V*erbal *C*onsent (PAC-VC) study was to compare patients' perspectives and understanding to verbal and written consents in acute myocardial infarction trials.

PAC-VC recruited patients from AMI RCTs: Remote ischemic conditioning in ST-Elevation myocardial infarction research (REMCON-STEMI), Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI (COMPLETE) and routine aspiration ThrOmbecTomy with PCI versus PCI ALone in patients with STEMI undergoing primary PCI (TOTAL). REMCON used verbal script delivered by paramedics during enrollment to obtain a verbal ascent. Once the patients have received their treatment and stabilized, a written consent is obtained by a research nurse within 72 hours. TOTAL and COMPLETE studies utilized the standard written consents in their recruitment.

PAC-VC consisted of two comparison arms, specifically verbal and written arms. Total of 18 patients were recruited from the three ongoing clinical AMI trials. The verbal ascent arm enrolled 12 patients from REM-CON STEMI trial. The written consent arm enrolled 6 patients from TOTAL and COMPLETE studies. Assessment questionnaires were administered within 72 hours following the initial recruitment to the original trials to test patient understanding and comprehension, in addition to their perspectives to the consent process.

PAC-VC study found that in the written consent arm only 33.3% of patients read the written information in its entirety. The majority of study participants 75% of patients of the verbal arm and 100% of the written arm did not believe that written information is very important to make the final decision. However, 25% of verbal and 16.7% of written arms wanted that written information to be presented during the consent process. Indeed, participants from the verbal ascent still wanted to have written information be part of the consent process. In addition, the majority of patients of the written consent 83.3% vs only 50% of the verbal ascent felt pressured during the consent process. Patient responses showed that patients with verbal ascent had an adequate understanding to most components of informed consent and comparable to those of written consent.

We concluded that in order to improve the quality of consent, focus should be more on methods of information delivery, and that the information included should concentrate on the content rather than the quantity. In addition, it has been proposed that perhaps more time be provided to patients to discuss the information presented, as this may have an effect on patients' recollection.

Preface

The study of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, study title PAC-VC, ID number Pro00046145.

This work is dedicated to my beloved wife, parents, brother and children, for their patience and support.

Thank you

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Chapter 1 **Introduction**

Informed consent, history and development:

The concept of informed consent has a legacy that extends back to 1767 when an English court prevented physicians from experimenting on patients without obtaining consent.[1] Decades later, the first proposed documented consent was implemented in 1900 by the army physician Dr. Walter Reed who asked research volunteers to sign a written contract outlining the risks of participating in his study which later successfully confirmed mosquitoes as the vector for yellow fever.[2]

The concept of informed consent, respect to individuals' autonomy and research ethics were not equally respected among researchers due to the absence of harmonized ethical codes. The emergence of the first internationally recognized ethical code connected to the famous Nuremberg trials where the Nazi physicians were trialed for experimenting on people unwillingly during world war II.[3] The code clearly made informed consent essential in protection of research participants by stating that "The voluntary consent of human subjects is absolutely essential". This code however, did not mention anything about vulnerable population who cannot give consent and their involvement in research. In 1964, the World Medical Association (WMA) published the Declaration of Helsinki that described specific conditions where research can involve participants without consent. The declaration restricted this condition only in the existence of a mental or physical condition that prevents obtaining informed consent provided that this condition is a necessary characteristic of the research population.

The Nuremberg Code and the Helsinki declaration had little impact on research ethics in the United States due to the absence of laws and regulations that would enforce statements proposed for conducting human research. Following the Tuskegee experiments scandal,[4] in 1974 the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created as the first national body to shape the bioethics policy in the US. Shortly after that in 1978,

the commission issued the well-known Belmont Report to state that consent should be sought from "those who are most likely to understand the incompetent subject's situation and to act in that person's best interest". In 1981, many of the Belmont's report were codified by the code of federal regulations mandating voluntary informed consent for research participation with few exceptions. The code allowed exceptions for research that carries no more than minimal risk to commence without obtaining informed consent. Minimal risk was defined as risk that would be normally encountered in daily life or during performance of routine physical or psychological examinations or tests. However, the regulations did not illustrate how minimal risk should be measured and whether it is an absolute amount or a proportional to the risk encountered by some patients similar in cases of trauma or resuscitation. Knowledge gap and scientific demand to confirm theories and experimental treatments that were thought to be potentially lifesaving urged investigators to develop a new version of "Deferred Consent" as an alternative method of obtaining consent in situations where consent was unfeasible as in brain resuscitation trials.[5] Researchers recommended using deferred consent in conditions where patients are comatose and it is not known whether standard or experimental therapy is best for treatment assumed that possible risks related to the experiment are not significant. Deferred consent continued to provide a convenient venue for researchers to conduct their trials without obtaining an immediate consent until 1993 when Dr. Gary Ellis, the director of the Office for Protection from Research Risks sent what is known as "Dear Colleagues letter". The letter warned institutional officials and IRBs that deferred consent is not compliant with the federal regulation. In reaction to this letter and trying to mitigate conflict existed between researchers and regulatory bodies, the Coalition conference of Acute Resuscitation and Critical Care Researchers developed a consensus statement.[6] The statement recommended adoption of research without informed consent in selective cases where risk is high,

however, additional protective measures must be taken by investigators to protect individuals' autonomy by leading "consultations" with potential trial participants.

In an attempt to adopt the recommendations of the Coalition conference and to resolve the dilemma of consent in emergency research, the Food and Drug Administration (FDA) with the Department of Health and Human Services (DHHS) issued regulations that allow research involving humans without consent. The code states that research without consent from participating subjects may be allowed if certain conditions existed. It also mandates researchers to take extra measures before commencing the trial to safeguard the welfare of individuals and the community where it is taking place.

In Canada, there are three federal research agencies that oversee and regulate research in Canada; The Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Social Sciences and Humanities Research Council of Canada (SSHRC), the *Tri-Council Policy Statement (TCPS): Ethical Conduct for Research Involving Humans*, which is a joint policy of the Canada's three federal research agencies; was first adopted in 1998. The statement brought forward three core principles on which the guidelines are based on. The first principle evolves around the concept of respect for Persons and it incorporates the dual moral obligations to respect autonomy and to protect those with developing, impaired or diminished autonomy. The second principle is concerned for a persons' welfare, quality of experience of life in all aspects. The last principle refers to justice and the obligation to treat people fairly and equitably.

In 2001, Canada's three federal research agencies, CIHR, NSERC and SSHRC together established the Interagency Advisory Panel on Research Ethics as part of a collaborative effort to promote the

ethical conduct of research involving human participants in which the Panel develops, interprets and implements the *Tri-Council Policy Statement* (TCPS).

Emmanuel et al [7] discusses what makes research ethical. They state that most documents emphasize certain ethical components while leaving out consideration others as these often come in response to an instigation issue during that time. Instead, Emmanuel et al proposes 7 core requirements as a guide to meet the appropriate criteria for an ethical research: (1) ethical research should hold a scientific or social value (2) be scientifically valid, fair to subject selection and have a favorable risk to benefit ratio. The research should involve an informed consent process and be reviewed by an independent review committee. It should also respect potential research participants' rights like autonomy, privacy and maintaining their welfare.

Informed consent, Since the inception this concept, it has gone through several adjustments to reach its final definition, in which the International council of harmonization (ICH) guidelines for good clinical practice defines informed consent as a process by which subjects voluntarily confirm their willingness to participate in a trial after having been informed of all aspects relevant to the subjects' decision. Informed consent relies on three principles: disclosure of adequate information about the study, subjects understand the information provided, and voluntariness to give consent.[8]

The role of clinical trials in developing new strategies and treatment guidelines of disease management is unquestionable.[9] With the increasing knowledge and rapidly evolving science and the breakthroughs in medical technology, randomized clinical trials are needed to confirm and illustrate the effectiveness and clinical impact of the new therapies and treatment strategies. Informed consent is a fundamental principle in research ethics. It serves as a tool that protects individual's autonomy. The special circumstances surround myocardial infarction make it difficult

to obtain an informed consent. It often entitles enrollment of critically ill patients who are distressed and require urgent therapy to prevent mortality and subsequent morbidity. Difficulties are often related to the time restraints or to patients mental and physical symptoms that leaves them incapable of deciding for themselves. Evidence suggests that patients in this category are generally in a suboptimal state to understand or remember facts related to their condition and planned interventions. [10-12] It also suggests that many patients who consent to AMI trials remember the main information, however their degree of understanding and perceived comprehension was subjective and often questionable.[13]

Given the emergency nature as AMI as an acute condition requires immediate medical attention, concerns about exposing emergency patients to additional risks related to delays to access treatment while waiting for consent process. Many trialists tried to overcome this issue by tackling the consent process through different ways. The GISSI [14] trials that investigated the effects of fibrinolytics in AMI, enrolled patients without obtaining informed consent. This was approved by their own independent ethics committee and adopted to protect the right of patients to not be exposed to an emotionally distressing process of informed consent. Instead, the patients were informed of the trial after recovering from the acute phase of AMI. On the other hand, Zelen design or Zelen single arm consent [15] was another strategy that was used in certain trials [16-18] to overcome challenges with consenting patients. The consent process is based on randomizing every eligible patients then, consenting only those who end up in the experimental arm. This way, recruitment rate is improved while protecting patients in the standard treatment arm from being exposed to an avoidable emotional stress during the consent process.

As the research in these circumstances is critical to advance medical knowledge and thereby patients' care, medical literature worked to evaluate patients understanding to informed consent and assess factors contributing to their level of comprehension.

The objectives of this project was to perform a narrative review, identify knowledge gaps of informed consent and prospectively assess patients' acceptance and comprehension to verbal and written consents in an acute myocardial infarction clinical trial.

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Chapter 2 **Informed consent in acute myocardial infarction research: a literature review**

Abstract

Background: Clinical trials in acute myocardial infarction present special challenges in regards to obtaining informed consent. Time constraints and patient's pain, anxiety and clinical condition are all factors affect patient's experience with consent process. The aim of this review is to summarize available literature examining patients' comprehension and recall in addition to attitudes towards consent process in acute myocardial infarction research.

Methods: Medline, Embase and Scopus were used to identify related research studies assessing patients' comprehension to consents in acute myocardial infarction (AMI) research published up until the end of March 2017, in addition to manual searches of reference lists.

Results: A total number of 8 studies were identified examining several elements mainly including information regarding understanding and recall, use of written information, attitudes toward consent process as well as Patients coercion by time and the emergency nature of AMI. Results suggest that most patients who consent to clinical trials remember the main information about the study, however their degree of understanding and perceived comprehension was subjective and often questionable. Majority of patients preferred a summary of verbal information and did not read the written material provided to them in its entirety prior to making decisions. Many of them found it irrational to expect patients to read written material in an acute phase of a heart attack. Instead, patients turn to oral information and explanations as a substitute. Opinions about consent process varied among patients and attitudes mainly corresponded to their self-assessed competence. Those who thought they were competent felt it is acceptable to be approached as long as they have the right to refuse.

Conclusion: Informed consent in the setting of AMI research is challenging. Limited data is available in the literature addressing this issue with multiple remaining gaps of knowledge.

Obtaining consent through traditional methods is not optimal and perhaps finding other means as verbal ascensent is warranted. Assessment of patient's comprehension should be assessed by objective methods.

Introduction

The role of clinical trials in developing new strategies and treatment guidelines of disease management is unquestionable[9]. Informed consent is an essential requirement to conduct clinical research and the very tool that serves to protect participants in human research. However, dealing with challenges raised by enrolling patients into research is inevitable. The special circumstances that rule some of acute conditions like stroke, trauma, myocardial infarction and cardiac arrest makes it difficult to obtain informed consent. This is mainly due to time constraints where prompt diagnosis and treatment are necessary. Symptoms associated with these conditions also stress patients and creates challenges to obtain informed consent. Since an ideal informed consent should be based on adequate disclosure of information, patient's understanding and voluntariness to provide consent;[8] the overall quality of informed consent is debatable and causes concerns. [19, 20]

As the research in these circumstances is critical to advance medical knowledge and thereby patients' care, efforts were previously made to evaluate patients understanding to informed consent and assess factors contributing to their level of comprehension.

The objective of this review is to summarize the literature looking into patient's comprehension and attitudes towards consent process in acute myocardial infarction (AMI) trials.

Methods:

A) Literature search, data source and study selection:

Medline, Embase, and Scopus were used to identify related research studies assessing patient's comprehension and attitudes towards informed consent in acute myocardial infarction research (AMI) published up until the end of March 2017, in addition to manual exploration of reference lists. The search was limited to studies conducted in humans and published in English, with no other limitations. The following terms were used to conduct the searches: exp Mental Competency, exp Myocardial Infarction, *Cognition/es [Ethics], personal satisfaction, exp Comprehension, exp Emergency Treatment/ or exp Myocardial Infarction/ or exp Emergency Medical Services/ or exp Heart Arrest/, exp Informed Consent, exp Biomedical Research, exp Memory/ or exp Mental Recall/ or information recall.mp.

The review included cross sectional survey studies interviewing patients with ischemic heart disease who experienced a heart attack and were approached to be enrolled into an acute myocardial infarction trial. Patients must be interviewed and assessed for understanding of informed consent or asked about opinions related to the consent process. (Figure 2.1)

B) Data extraction:

Two reviewers (RK and SE) independently reviewed the generated results and identified eligible studies that met the selection criteria. Full text articles were retrieved in cases where the abstracts had not provided enough information. The final list included in the review was chosen by both reviewers with no conflict in the final selection group. Total of 11 studies were initially selected for review [9, 11, 21-28]. Upon full text review, three studies were later excluded [27-29] as the first interviewed patients with AMI, who were not originally enrolled into a trial but theoretically

asked about their opinions towards consent process. The second one assessed capacity of patients using Wechsler adult intelligence scale revised test, to quantify cognitive ability as a surrogate measure to capacity. The third interviewed patients who were enrolled after at least 5 days from the AMI and was not during the acute phase.

The following items were collected from the studies and used in the analysis: study objectives, methods, results, items examined results and conclusions.

Results:

Total of 8 studies published from 2000 to 2015 have been included in the review as they addressed different aspects of informed consents in acute myocardial infarction (AMI) research. All studies interviewed patients whom have been approached to be enrolled into AMI research trials have been selected in the review. Most of studies used either in person interviews or paper-based questionnaires. Studies sample size ranged from 20[9, 26] to 399[11].

The studies approached consents from different aspects, results were mainly grouped into four domains: information understanding and recall, attitudes towards consent process, use of written information and finally patients' coercion by time and the nature of the disease during consent process.

1) **Information understanding, recall and competence:** Total number of 6 studies assessed patient understanding to information presented during consent process. [9, 11, 21-25] Overall evidence suggests that patients in this category are generally in a suboptimal state to understand or remember facts related to their condition and planned interventions. Some patients had little recall of consent process while others did not even recognize that they were participating in a study. [10, 11, 30] Kucia et al[9] used a scoring system to evaluate

the understanding of 20 patients and showed an overall average score of 52%. Interestingly, the mean score of knowledge of benefits was 85% vs knowledge of risks 35% [P<0.0001]. Additionally, Gammelgaard et al [24] showed 72% of study participants felt that they understood that they were asked to participate in a research study and recognized the purpose of this study, however, they reported less understanding when it came to the details. On the other hand, In another smaller study [25] by the same author, study participants fell into two groups, one which understood that they were enrolled into a trial but understanding was suboptimal while the second group believed that they consented to a treatment. Williams et al [11] reported that 21% of patients had good overall comprehension of information whereas 67% and 12% reported partial and poor comprehension respectively. Agard et al [22] investigated patients experience with consent procedure included in three randomized interventional AMI trials. They found that patients had fragmentary knowledge about the trials and concluded that patients often appear to lack sufficient knowledge to reach an autonomous decision.

Yuval et al [21] examined the perspectives of a cohort of patients who participated in ISIS-4 trial [31] and reported that only 31% of study participants had full comprehension vs 50% and 19% had partial or no understanding to the information respectively. Of note, 63% of patients remembered verbal information whereas only 5% of the patients recalled the written description. Yuval et al [23] in another study compared patients' comprehension in AMI and chronic heart failure "CHF" trials and found the reported full understanding was 31% in AMI research while and 27% in CHF trials. Total of 20% of patients in both groups reported little or no understanding at all. Dickert et al [26] showed 55% of patients

remembered being asked to participate in a trial however comprehension of study details was limited.

2) **Attitudes toward consent:** Total number of 6 studies assessed attitudes toward consent in which researchers explored patients' thoughts toward the consent process, and their ability to make decisions during the acute phase of AMI trials. In the study by Gammelgaard et al [24], 50% of trial participants and 34% of the non-participants found it acceptable to patients in their situation to make a decision as long as they felt able to decide. However, 26% of the participants and 51% of the non-participants had a different opinion and commented that it was impossible to decide under these stressful conditions. They did not want to be asked to make any decisions. In their qualitative study by Gammelgaard et al [25], patients were asked if it is acceptable to involve AMI patients in an informed consent process. The answers varied among patients, and were mainly dependent on patients' self-assessed competence. Those who thought they were competent found it acceptable to be involved in the process as long as they could refuse, whereas those who thought they were not able to make a decision did not find the consent situation suitable.

   Nonetheless, when a total of 31 AMI trial participants interviewed by Agard et al [22] were asked how they should be treated if they were too ill to be asked to participate in a study of an emergency nature, total of 26 participants preferred physicians to decide on their behalf while 4 were uncertain and only one preferred to refrain from the research. When asked about the idea of being asked to provide a written consent in a such acute circumstances, responses varied widely. Some patients felt being subjected to unwanted experiments where they had no real choice, also becoming unwillingly responsible for the

choice of treatment. Others thought it was acceptable considering the legal aspects of the consent process and looked at it as a mandatory step that physicians had to fulfill for legal purposes. Dickert et al [26] revealed in their study that patients generally felt they were able to make a decision at presentation despite some limitations such as pain and time and still wanted to be the primary decision maker. A perceived medical benefit was a common reason indicated for a favorable attitude toward enrollment.

Yuval et al [21] reported that 25% of patients believed they received better treatment due to participation, while 49% thought their involvement will not affect the quality of their treatment and 27% were not certain. In addition, one third of participants (36%) stated that the study gave them a sense of greater security, 31% indicated that involvement gave them an interest in medical science and 23% had no benefit. Williams et al [11] stated reasons of beneficence ranged from willingness to participate in trial research to "help someone" in 12% of those who answered, another 7% accepted due to their trust in the medical profession.

3) **Use of written material as a source for information:** Studies examined this topic and showed that many patients do not read the consent form or the written information sheet before making a decision. A total of 6 studies had examined this aspect. [11, 22, 24-26] The majority of patients interviewed by Agard et al [22] preferred summary of verbal information and wanted to be spared signing a paper which they had not read. When participants consulted about what type of information they feel necessary to provide during enrollment, 84% preferred only verbal information and consultation, while 7% wanted written information to be included in the consent procedure. Gammelgaard et al[24] have

shown that only 28% of study participants and 7% of the non-participants had read the information sheet before making their decision. In their other qualitative study [25] many patients found it irrational to expect patients in acute phase of a heart attack to read and understand a written information. They also indicated that patients were adequately informed orally and thought the consent process is likely to be improved by enhancing the presentation of verbal information. Moreover, Williams et al [11] reported that 81% of patients who gave consent and 92% of those who refused did not read the written information before giving or refusing consent.

Interestingly, 63% of patients reported by Yuval et al [21] recalled verbal explanation versus 5% for only written description. Participants interviewed by Dickert et al [21] stated that they relied on the oral information given by the physician and only 4 out of 20 patients reported actually reading the consent form.

4) **Patients' coercion by time and the emergency nature of AMI:** Gammelgaard et al[24] reported that 40% of trial participants felt under pressure at the time of the consent procedure. Patient who declined participation as reported by Williams et al [11] were more likely to believe that they had not been given adequate time to decide than were those who gave consent (61% vs 25%, p=0.01) and reported that this factor had affected their decision about participation in the HERO-2 trial [32]. Gammelgaard et al, [25] reported that patients revealed that they were willing to consent to anything in a desire to be treated as soon as possible and receive relief from their state of pain. Furthermore, participants interviewed by Agard et al [22] stated that they felt rushed into making a prompt decision, which put the participants under stress. Moreover, participants interviewed by Dickert et al [26]

explained that one of the limitations to making informed decisions was time pressure and the sole concern at the time was stopping the pain and receiving treatment.

Discussion:

Randomized clinical trials are essential to develop and refine treatment strategies for medical conditions. Appropriate informed consent is essential to conduct clinical research. However, the emergency nature of the AMI as a disease poses extra challenges to obtain an ideal informed consent. AMI is associated with many distressing symptoms and emotions that might impair one's judgment and comprehension. This review has identified 8 studies interviewed patients with AMI whom had been approached to participate in research trials. Four different aspects of consent process were examined. Information understanding and recall, use of written information, the attitudes toward consent process in addition to coercion by time and the emergency nature of AMI were discussed in this review.

Results suggest that most patients who consent to clinical trials remember the main information about the trials, however their degree of understanding and perceived comprehension varied among studies, was subjective and often sub-optimal to the details. This variation in patients understanding can be explained by the impaired cognition on the patient's side, poor method of information delivery or both [9]. Patients usually performed better remembering benefits vs recalling risks[9, 24]. Majority of patients preferred a summary of verbal information and did not read written material. They also made enrolment decisions prior to reading written script. Many of them found it irrational to expect patients to read written material in an acute phase of a heart attack. Instead, patients turn to verbal information and explanations as a substitute. The fact that may suggest reading needs more time and special attention to analyse the facts enlisted in a written

format. Instead, patients turn to oral information and explanations as a substitute. An observation that show a potential opportunity of an improvement in the process of informed consent. This can be either through wisely choosing the information being presented and emphasizing the role of verbal discussions as a tool of information delivery. This is supported by Williams et al [11] when mentioned that patient information sheet needed a higher educational level than most of what patients had achieved.

Opinions about consent process varied among patients and attitudes mainly positively corresponded to their self-assessed competence. Those who thought they were competent felt it is acceptable to be approached as long they maintained the right to decline participation. These attitudes were less frequently observed in patients who refused to participate. They felt that they should always be approached for consent if required. In case they were not able to give consent, several patients were comfortable leaving the decision for the physicians to decide on their behalf. Since delay in treatment of AMI increases the rate of adverse outcomes and risk of death [33], consent for participation in AMI trials is needed urgently from patients. This fact may force patients to consent. Many patients felt pressured by time during consent process. This was more reported by patients who declined participation. Patients rushed to make decisions instead of thinking about the consent. Their main concern was to relieve their symptoms and receive treatment rather than processing research information.

Absence of pain at trial entry, level of education, male sex, time spent for discussion and questions prior consenting were determinants affecting a patient's level of understanding. Conversely, anxiety, dyspnea, morphine administration, seniority of medical officer obtaining consent, age of the patient and whether English was first language of the patient did not seem to affect understanding.[9, 11, 21]

Patients' poor understanding and recollection to information provided through the consent did not change patients attitudes to forgo the consent process and most of them still wanted to be asked if they wanted to be enrolled into research despite recognizing their limitation[26].

Knowing the importance of AMI research to improve patients' outcomes, invites for more trials in this field. However, recognizing the difficulties associated with obtaining an appropriate consent, urges to propose different methodologies to improve consent process. Several strategies were previously suggested including the use of videos, interactive computer multimedia, Q&A sessions during consent process.[34-38] Emphasis on methods of verbal information delivery provided to patients should be examined and assessed as a potential alternative to the formal written consents. This is supported by the literature as it clearly illustrates a preference to this tool of information delivery for most patients since it is quicker, concise and likely more interactive. Prospective consents should also be considered as this was brought up with patients by Dickers et al [26] and found to be an interesting idea where it can be implemented through subspecialty clinics with high risk patients for developing AMI and discussed beforehand.

Current knowledge gap:

The efficiency of the role of written consent in protecting patients' rights and serving as a tool for information delivery has been examined in the literature; however, to our knowledge, verbal ascent has not been examined nor compared to the conventional written consent. The definition of understanding and determining what is adequate is controversial. Unfortunately, there are no standardized testing to quantify comprehension or define how much understanding is enough to consider the consent is satisfactorily meeting the principal requirements. This is another area that needs to be addressed, perhaps by developing standardized testing tools that would objectively

assess patients' comprehension and quantify their understanding. Factors associated with AMI like pain, anxiety and pain medication use in addition to other patients' demographics should also be further studied in larger populations to validate previous reported results.

Limitations:

This review was primarily limited by the different methodologies applied in each selected study. Factors such as age, gender, pain and anxiety, education level, analgesics and sedatives were not consistently reported. Timing of interviews after trial enrollment was varied among studies. Number of patients interviewed were usually low to safely infer conclusions and thus adequately powered studies are needed. The protocols of the studies were also not standardized throughout and varied among studies.

Conclusion:

Informed consent in the setting of AMI research is challenging. Limited data is available to address this issue leaving multiple knowledge gaps. Obtaining consent through traditional methods is not optimal and perhaps finding alternative means is warranted. To improve the quality of consent, focus should be more on methods of information delivery, providing more time to patients to discuss the information presented as this appears to have effect on patients' recollection. Information provided should be chosen wisely and to focus on the contents rather than quantity.

Acknowledgment:

I would like to acknowledge Samya Elkhatali for the assistance with the abstract review and selection as an independent reviewer.

Conflict of Interest:

The authors declare no conflict of interest.

Figure 2.1 Flow chart of included studies

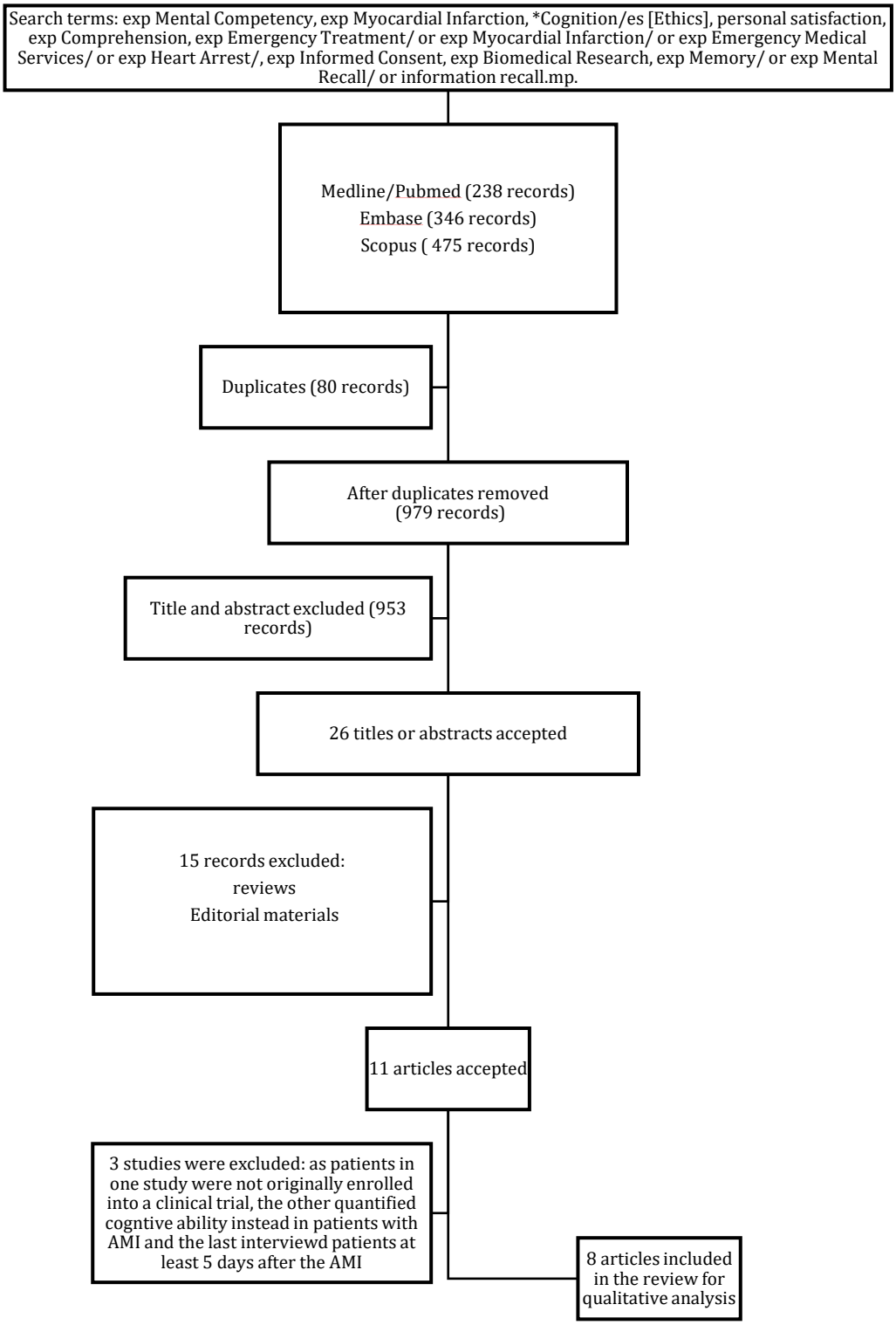

Table 2-1 Summary of included studies

Study	Objectives	Methods and Design	Items examined	Results	Conclusions
Yuval *et al.* 150 participants (2000)[21]	To study the patients perspective after participation in the fourth international study of infarct survival (ISIS-4) trial.	Mailed written questionnaire sent within 1 to 3 months after the acute event	Explanation of the study and patient comprehension at the time of the consent Feelings and reactions during the study Response and emotions of the patients after completion of the study	31% of participants stated that they had full comprehension, 50% claimed partial comprehension and 19% had little or no comprehension at all. 63% of patients recalled oral explanation versus 5% for only written description 25% of patients believed they received better treatment due to participation.	Authors concluded that despite the fact that the consent process met ethical and legal requirements, perceived patients comprehension was incomplete with much more could be done to improve the process.
Kucia *et al.* 20 participants (2000)[9]	To explore pevalence, pattern, and determinants of patient comprehension for clinical trials in ACS.	Written interview questionnaire administered twice at 10.2(±3.8) and 24.2(±2.9) hours post randomization.	The name and/or position of the doctor obtaining consent, the name and/or nature of the medical condition to be treated, the names of the drugs involved and the concept of randomization,	The poorest knowledge demonstrated was that of treatment alternatives, with a score of 10.0% (±15.6%) The highest score was achieved in knowledge of the purpose/potent	Primary understanding of the research protocols for patients with ACS was imperfect, particularly of risk, this was found to improve markedly with repetition.

			the purpose/potential benefit of the drug(s), the potential risk(s) of the drug(s), any incremental tests/procedures attributed to clinical trial participation, and any available treatment alternatives	ial benefit of the investigational drug with a score of 85.0% (±33.3%) Knowledge of risk was the second lowest scoring area with a score of 35.0% (±36.6%) Patients who had no secondary education had poorer understanding of the protocol (P < .05). Sex was also a significant determinant, with men demonstrating better understanding (P < .05). Patients with pain at the time of enrollment to the UAP/NQAMI trial had significantly poorer understanding (P < .05) Upon repeat interview, after repeated education about the protocol,	Female sex, limited education and presence of pain during study enrollment were significant determinant to poor initial score of understanding. Young age was the only determinant of improvement on repeat assessment.

				patients showed an improvement in knowledge.	
Agard *et al.* 31 participants (2001)[22]	To explore the patients' experience of the consent procedure during the early phase of acute myocardial infarction.	A combined qualitative and quantitative interview	Decision making/ competence Method of presenting the study information Attitudes towards participation in a trial	Hardly any of the respondents were judged competent. (84%) would prefer only verbal information and consultation when deciding whether or not to participate in a study. The majority (n = 26/30) of the interviewees felt that the physician alone should be able to decide to include a patient with acute myocardial infarction in a trial when the patient was too ill to be asked for consent to participate in the study.	The results raise questions to whether patients have the capacity to make normally autonomous decision. Interviewees had fragmentary knowledge about the trial to which they had given consent. Most preferred summary verbal information and wanted to be spared signing the consent.
Williams *et al.* 399 participants (2003)[11]	Determine whether patients with acute myocardial infarction	Verbal questionnaire involved patients eligible to enrol in	Assessed readability of patient information sheets, patients' educational	The patient information sheet needed a year 13 (age 18) educational level for	Few patients gave consent that was truly autonomous and

	could understand written and verbal information and whether they were competent to give autonomous informed consent to participate in a clinical trial.	HERO-2 study were included in consent substudy.	status, their views of the consent process, comprehension of verbal and written information, and competence to give consent	comprehension. 21% patients self reported good overall comprehension of verbal and written information provided at the time of the consent process. Only 63 of 346 (18%) read the patient information sheet before giving or refusing consent to participate. However 93% of patients who consented or refused consent recalled the HERO-2 consent process. Patients who gave consent were more likely to report good or partial comprehension of the information provided than were those who refused consent (272 [89%] *vs*	informed. Authors felt that even though the consent process met regulatory requirements it was inappropriate for most patients' needs.

				14 [70%], respectively In an assessment of competence to make an autonomous decision, 75 of 145 (52%) were ranked at the lowest grade and 26 (18%) were not competent to consent.	
Yuval *et al.* 220 participants (2003)[23]	Comparison of patient perception, comprehension and satisfaction in acute (acute myocardial infarction) and chronic (outpatient heart failure) clinical trial.	Mailed written questionnaire sent within at 1 to 3 months after participated in a clinical cardiovascular trial.	Patient comprehension	Results similar in both groups. 27% of chronic and 31% of acute patients perceived full comprehension while almost 20% of both groups reported little or no understanding of the trial. Likewise, patients in both acute and chronic patients, (51% chronic; 63% acute) preferentially recalled the oral rather than written explanation of the trial.	Emphasis should be placed on improving the duration of oral explanation to reach better level of informed consent.

Gammelgaard *et al.* 32 participants (2004)[25]	To examine how patients experience the process of informed consent during AMI in addition to the various factors that influence their experience of the consent process	Strategically sampled patients, both those who gave consent or refused to in the DANAMI-2 trial, were contacted after which oral qualitative interviews were performed.	Attitudes to the consent process Study understanding Use of written info. Decision making/ competence Voluntariness Motivation for consenting or declining	Patients found it acceptable to be informed about the trial Patients mostly made decisions based on oral and not written information.	Patients' ability to make a decision needs to be addressed much more explicitly during the informed consent process.
Gammelgaard *et al.* 181 participants (2004)[24]	To study how AMI patients experience the process of informed consent.	Two types of follow up written questionnaires were sent depending on whether patients gave consent or refused to consent to the DANAMI-2 trial.	-Decision making/ competence -Attitudes to the consent process -Information recall	76% of the trial participants and 63% of the non-participants felt able to make a decision. 50% of the trial participants and 34% of the non-participants found it acceptable that are asked to make such a decision Only 28% of the trial participants and 7% of the non-participants read the information sheet before	Informed consent should be sought in acute myocardial infarction More focus should be put into improving the oral information delivered by physicians and research ethics committees.

				they made the decision In general, non-participants recalled less of the information or were less well informed than those who chose to participate.	
Dickert *et al.* 20 participants (2015)[26]	Improve understanding of patients' viewpoints on informed consent for clinical trial enrollment during (STEMI)	Verbal structured interview was performed in which this study was enclosed within a pilot trial of a coronary ischemic post-conditioning procedure at the time of primary percutaneous coronary intervention for STEMI.	Knowledge of the study Perceptions of involvement in participation decisions Satisfaction with the consent process Views on research enrollment in AMI Views of the consent form	Only (55%) of the participants initially remembered being asked to participate in a trial. Understanding of study details was limited. Patients generally felt they were able to make a decision at presentation and wanted to be the primary decision maker. Only 4 out of 20 patients reported reading the consent form. Some mentioned that they relied on the oral information given.	Patients participating in clinical trials for acute STEMI have limited recall and understanding. However, they do desire involvement in decisions

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Chapter 3 ***P*atients *A*cceptance and *C*omprehension to Written and *V*erbal *C*onsent (PAC-VC)**

Abstract:

Background:

Acute myocardial infarction (AMI) randomized clinical trials (RCT) presents a special challenge as it requires enrolment of acutely ill patients. Patients in this category are generally in a suboptimal state for providing informed consent. Patients' understanding to verbal ascents have not been previously examined nor compared to the conventional written consents in AMI research. *P*atients *A*cceptance and *C*omprehension to Written and *V*erbal *C*onsent (PAC-VC) compared patients' understanding and attitudes to verbal and written consents in AMI RCTs.

Methods:

PAC-VC recruited patients from 3 AMI RCTs using both verbal N=12 and written N=6 consents. We compared patients' understanding using two locally developed survey questionnaires. The first questionnaire used open-ended questions with multiple choice answers to perform an objective assessment. Questionnaires were administered within 72 hours from their enrollment to the original trials. Overall average scores were categorized into three groups: Adequate understanding (71-100), Partial understanding (41-70) and Inadequate understanding (0-40). The second questionnaire used a 5-point Likert scale to

measure patients understanding and attitudes to the consent process. Answers were assigned scores as follows: Correct, incorrect and “Do not know” responses were assigned a score of 100%, 0 % and 50% respectively.

Results:

Responses showed that patients with verbal ascent had an adequate understanding (scores >70%) to most components of informed consent, close to those of written consent. The degree of understanding is partial and sometimes inadequate to the components requiring abstract thinking. Most patients did not read written information entirely and believed that it is not important to make a final decision. Patients still preferred to have written information be part of the consent but not necessarily presented during the consent process. Patients felt less pressured in the verbal ascent arm than those of written consent.

Conclusion:

Patients with verbal ascent had adequate understanding to most components of informed consent and comparable to those of written consent. Adopting verbal ascents as standard should be encouraged in the acute care setting.

Introduction

The concept of informed consent has a legacy of going back to the 1767 when an English court prevented subjects from experimenting on patients without obtaining consent.[1] Since the inception of this concept, informed consent has gone through many adjustments to reach the final definition. The International council of harmonization (ICH) defines informed consent as a process by which subjects voluntarily confirm their willingness to participate in a trial after having been informed of all aspects relevant to the subjects' decision. Informed consent relies on three principles: disclosure of adequate information about the study, subjects understand the information provided, voluntariness to give consent.[8]

Randomized clinical trials (RCTs) are essential to develop new treatment strategies as well as to refine existing ones for acute and chronic medical conditions. Acute myocardial infarction (AMI) research presents special challenge. It often entitles enrollment of critically ill patients who are distressed and require urgent therapy to prevent mortality and subsequent morbidity. Evidence suggests that patients in this category are generally in a suboptimal state to understand or remember facts related to their condition and planned interventions.[10-12] It also suggests that many patients who consent to AMI trials remember the main information, however their degree of understanding and perceived comprehension was subjective and often questionable.[13] Patients in this category of AMI research found it irrational to be expected to read written material in an acute phase of a heart attack.[13] Instead, patients turn to oral information and explanations as a substitute.[11, 23, 39]

Despite the current evidence, verbal ascents has not been formally examined nor compared to the conventional written consents. Additionally, previously studies assessed patients comprehension by simply seeking their subjective opinions about their level of understanding or using the degree of information recollection. *P*atients *A*cceptance and *C*omprehension to Written and *V*erbal *C*onsent (PAC-VC) is designed to compare patients' perspectives and understanding to verbal and written consents in acute myocardial infarction trials.

Methods

Study design

PAC-VC recruited patients from AMI RCTs: Remote ischemic conditioning in ST-Elevation myocardial infarction research (REMCON-STEMI), Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI (COMPLETE) and routine aspiration ThrOmbecTomy with PCI versus PCI ALone in patients with STEMI undergoing primary PCI (TOTAL). REMCON used verbal script delivered by paramedics during enrollment to obtain a verbal ascent. Once the patients have received their treatment and stabilized, a second formal written consent is obtained by a research nurse within 72 hours. TOTAL and COMPLETE trials used the traditional written consents process. Consents readability level ranged from 10 to 13 at the Flesch-Kincaid Grade Level test.

PAC-VC consists of two parallel arms: verbal and written. Verbal arm enrolled patients from the REMCON-STEMI trial who were exposed to the verbal ascent and have not yet provided the written consent. The written arm consent arm enrolled patients from the

COMPLETE and Total trials. Patient from all studies were approached within 72 hours from their enrollment once deemed medically stable, and the assessment of their comprehension was done by administering a survey questionnaire. Figure.1

Inclusion criteria

All patients consented to REM-CON, COMPLETE and/or TOTAL trials were eligible if they do not meet the exclusion criteria of PAC-VC. Exclusion Criteria included any of the following: Unconscious patients, hemodynamic instability, dementia, mental illness and patients who gave consent through a proxy or a substitute decision maker

Tools of assessment

PAC-VC used two sets of survey questionnaires to assess qualitative and quantitative responses of the subjects. The first set used open-ended questions with multiple choice answers. The questions tested patients' understanding of the core components of informed consent. This part was designed to objectively test patients' understanding. The second part used a Likert scale to measure the perceived patients' understanding about the trials in addition to the assessment of patients' attitudes and perspectives towards the consent process. Both parts of the questionnaire were reviewed by an external expert.

Scoring

Patients' responses for the objective assessment (Part 1) were assigned scores according to the answers. Correct answers were granted a complete score of 100%. Incorrect answers were scored 0%. "Do not know "responses were considered as partial knowledge given the insight to lack of knowledge and granted a score of 50%. Average scores were calculated for the consent components assessed through the questionnaire. Overall scores were categorized into Adequate understanding (71-100%), Partial understanding (41-70%) and

Inadequate understanding (0-40%). These cutoffs scores were chosen arbitrary as there was no previous consensus to the definition of adequacy of understanding.

Statistics: SPSS was used for descriptive analysis. Nonparametric tests were used used to assess for statistically significant differences among the two groups. Results are reported in actual numbers of patients and their percentages in addition to overall response mean scores.

Results

Patient characteristics

PAC-VC enrolled 18 AMI RCTs participants divided into two arms according to the initial informed consent used: 12 participants in the verbal ascent arm and 6 participants in the written consent arm. Males were 83.3% of the total participants. Median age is 54. English was the first language for 72.2% of participants. Fifty percent had college education. Previous history of MI was observed in only one patient. Previous enrollment into research was reported by 4 (24%) patients. Previous Ambulance transport and hospital admissions were reported by 52.9% and 70.6% of participants respectively. Attention, stress, pain and anxiety rated by the participants on a scale from 1-10 during the consent process is shown in Table 1.

Patients' degree of understanding and comprehension

Participants from both arms had adequate comprehension to the purpose of consent with scores 91.7% vs 100% in the verbal and written consent groups respectively, however they had a partial understanding to the details when asked about the purpose of the study with

average scores 41.67% and 66.7% in verbal and written consents respectively. This was consistent with the overall feeling of patients in both groups as was demonstrated by the responses in the second questionnaire Table 2.

The concept of randomization was challenging to participants in both groups where they showed inadequate to partial comprehension with an average score of 37.5% and 50% in the verbal and written consents respectively. The difference in scores did not reach statistical significance. Participants' comprehension to the risks was adequate in the verbal group while inadequate in the written group 70.8% vs 33.3%. On the other hand, both groups showed adequate comprehension to the benefits with average scores 70% and 100% in the verbal and written consent arms respectively.

Study participants showed adequate comprehension to the concept of autonomy and treatment alternatives in both arms with an average score of 83.3% vs 91.7% and 75% vs 83.3 %in the verbal and written groups respectively.

Participants in both groups equally showed an adequate comprehension to confidentiality with an average score of 83.3% in both groups.

Patients perspectives and attitudes

Only 33.3% of patients read the written information. Most patients, 75% of the verbal arm and 100% of the written arm do not think written information is very important in making the final decision to whether chose to participate or not. However, participants from the verbal ascent (75%) still wanted to have written information to be part of the consent process and only 25% of verbal and 16.7% of written arms wanted the written information

to be presented during the consent process. Majority of patients of the written consent 83.3% vs only 50% of the verbal ascent felt pressured during the consent process Table 3.

Post-verbal/Post-written consent interviews:

REMCON-STEMI patients in the verbal arm were asked to take part of the questionnaire for a second time once completed formal written consent. Among 12 patients, only 2 agreed to answer the questionnaire for the 2nd time. Overall responses showed knowledge improvement in some areas (Figure 3.2). Interestingly, patients' attitudes and opinions did not change after exposure to the written consent.

Discussion

The role of AMI clinical trials in developing new strategies and refining treatment guidelines of disease management is important. However, the emergency nature of the AMI as a disease poses extra challenges to obtain an ideal informed consent.

To our knowledge, PAC-VC is the first study to utilize a questionnaire that objectively compares patients' perspectives and comprehension of verbal ascent to written consent. Our results show that patients understanding to verbal ascent is comparable to written consents with an adequate understanding to the core components of the consent. These include the purpose of consent, autonomy, benefits, alternative treatments, choice to refuse participation and confidentiality. However, when attention to details was required, participants showed partial to inadequate understanding to other components like the concept of randomization, blindness, alternative treatments and side effects. These results confirm previous findings shown in the literature suggesting that patients who consent to clinical trials remember the main information about studies, however it is often sub-optimal

to the details.[11, 21-23, 40-42] This was clearly illustrated in our cohort when participants performed poorly in understanding alternative treatments, randomization and side effects. Abstract thinking required to interpret these components may not be possible and difficult to process by severely sick patients in an acute phase of a disease. Despite that it has also been previously suggested that poor understanding and recall to side effects may be influenced by patients inability to accept potentially unpleasant realities.[43] Interestingly, patients in the verbal arm of our cohort showed an adequate understanding to the side effects. This may suggest the fact that verbal information is easier to assimilate and often emphasize important components of informed consent.

Patients' attitudes to the consent process are consistent with the current literature. Most patients in our cohort did not read written information neither thought it was very important in making their final decision in regards to participation. Patients did endorse the importance of having written information available, yet not necessarily be presented during the acute phase of consent process. These findings are consistent with the literature as patients do not read the written material provided to them prior to making decisions.[11, 22, 39, 41, 42, 44] Instead, patients prefer a summary of verbal information and turn to oral explanations as a substitute.

Delay in treatment of AMI increases the rate of adverse outcomes and risk of death.[33, 45-47] Hence, consent for participation in AMI trials is needed urgently. This fact might coerce patients to consent. Majority of patients in the written consent arm 83.3% felt pressured during the consent process. It has been shown in the literature that participants

felt pressured at the time of consent process and rushed into making a prompt decision, which put the participants under stress. [22, 44] These findings were less observed in the verbal ascent arm (50% of participants). This can be interpreted as reading needs more time and special attention to analyze the facts enlisted in a written format, on the other hand, patients may find oral information and explanations as an easier substitute to process the data and make a quicker decision without feeling pressured.

Strengths and limitations:

This study to our knowledge is the first to assess patients understanding to verbal ascents and compare it to written consents in AMI research. PAC-VC used a multiple-choice answers type questionnaire to assess objectively patients understanding in contrast to other previous studies using self-reporting to measure understanding. The definition of adequate understanding is controversial. Unfortunately, there are no standardized testing to quantify comprehension or define how much understanding is enough. Since the lack of a grading system, we opted to construct our own to simplify the interpretations of the results. One which can create controversy in defining what is acceptable comprehension and what is not. Definitions of adequate and poor are subjective and one can argue that optimal understanding would require a different set of criteria. Study participants were recruited from different AMI trials addressing multiple research questions and differ in complexity and study protocols. This may reflect on patients understanding variably and on the study's results. Although COMPLETE trial recruited patients with AMI, patients were in a stable condition in contrary to the acute patients recruited to REMCON and TOTAL. Finally, the

numbers of study participants are relatively low and may need a larger population to generalize results.

Conclusion

PAC-VC is a prospective study assessing patients' comprehension to verbal and written consent in AMI research. The study shows that patients with verbal ascensent had an adequate understanding to most components of informed consent comparable to those of written consent. Most patients do not read written information and feel that it is not important in making a final decision. Patients would still prefer written information to be part of the consent process yet not necessarily be presented when obtaining consent process. Patients felt less pressured in the verbal arm than those of written consent. These finding are consistent with previous literature. These findings promote for further utilization of verbal ascents in AMI research as an alternative to the traditional written consents.

Tables:

Table 3-1 Baseline characteristics (consent type)

	Verbal	Written	Total
N (%)	12(66.7)	6(33.3)	18
Males	11 (91.7)	4(66.7)	15(83.3)
Age	60.83 (Median 57.5)	48.83 (Median 51.5)	56.83(M=54)
1st language is English	7(58.3)	6(100)	13(72.2)
College education	6(50)	3(50)	9(50)
PREVIOUS HISTORY			
MI	1(9)	0	1(6)
Research	3(27.3)	1(16.7)	4(24)
Hosp. Admission	9(81.8)	3(50)	12(70.6)
Ambulance transport	6(54.5)	3(50)	9(52.9)
PHYSCAL SYMPTOMS (Mean out of 10)			
Attention	5.73	6.17	5.88
Stress	7.18	6.67	7
Pain	5.27	5	5.18
Anxiety	6.91	6.83	6.88

Table 3-2 Objective questionnaire scores described in means out of 100

Consent component	Consent type	
	Verbal Ascent	Written Consent
Purpose of consent	91.67	100.00
Purpose of study	41.67	66.67
Duration of study	45.83	25.00
Nature of study intervention	50.00	66.67
Number of study groups	50.00	75.00
Understanding of alternative treatments	33.33	33.33
Randomization	37.50	50.00
Blindness	25.00	25.00
Side effects	70.83	33.33
Contacts in case of side effects	62.50	25.00
Compensation in case of harm	58.33	75.00
Voluntariness of withdraw	83.33	91.67
Treatment options if refused to participate	75.00	83.33
Benefits of participation	70.00	100.00
Financial benefits of participation	83.33	91.67
Confidentiality	83.33	83.33
Whom to contact for any complaints	83.33	75.00
Total Score	61.47	64.71

Table 3-3 Subjective questionnaire and patients perspectives

		Consent type	
		Verbal Ascent	Written consent
		N %	N %
I would prefer only verbal information presented during the consent process	Agree	2(16.7%)	2(33.3%)
	Cannot decide	1(8.3%)	2(33.3%)
	Disagree	9(75.0%)	2(33.3%)
I would prefer written information presented during the consent process	Agree	3(25.0%)	1(16.7%)
	Cannot decide	3(25.0%)	3(50.0%)
	Disagree	6(50.0%)	2(33.3%)
I read the written information about the research study before making my decision	Agree	2(16.7%)	2(33.3%)
	Cannot decide	2(16.7%)	0(0.0%)
	Disagree	8(66.7%)	4(66.7%)
I believe written information is very important in making my final decision to participate	Agree	2(16.7%)	0(0.0%)
	Cannot decide	1(8.3%)	0(0.0%)
	Disagree	9(75.0%)	6(100.0%)
I feel satisfied and comfortable with the consent process	Agree	0(0.0%)	0(0.0%)
	Cannot decide	3(25.0%)	0(0.0%)
	Disagree	9(75.0%)	6(100.0%)
I felt pressured by time when I made my decision during the consent process	Agree	6(50.0%)	5(83.3%)
	Cannot decide	3(25.0%)	1(16.7%)
	Disagree	3(25.0%)	0(0.0%)

Table 3-4 Subjective questionnaire and patients subjective understanding

		Consent type			
		Verbal Ascent		Written Consent	
		Count	Column N %	Count	Column N %
You understand the purpose of study	Agree	1	8.3%	0	0.0%
	Cannot decide	2	16.7%	0	0.0%
	Disagree	9	75.0%	6	100.0%
You know how long you will be enrolled in this study.	Agree	3	25.0%	3	50.0%
	Cannot decide	4	33.3%	0	0.0%
	Disagree	5	41.7%	3	50.0%
You understand what will be done in this study and what you are being asked to do	Agree	1	8.3%	1	20.0%
	Cannot decide	3	25.0%	0	0.0%
	Disagree	8	66.7%	4	80.0%
You recognise the experimental part that may be used in your treatment. (Study intervention)	Agree	1	8.3%	0	0.0%
	Cannot decide	2	16.7%	0	0.0%
	Disagree	9	75.0%	6	100.0%
You recognize the possible risks or discomforts that may result due to participation in this study	Agree	0	0.0%	0	0.0%
	Cannot decide	2	16.7%	1	16.7%
	Disagree	10	83.3%	5	83.3%
You recognize the possible benefits you may gain from participation	Agree	0	0.0%	0	0.0%
	Cannot decide	2	16.7%	0	0.0%
	Disagree	10	83.3%	6	100.0%
You recognize the possible benefits that may help future patients.	Agree	0	0.0%	0	0.0%
	Cannot decide	0	0.0%	0	0.0%
	Disagree	12	100.0%	6	100.0%
	Agree	2	16.7%	1	16.7%

You know alternative options/treatments you may have if you had chosen to ***NOT*** participate.	Cannot decide	1	8.3%	1	16.7%
	Disagree	9	75.0%	4	66.7%
You understand that your information is being kept confidential and disclosed only to authorized personnel	Agree	0	0.0%	0	0.0%
	Cannot decide	0	0.0%	0	0.0%
	Disagree	12	100.0%	6	100.0%
You know whom you should contact in case of side effects or injuries that may result due to participation in the study	Agree	1	8.3%	2	33.3%
	Cannot decide	2	16.7%	0	0.0%
	Disagree	9	75.0%	4	66.7%
You know what compensation or treatment is available for you in case of side effects or injury	Agree	3	25.0%	3	50.0%
	Cannot decide	3	25.0%	0	0.0%
	Disagree	6	50.0%	3	50.0%
You understand that your participation is completely voluntary and it is not going to affect your treatment if you choose to withdraw	Agree	0	0.0%	0	0.0%
	Cannot decide	0	0.0%	0	0.0%
	Disagree	12	100.0%	6	100.0%
You understand that you can withdraw from this study at any time you wish to do so	Agree	0	0.0%	0	0.0%
	Cannot decide	0	0.0%	0	0.0%
	Disagree	12	100.0%	6	100.0%
You know whom you should contact in case you have questions, comments, concerns or complaints about the study	Agree	2	16.7%	2	33.3%
	Cannot decide	2	16.7%	0	0.0%
	Disagree	8	66.7%	4	66.7%

Figure 3.1 Total score of patients' understanding to the components of consent

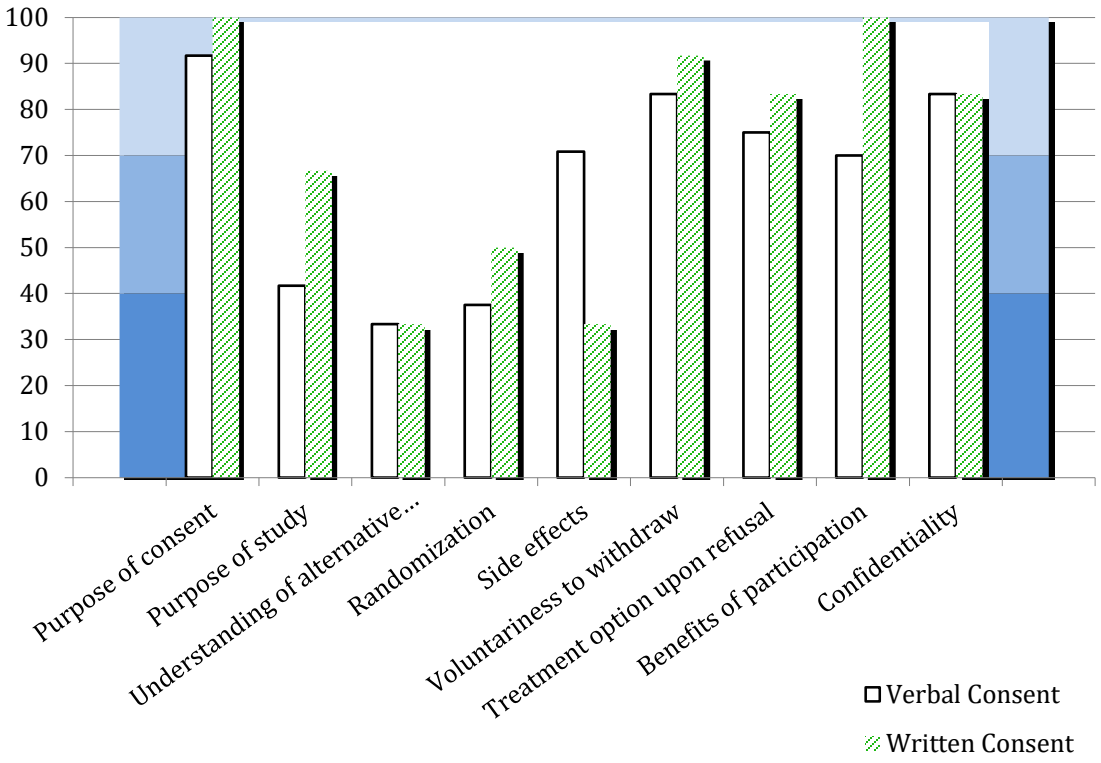


Figure 3.2 Post-verbal/Post-written consent interviews responses

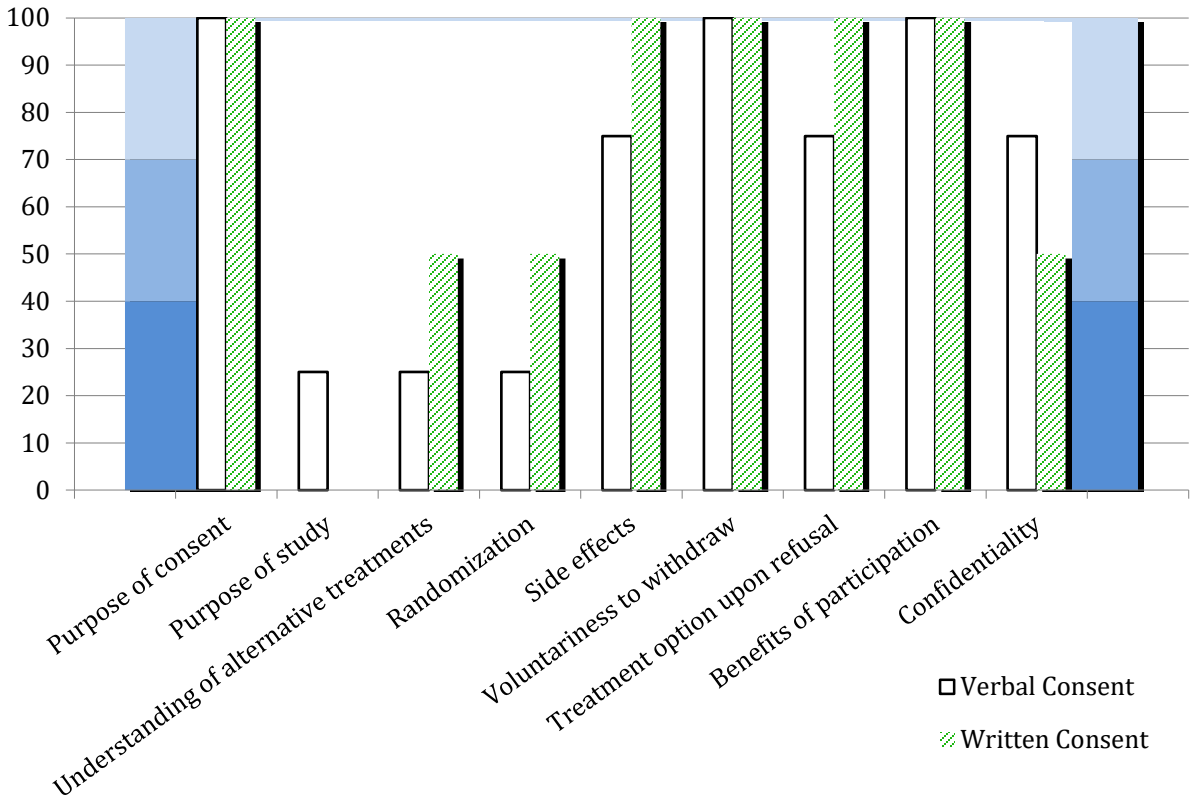
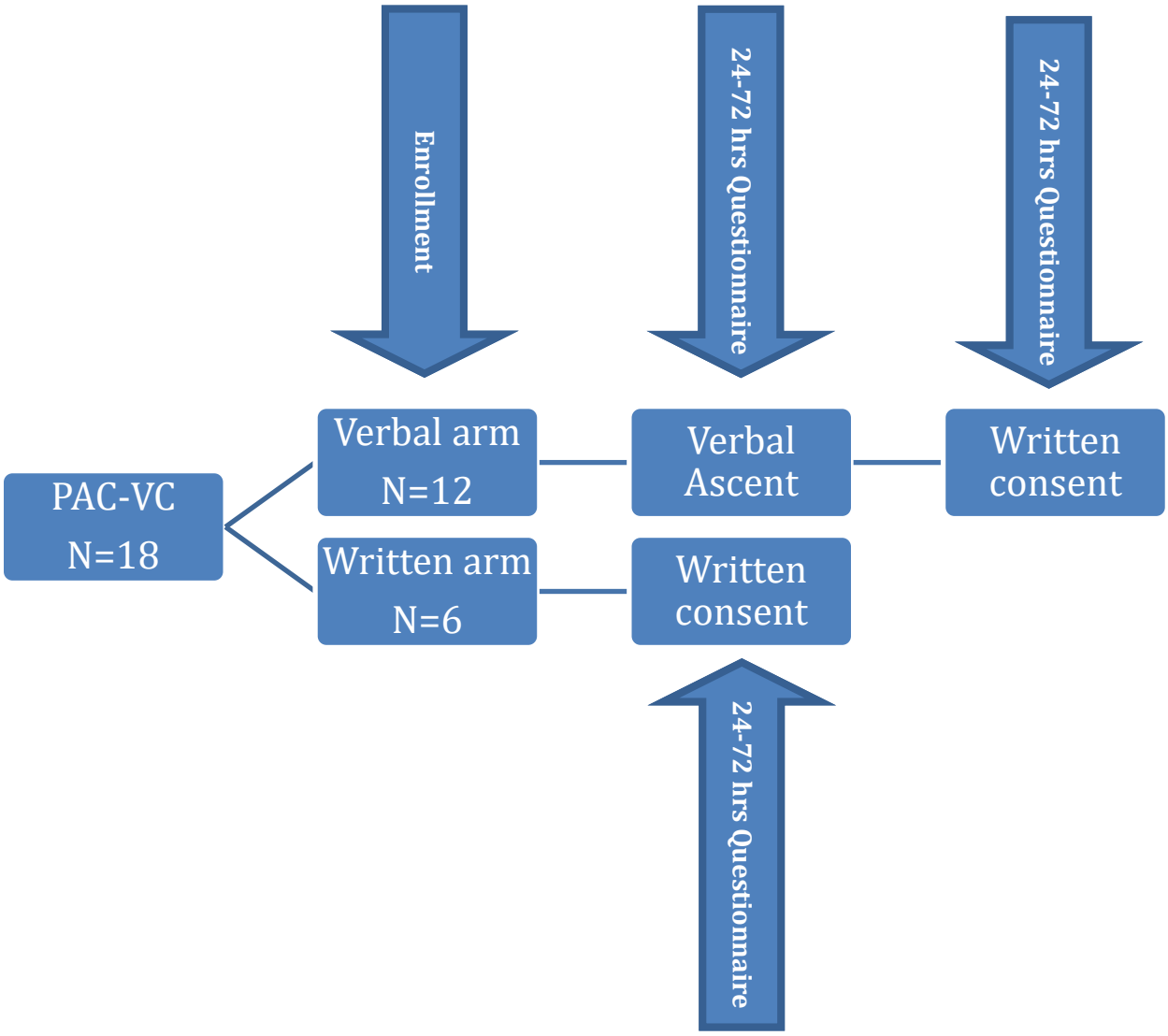


Figure 3.3 PAC-VC methods flow chart



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Chapter 4 **Discussion and Summary**

The issues and concerns related to patients' comprehension to informed consent in the setting of acute myocardial infarction research were explored. Initially, we briefly outlined the history of informed consent and the stages it has gone through since the inception of the informed consent until its current definition by the ICH.

In the second chapter, a literature review regarding the evidence evaluating patients' comprehension and understanding to informed consent in acute myocardial research was conducted. A total of 8 studies published from 2000 to 2015 were included in the review. They addressed different aspects of informed consent in acute myocardial infarction (AMI) research. Results were mainly grouped into four domains: information understanding and recall, attitudes towards the consent process, use of written information and patients' coercion by time and the nature of the disease during consent process.

Results suggest that most patients who consent to clinical trials remember the main information about the trials, however their degree of understanding and perceived comprehension varied among studies. It was subjective and often sub-optimal to the details. This variation in patients understanding could be explained by the impaired cognition on the patient's side, poor method of information delivery or both [9].

Patients sometimes performed better in remembering benefits vs recalling risks [9, 24]. Majority of patients preferred a summary of verbal information and did not read written material. Many of them found it irrational to expect patients to read written material in an acute phase of a heart attack. Instead, patients turn to verbal information as a substitute, an observation that offers a potential opportunity of improvement in the process of informed consent. The opportunity that highlights the importance of wisely choosing the information being presented and the role of verbal discussions during the consent process. A note that

was reported by Williams et al [11], when mentioned that to understand the information sheet, a higher educational level was needed than most of what patients had achieved.

The attitudes toward consent process varied among patients and positively corresponded to self-assessed competence. Patients who thought they were competent felt it is acceptable to be approached as long they maintain the right to decline participation. These attitudes were less frequently observed in patients who refused to participate.

Since delay in treatment of AMI increases the rate of adverse outcomes and risk of death, [33] consent for participation in AMI trials is needed urgently. This fact might coerce patients to consent. Many patients reported feeling pressured by time. This was reported more by patients who declined participation. Patients felt rushed into making decisions and their main concern at the time of consent was relieving symptoms and receiving treatment. Results suggest that most patients who consent to clinical trials remember the main information about the study, however their degree of understanding and perceived comprehension was subjective and often questionable. Majority of patients preferred a summary of verbal information and did not read the written material provided to them prior to making decisions. Many of them found it irrational to expect patients to read written material in an acute phase of a heart attack. Instead, patients turn to oral information and explanations as a substitute. Opinions about consent process varied among patients and attitudes mainly corresponded to their self-assessed competence. Those who thought they were competent felt it is acceptable to be approached as long as they have the right to refuse.

We also identified several knowledge gaps that can be addressed in future work. We outlined that the efficiency of the informed consent in AMI trials has been previously

examined, however results were often subjective and most of the time used patients' self-assessments. The utility of using verbal ascents has never been assessed previously. Furthermore, despite the repeated assessments of patients' comprehension, there are no standardized testing to quantify and define how much understanding is enough to consider the consent is meeting its minimal requirements. This was another area that needed to be addressed, perhaps by developing standardized testing tools that would objectively assess patients' comprehension and quantify their understanding. Variables associated with AMI like pain, anxiety and analgesics use in addition to other patients' demographics should also be further studied in larger populations to identify predictors of adequate understanding and validate previously reported results.

In the second part of this thesis, we conducted a study that evaluated patients' acceptance and comprehension to verbal and written consent. Despite the current evidence, verbal ascent has not been formally examined nor compared to the conventional written consent. Moreover, studies assessed level of comprehension by simply seeking patients' subjective opinions about their level of understanding or by measuring the degree of information recollection. We used an assessment tool that consisted of two sets of questionnaires seeking both the objective and self-assessed understanding of patients. Patients Acceptance and Comprehension to Written and Verbal Consent (PAC-VC) was designed to compare patients' perspectives and understanding to verbal and written consents in acute myocardial infarction trials.

Responses show that patients with verbal ascent had an adequate understanding to most components of informed consent and comparable to those of written consent. The degree

of understanding is partial and sometimes inadequate to elements requiring abstract thinking. Most patients do not read written information and believe that it is not important to make a final decision. Patients would still prefer to have written information be part of the consent but not necessarily be presented during the consent process. Patients felt less pressured in the verbal ascent arm than those of written consent.

Conclusion

Informed consent in the setting of AMI research is challenging. Limited data is available in the literature addressing this issue with multiple remaining gaps. Obtaining consent through traditional methods is not optimal and perhaps finding alternative approaches is warranted. To improve the quality of consent, focus should be more on methods of information delivery, providing more time to patients to discuss the information presented, as this appears to have an effect on patients' recollection. Information provided should be chosen wisely and to focus on the contents rather than quantity. PAC-VC showed that patients with verbal ascent had an adequate understanding to most components of informed consent comparable to those of written consent. Most patients do not read the written information and feel that it is not important in making a final decision. Patients would still prefer written information be part of the consent but not necessarily be presented during the consent process. Patients felt less pressured in the verbal ascent arm than those of written consent. These finding are consistent with previous literature. These findings promote for further utilization of verbal ascents in AMI research as an alternative to the traditional written consents.

Future work:

Our work has identified several areas that need to be addressed. Developing a standardized assessment tool with predefined criteria that recognizes adequate and acceptable understanding that guarantees patients autonomy and meets the basic principles of informed consent. Modifiable factors like pain, anxiety, sedatives, time of interview, experience of research personnel should be further assessed to identify their effect on patient understanding and how they can be used to improve consent process.

Verbal ascent as a tool for information delivery is a promising mode and should be assessed in larger studies.

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