TITLE: The Platelet Aggregation After tiCagrelor Inhibition and FentanYl Trial (PACIFY)

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JHM IRB - eForm A – Protocol

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1. Abstract

With potent analgesic properties, perceived hemodynamic benefits and limited alternatives, opiates are the analgesic mainstay for acute coronary syndrome (ACS) patients reporting peri-procedural pain or nitrate-resistant chest pain. However, large observational studies suggest that opiate administration during ACS may result in adverse cardiovascular outcomes. Complimenting this, a number of recent mechanistic studies have demonstrated delayed and attenuated effects of oral dual anti-platelet therapy (DAPT) on platelet inhibition endpoints among subjects receiving intravenous morphine. These studies support the hypothesis that morphine delays the gastrointestinal absorption of DAPT medications. However, no data exist on the impact of intravenous fentanyl, a systemic opioid analgesic routinely administered during percutaneous coronary intervention (PCI) procedures, on the platelet inhibition effects of DAPT. We hypothesize that, similar to morphine, fentanyl administered at the time of PCI will reduce and delay the effect of DAPT on platelet function. As such, the primary aim of this study is to test the impact of intravenous fentanyl on residual platelet reactivity by randomizing patients undergoing PCI to a strategy of peri-procedural benzodiazepine plus non-systemic local analgesia or to the current standard of benzodiazepine plus intravenous fentanyl. Our study will address a major gap in knowledge. PCI analgesia with fentanyl is often administered concurrently with loading doses of DAPT, particularly in ACS. Given the critical need for rapid and robust inhibition of platelet function during PCI, our research study has true potential to change clinical practice, particularly if we demonstrate reduced DAPT absorption and elevated residual platelet reactivity among patients receiving fentanyl during PCI. As such, this research could result in a paradigm shift in the analgesia management of PCI and have a profound impact on optimization of post-PCI cardiac outcomes.

2. Objectives

Primary Objective: We will test the hypothesis that randomization to fentanyl will be associated with higher residual platelet reactivity, as determined by mean P2Y12 reactivity units (PRUs) at 2 hours, among persons undergoing PCI with IV fentanyl analgesia (as well as aspirin and ticagrelor), compared to subjects randomized to undergo PCI with non-systemic analgesia.
Secondary Objective: To test the hypothesis that fentanyl administered during PCI will adversely impact the pharmacokinetics of ticagrelor, as determined by the area under the curve of active metabolite measured using liquid chromatography tandem mass spectrometry.
Secondary Objective: To test for differences in patient reported pain scores and biomarkers of myocardial injury, comparing PCI patients randomized to peri-procedural benzodiazepine plus non-systemic local analgesia or to the current standard of benzodiazepine plus intravenous fentanyl.

3. Background

Morphine has long played a central role in the management of ACS [1-4]. However, a 2005 observational study suggested that patients receiving morphine for pain relief in ACS had worse outcomes [5]. In this context, recent research demonstrates that intravenous morphine delays and inhibits the absorption of oral DAPT with resultant delay in the time to maximal platelet inhibition [6-9]. Hobl *et al.* administered a loading dose of 600mg clopidogrel together with either placebo or 5mg morphine intravenously in a randomized, double-blind, cross-over mechanistic trial [6]. Morphine injection delayed clopidogrel absorption (T_{max}: 105 vs. 83 min, p = 0.025) and reduced the total exposure to its active metabolite by 34% (p = 0.001, **figure 1**). Morphine also resulted in higher residual platelet aggregation and delayed maximal inhibition of platelets by 2 hours (n = 24; p<0.001) [6]. Similar results have recently been reported for subjects receiving ticagrelor. [9, 10] Morphine's association with emesis, inhibition of gastric emptying and reduced GI motility is hypothesised as the cause.

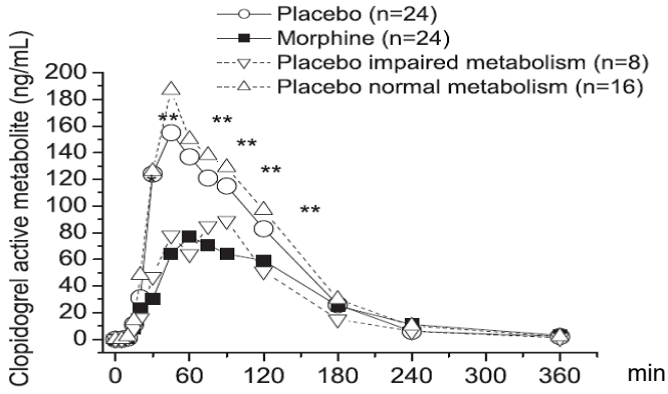


Figure 1- Morphine Lowers Plasma Concentrations of Clopidogrel Active Metabolite. **p≤0.01 JACC 2014;63:630–5

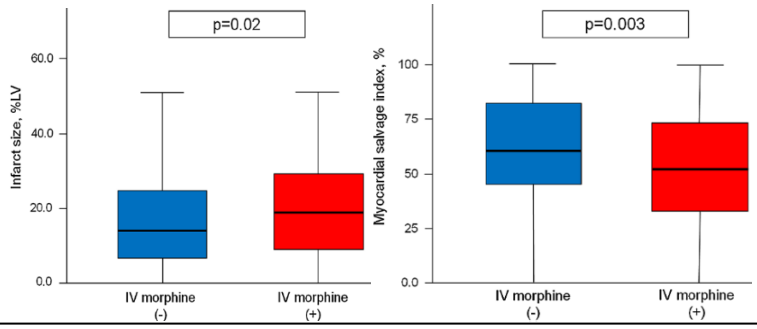


Figure 2- Morphine adversely impacts post PCI infarct size & myocardial salvage index by MRI. Clin Res Card 2015;104:727–34

Delayed and reduced absorption of DAPT in ACS patients is likely to translate into worse cardiovascular outcomes because maximal inhibition of platelet function is necessary to treat intracoronary atherosclerotic plaque rupture and thrombosis, as well as to minimize the risk of in-stent thrombosis among patients who receive coronary stents at the time of PCI. In keeping with this, morphine has also recently been associated with suboptimal reperfusion after PCI in patients with ACS (**figure 2**). [11] As a consequence, 2015 European guidelines now state, "*in ACS patients whose ischemic symptoms are not relieved by nitrates and beta-blockers, opiate administration is reasonable…, with the caveat that morphine may slow intestinal absorption of oral platelet inhibitors.*"[4]

However, no data exist as to the impact of **fentanyl**, another IV opiate, on DAPT absorption and platelet inhibition. This represents a major gap in current knowledge. Indeed, fentanyl is used for analgesia in the vast majority of PCI procedures in Europe and the US, often being administered concurrently with loading doses of DAPT. It is known that fentanyl has similar effects to morphine on GI motility [12] and that the typical fentanyl PCI dose, 25-50mcg, is equipotent with the morphine dose used by Hobl and Kubica in two recent trials (5mg). [6, 9] Given the critical need for rapid and robust inhibition of platelet function among patients receiving intracoronary stents during PCI, this research proposal has true potential to change clinical practice, particularly if our results confirm reduced DAPT absorption and elevated residual platelet reactivity among patients receiving fentanyl during PCI. As such, this research could result in a paradigm shift in the analgesia management of PCI and have a profound impact on optimization of post-PCI clinical outcomes.

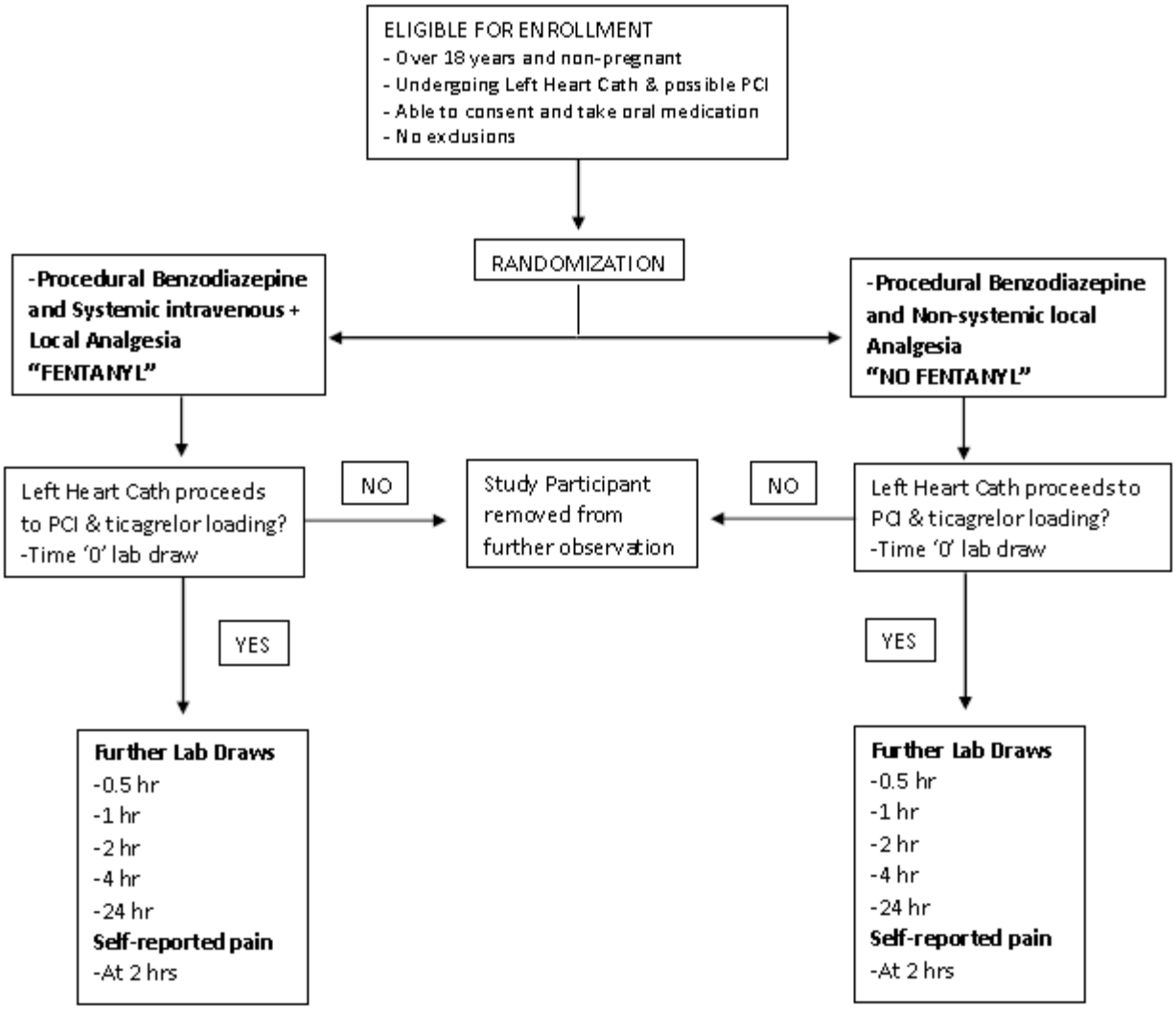
4. Study Procedures

a. Study design, including the sequence and timing of study procedures

This is an open-label randomized controlled trial. We will accrue 70 patients undergoing loading of oral DAPT (aspirin and ticagrelor 180mg [the latter only being administered if a stent procedure is necessary]) as part of routine clinical care. This may require that up to 300 patients will need to be approached for consent. The reason for this is that only about 1 in 4 patients who undergo left heart catheterization actually need DAPT loading for stent placement (many do not need stents) and it is impossible to know who these patients will be before the catheterization procedure is performed.

Consenting patients will be randomized, 1:1, to peri-procedural intravenous benzodiazepine plus non-systemic local analgesia or to the current standard of peri-procedural intravenous benzodiazepine plus intravenous fentanyl plus local analgesia (**figure**).

Peri-procedural analgesia is part of routine clinical care, thus, the primary research procedure in this study is the randomization to the type of analgesia (fentanyl vs. no fentanyl).



Subsequent to randomization, clinical care will then proceed as per normal practice (e.g. patients requiring coronary stenting will undergo the procedure at the discretion of the interventional cardiologist). However, because ticagrelor is a newer DAPT option and is less commonly given at our hospital than clopidogrel, we will require that patients enrolled into our study not be switched from ticagrelor to clopidogrel within the first 12 hours of the initial ticagrelor load in the catheterization lab (this is due to theoretical concerns that clopidogrel loading is less effective

within the first 12 hours of ticagrelor loading due to competition for platelet receptors). As such, we require all patients enrolled into the study to be admitted for observation for 12-24 hours after enrolment. Ticagrelor was chosen for this study as it is a potent and fast-acting agent, has been demonstrated to be superior to clopidogrel, and will allow us to answer the main research question as to whether, or not, fentanyl delays the GI absorption of oral anti-platelet agents.

In order to address our research objectives, enrolled patients will need to undergo sampling of blood after randomization (**figure**). While such blood sampling is typical in routine clinical care, we will also be obtaining blood for the sole purposes of research. Blood will be sampled at 0, 0.5, 1, 2, 4, and 24 hours after randomization. Where possible, blood will be drawn from existing IV access. For research purposes, we will also obtain patient-reported procedural pain data using the visual analog scale and the numeric rating scale at 2 hours (NRS). [13]

b. Study duration and number of study visits required of research participants.

The duration of the study will be over 24 hours. The only study visit required is the admission during which the PCI is being performed as part of routine clinical care. Of note, patients undergoing PCI are routinely kept in the hospital for a minimal of 24 hours.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Patients will not be blinded to the analgesia strategy (benzodiazepine sedation and local vs systemic analgesia) as the coronary angiogram is being performed as part of routine clinical care and it will not be possible to blind medical providers to the medications administered during the procedure. However, the collaborators who perform the analyses of blood samples will be blinded to the randomized allocation in order to minimize ascertainment bias.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

All subjects enrolled will receive standard clinical care. The only change from standard practice is the 50% chance of being randomized to peri-procedural intravenous benzodiazepine plus non-systemic local analgesia. This will consist of benzodiazepine and local anaesthetic (e.g. subcutaneous lidocaine), as described below. We believe this is ethically justifiable for the following reasons; 1) the procedural pain is typically minimal, with the vast majority of patients undergoing radial approach to left heart cath; 2) benzodiazepine and local anesthetic are well known to provide effective comfort for patients who can't receive opiates (e.g. due to allergy); 3) those patients who complain of breakthrough pain in the non-systemic analgesia arm **are allowed receive bail-out IV opiates** in our research protocol; and 4) our hypothesis is that IV opiates may themselves be causing **indirect harm** in the setting of PCI by attenuating the effects of DAPT. Indeed- in the context of research demonstrating that morphine reduces and delays the effect of DAPT on platelet inhibition- our primary hypothesis is that the impact of intravenous fentanyl on platelet inhibition outcomes will be similar. However, because no studies have evaluated this question, there is a state of clinical equipoise. The only way to answer this pressing clinical question is to randomize patients to non-systemic analgesia, while ensuring patient discomfort is no different, and to compare platelet function results in these patients to a similar group of patients who are randomized to the current standard of peri-procedural intravenous benzodiazepine plus intravenous fentanyl.

e. Justification for inclusion of a placebo or non-treatment group.

There is no placebo or non-treatment group in this randomized trial.

f. Definition of treatment failure or participant removal criteria.

Treatment failure will be defined as subject-report of uncontrolled pain or discomfort during the PCI procedure. As part of routine care patients are regularly asked to report any pain during the procedure. In all instances, and most notably in the group randomized to initial intravenous benzodiazepine plus non-systemic analgesia, post randomization analgesia will be managed as per usual by the procedural team. Specifically, the study protocol only provides initial guidance on analgesia, based on the randomized allocation. Once the initial analgesia has been provided, should patients subsequently report uncontrolled pain or discomfort, the treating team can administer any analgesia that they feel is clinically indicated, including intravenous fentanyl in either arm of the study. There are no protocol-based removal criteria. However, participants can remove themselves at any time from the study as participation is voluntary.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

When the study ends or should participation end prematurely, all subjects enrolled will undergo routine treatment as per usual best practice. Participants will be analyzed on an intention to treat basis. Therefore, participants will be analyzed based on their initial randomized analgesia allocation and whether or not their participation in the study ended prematurely.

5. Inclusion/Exclusion Criteria

Key inclusion criteria are: undergoing clinically indicated PCI; >18 years of age; able for PO medications and to provide informed consent. Key exclusion criteria: pregnant; any **DAPT(clopidogrel, prasugrel, ticagrelor) within 14 days of enrollment;** known coagulation disorders; active treatment with oral anticoagulant or low molecular weight heparin; impaired renal or hepatic function; platelets < 100 x10 ^{3} /mcl; planned use of GP2b3a for PCI; Prior TAVR or planned TAVR post PCI; and contraindications to ticagrelor or opiates.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Subjects randomized to the current standard of peri-procedural intravenous benzodiazepine plus intravenous fentanyl will receive an initial dose of 1 mg of midazolam and 25-50 mcg of fentanyl. Subsequent doses of either medicine can be provided as necessary. The rationale for this dosing schedule is that it is the standard of care. Furthermore, 25-50mcg of fentanyl is equipotent with the morphine dose used by Hobl and Kubica in two recent trials (5mg). [6, 9] Subjects randomized to the research strategy of peri-procedural intravenous benzodiazepine plus non-systemic analgesia will receive an initial dose of 1 mg of midazolam (with titrations allowed as necessary) and local anaesthetic (e.g. subcutaneous lidocaine). The rationale for this strategy is to maintain comfort during the case without exposing the subjects to opiates.

b. *Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.*
N/A

c. *Justification and safety information if non-FDA approved drugs without an IND will be administered.*
N/A

7. Study Statistics

a. Primary outcome variable.

In both randomized groups P2Y12 reactivity units (PRUs), measured using VerifyNow, will be determined at 0, 0.5, 1, 2, 4, and 24 hours. The primary outcome will be mean PRU at 2 hours.

b. Secondary outcome variables.

Additional secondary platelet outcomes will include light transmission aggregometry (LTA) at 2 hours, and also time-averaged PRU using mixed effects models. Given we hypothesize fentanyl may impair platelet inhibition due to reduced gastrointestinal absorption of ticagrelor, we will also compare ticagrelor pharmacokinetics in both arms, as determined by the area under the curve of active metabolite by liquid chromatography mass spectrometry (at 0, 0.5, 1, 2, 4 and 24 hours). We will also determine the impact of fentanyl on myocardial injury, as measured by high-sensitivity Troponin-I in the serum. In all 300 patients consented, we will also compare patient reported pain among both groups using the visual analog scale and the numeric rating scale (NRS). (12) These simple to perform subjective assessments can measure clinically meaningful differences in pain (e.g. a difference of 30% on the NRS). (12)

	YES	NO	Collection Date and TIME
Pre Procedure Blood – Hour 0 • Platelet Function - Verify Now	☐	☐	____/____/ _____
Intra Procedure Blood- Hour 0.5 • Pharmacokinetics • Platelet Function - Verify Now	☐	☐	____/____/ _____
Intra Procedure Blood- Hour 1 • Pharmacokinetics • Platelet Function - Verify Now	☐	☐	____/____/ _____
Post Procedure Blood – Hour 2 • Pharmacokinetics • Platelet Function - Verify Now - ADP-based LTA • High Sensitivity Troponin • Pain by Self-Report (visual scale)	☐	☐	____/____/ _____
Post Procedure Blood – Hour 4 • Pharmacokinetics • Platelet Function - Verify Now • High Sensitivity Troponin	☐	☐	____/____/ _____
Post Procedure Blood – Hour 24 • Pharmacokinetics • Platelet Function - Verify Now	☐	☐	____/____/ _____

c. Statistical plan including sample size justification and interim data analysis.

Based on prior data [14], we anticipate a 2 hour PRU of ~230 (Standard Deviation of 25) among patients receiving 180 mg ticagrelor without opiate and estimate a conservative effect size of 20% increase in 2hr PRU among those who receive fentanyl [8, 15]. These calculations yield a sample size estimate of ≤23 subjects per group (approx. 50 total) to achieve 90% power (2 sided alpha 0.05). Accounting for drop out and unanticipated increases in 2hr PRU variability, and to provide power for subgroup analyses, we will accrue 70 patients who undergo DAPT loading in total. In all analyses a value of $p < 0.05$ will be considered statistically significant.

d. Early stopping rules.

N/A

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

It is possible that the non-systemic analgesia arm could report increased peri-procedural pain, however IV opiates are permitted at any time, for any participant, based on *break-through pain reported* during the case. The other main medical risks are the bleeding and bruising from venipuncture. Where possible we will draw blood from IV access to minimize venipuncture. As our research protocol includes the administration of ticagrelor as the anti-platelet agent used for the stenting procedure, some providers may wish to transition their patients from ticagrelor to other anti-platelet agents (such as clopidogrel or prasugrel) after completion of participation in our study. This change may be motivated by clinical or patient preference reasons. However, if the provider elects to make such a change after the participant has completed the study, we will require them to not change to either clopidogrel (starting with a 600mg load) or prasugrel (starting with a 60mg load) within the first 12 hours of the initial ticagrelor load (specifically, they will need to wait until 12 hrs has passed from the last ticagrelor dose and then load with the alternative agent at the time the next dose of ticagrelor would have been due. This requirement will minimize the risk that patients who are switched from ticagrelor to an alternative anti-platelet agent will not be exposed to the potential risk of suboptimal platelet inhibition in the period around which this change is made.

b. Steps taken to minimize the risks.

As already mentioned, blood will be drawn from existing iv heparin locks when available. Furthermore, we plan to minimize difference in pain by applying effective non-systemic analgesia that will consist of a rigorous pain relief strategy of potent benzodiazepine and effective local anaesthetic (e.g. subcutaneous lidocaine). In addition, patients can request more pain relief (including opiates) after the initial randomized analgesia has been allocated and can withdraw at any time from the study.

c. Plan for reporting unanticipated problems or study deviations.

Any unanticipated problems will be reported to the IRB.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Date will be stored on a secure and encrypted P.I.'s computer.

e. Financial risks to the participants.

There are no financial risks to the participants

9. Benefits

a. Description of the probable benefits for the participant and for society.

There are no guaranteed individual benefits for the participant. However, given the critical need for rapid inhibition of platelet function during PCI, this research proposal has true potential to change clinical practice, particularly if our results confirm reduced DAPT absorption and elevated residual platelet reactivity among patients receiving IV fentanyl during PCI. As such, this research could result in a paradigm shift in the analgesia management of PCI and have a profound impact on optimization of post-PCI clinical outcomes.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Subjects will not be compensated for participation in this study.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The research performed on the blood samples will be paid for by the P.I. and not billed to the patient.

REFERENCES

1. Moore F. Intravenous morphine in coronary thrombosis. *The Lancet*. 1930:959-960
2. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG. Aha/acc guideline for the management of patients with non-st-elevation acute coronary syndromes: A report of the american college of cardiology/american heart association task force on practice guidelines. *J Am Coll Cardiol*. 2014;64:138-228
3. O'Gara PT, Kushna FG, Ascheim DD. Accf/aha guideline for the management of st-elevation myocardial infarction: Executive summary: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *Circulation*. 2013:529-555
4. Authors/Task Force M, Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 esc guidelines for the management of acute coronary syndromes in patients presenting without persistent st-segment elevation: Task force for the management of acute coronary syndromes in patients presenting without persistent st-segment elevation of the european society of cardiology (esc). *European heart journal*. 2015
5. Meine TJ, Roe MT, Chen AY. Association of intravenous morphine use and outcomes in acute coronary syndromes: Results from the crusade quality improvement initiative. *Am Heart J*. 2005:1043-1049
6. Hobl EL, Stimpfl T, Ebner J, Schoergenhofer C, Derhaschnig U, Sunder-Plassmann R, Jilma-Stohlawetz P, Mannhalter C, Posch M, Jilma B. Morphine decreases clopidogrel concentrations and effects: A randomized, double-blind, placebo-controlled trial. *Journal of the American College of Cardiology*. 2014;63:630-635
7. Hobl EL, Reiter B, Schoergenhofer C, Schwameis M, Derhaschnig U, Lang IM, Stimpfl T, Jilma B. Morphine interaction with prasugrel: A double-blind, cross-over trial in healthy volunteers. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2015
8. Parodi G, Bellandi B, Xanthopoulou I, Capranzano P, Capodanno D, Valenti R, Stavrou K, Migliorini A, Antoniucci D, Tamburino C, Alexopoulos D. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with st-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation. Cardiovascular interventions*. 2015;8
9. Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, Stankowska K, Buszko K, Navarese EP, Jilma B, Siller-Matula JM, Marszall MP, Rosc D, Kozinski M. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: The randomized, double-blind, placebo-controlled impression trial. *European heart journal*. 2015
10. Hobl EL, Reiter B, Schoergenhofer C, Schwameis M, Derhaschnig U, Kubica J, Stimpfl T, Jilma B. Morphine decreases ticagrelor concentrations but not its antiplatelet effects: A randomized trial in healthy volunteers. *European journal of clinical investigation*. 2015
11. de Waha S, Eitel I, Desch S, Fuernau G, Lurz P, Urban D, Schuler G, Thiele H. Intravenous morphine administration and reperfusion success in st-elevation myocardial infarction: Insights from cardiac magnetic resonance imaging. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2015;104:727-734
12. Wallden J, Lindberg G, Sandin M, Thorn SE, Wattwil M. Effects of fentanyl on gastric myoelectrical activity: A possible association with polymorphisms of the mu-opioid receptor gene? *Acta anaesthesiologica Scandinavica*. 2008;52:708-715
13. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual analog scale for pain (vas pain), numeric rating scale for pain (nrs pain), mcgill pain questionnaire (mpq), short-form mcgill pain questionnaire (sf-mpq), chronic pain grade scale (cpgs), short form-36 bodily pain scale (sf-36 bps), and measure of intermittent and constant osteoarthritis pain (icoap). *Arthritis care & research*. 2011;63 Suppl 11:S240-252
14. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the onset and offset of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: The onset/offset study. *Circulation*. 2009;120:2577-2585
15. Scott KM, Caldwell PH, Barnes EH, Barrett J. "Teaching by humiliation" and mistreatment of medical students in clinical rotations: A pilot study. *The Medical journal of Australia*. 2015;203:185