

Hanjo Ko

CASE

78M with history of heavy asbestos exposure who presented with new onset of dyspnea and was found to have significant right pleural thickening concerning for mesothelioma one month ago. He is scheduled for diagnostic bronchoscopy and mediastinoscopy with biopsy for cancer staging.

In the preoperative area, he complains of chest pain radiating to his jaw and left arm that started 30 min ago and has only started to subside now after he managed to get back in bed with the help of his wife.

Medications:

Metoprolol 100 mg daily
Isosorbide mononitrate 60 mg daily
Lisinopril 10 mg daily
Aspirin 81 mg daily
Atorvastatin 80 mg daily
Clopidogrel 75 mg daily (held for 7 days)
Lantus 35 units daily and aspart 5 units with meals

Allergies: NKDA

Past Medical History:

CHF—EF 55–60% with moderate MR on prior TTE obtained one year ago

CAD with MI in the past—drug-eluting stents (DES) to LCx and ramus intermedius 5 years ago, DES to OM1 and RCA with balloon angioplasty to LCx 4 years ago

DM2—poorly controlled with baseline Hgb A1c of 11.6 one month ago

Physical Exam:

Vitals: HR 94, BP 178/89, RR 24, SpO2 92% on 2L NC MP4, full range of motion, normal mouth opening, normal thyromental distance

He is in mild distress, slightly diaphoretic, but able to lie flat and finish sentences without difficulty.

Bedside EKG showed ST elevation in V1 through V4 and II, III, aVF.

1. What is myocardial infarction (MI)?

MI represents a disease process in which myocardial oxygen demand exceeds myocardial oxygen supply leading to myocardial ischemia and subsequent myocardial necrosis. MI typically occurs in patients with prior coronary artery disease (CAD) due to the formation of atherosclerotic plaques and progressive narrowing of the coronary arteries. Non-ST elevation MI (NSTEMI) represents subendocardial ischemia while ST elevation MI (STEMI) suggests a more devastating and serious myocardial insult that affects the full thickness of myocardium, spreading from endocardium to epicardium. STEMI is more typically caused by the sudden thrombotic occlusion of a coronary artery that was not previously severely stenotic, and unlike NSTEMI, it is considered a medical emergency and requires immediate intervention to restore blood flow in order to salvage the remaining myocardium. Given that the amount of myocardial injury occurs, not in a linear fashion, but rather curvilinear as time passes, a careful selection and timely implementation of a reperfusion strategy has become the hallmark treatment of STEMI where “time is muscle” [1].

2. What are different types of MIs?

In 2012, the joint ESC/ACCF/AHA/WHF Task Force for Redefinition of Myocardial Infarction published the expert consensus to redefine myocardial infarction, especially in the era where new biomarkers (such as troponin C or I) and interventions are becoming increasingly available [2]. The new definition not only allows for better characterization of the various etiologies of MI but also helps to develop more tailored treatment to a specific type of MI (see Table 2.1).

H. Ko (✉)

Department of Anesthesiology, Perioperative and Pain Medicine,
Brigham and Women’s Hospital, 3737 Chestnut St., Apt 2604,
Philadelphia, PA 19104, USA
e-mail: hanjoko@gmail.com

Table 2.1 Types of MI

Type 1	Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2	MI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension
Type 3	Sudden unexpected cardiac death, often with symptoms suggestive of myocardial ischemia
Type 4a	MI associated with percutaneous coronary intervention (PCI)
Type 4b	MI associated with stent thrombosis as documented by angiography or at autopsy
Type 4c	MI associated with PCI restenosis or >50% stenosis on coronary angiography
Type 5	MI associated with coronary artery bypass graft (CABG)

MI can also be described by size and location: microscopic (focal necrosis), small (<10% of left ventricular myocardium), moderate (10–30%), and large (>30%). Pathologically, it can be described as acute (identified by presence of polymorphonuclear leukocytes), healing (absence of polymorphonuclear leukocytes but presence of mononuclear cells and fibroblasts), or healed (scarred tissue without cellular infiltration). The entire healing process usually takes at least 5–6 weeks. One should keep in mind that the manifestation of MI may not correspond exactly with pathological findings, and the most appropriate treatment should always be based on clinical assessment of each individual patient at any given time.

3. What is percutaneous coronary intervention (PCI)?

Reperfusion strategy depends on the onset and duration of MI, location of occluded coronary arteries, facility capability, and patient's overall medical condition and clinical stability. One can further divide reperfusion strategy into three main categories: PCI, fibrinolytic therapy, and surgical graft revascularization. Primary PCI consists of balloon angioplasty (with or without stenting), without the previous administration of fibrinolytic therapy or platelet glycoprotein IIb/IIIa inhibitors, to open the culprit coronary artery that's responsible for clinical MI [3].

Under fluoroscopic guidance, a culprit vessel is identified and a metal wire is past beyond the thrombosis. A balloon catheter (with or without stent) is then inflated at the site of occlusion to mechanically restore distal blood flow. When anatomically feasible and appropriate, PCI is the preferred mode of reperfusion as long as it can be accomplished in a timely fashion (typically defined as “door-to-balloon” time ≤ 90 min) by an experienced operator in a facility that is capable of providing additional surgical assistance and/or transferring patients to a tertiary care center where such support exists. The “door-to-balloon” time can be extended beyond 90 min in those patients with the following [4–7]:

- contraindication to fibrinolytic therapy
- high risk of bleeding with fibrinolytic therapy, including patients >75 years old due to increased risk of intracranial hemorrhage
- clinical evidence suggesting a high risk of an infarct-related mortality such as hypotension or pulmonary edema
- cardiogenic shock

Finally, assuming no contraindications and that the culprit lesion is anatomically feasible for stent deployment, stents (drug-eluting stents preferred over bare-metal stents) have better outcomes than balloon angioplasty in terms of frequency of recurrent angina, rates of restenosis, and the need for repeat revascularization procedures [8, 9].

4. What is fibrinolytic therapy?

There is reasonable amount of discussion on the topic of when and/or for whom fibrinolytic therapy is preferred over PCI. In general, there are a greater number of limitations with fibrinolytic therapy compared to PCI. For example, 27% of the eligible patients have a contraindication to fibrinolysis such as recent surgery (less than 3 months prior to event) or history of cerebrovascular disease or uncontrolled systolic blood pressure >200 mmHg [10]. The utilization of systemic fibrinolytic therapy, unlike successful PCI, does not necessarily guarantee thrombolysis within the culprit vessel. Furthermore, a higher risk of reinfarction and 2-year mortality is also observed in patients receiving fibrinolytic therapy compared to PCI [11].

Nevertheless, fibrinolytic therapy still yields better clinical outcomes when compared to medical optimization without any reperfusion treatment [12]. Furthermore, there are certain conditions where fibrinolytic therapy is preferred over PCI. For example, in patients who seek medical attention less than 1 h after the onset of symptoms, fibrinolytic therapy may abort the infarction completely.

5. How does one decide which reperfusion strategy is best suited for certain patients?

There are certain scenarios that would favor one or the other but in general, each decision needs to be tailored to individuals' clinical conditions and needs, instead of following a simple algorithm. For example, balloon angioplasty may be preferred in patients with left main disease who are candidates of CABG within days in order to avoid administration of clopidogrel. In patients whose adherence to dual antiplatelet therapy (DAPT) might be questionable, balloon angioplasty may be more ideal than DES despite no other physiological contraindications to DES. CABG, on the other hand, typically is preferred in diabetic patients with multivessel coronary artery disease [13]. However, the presence of significant chronic kidney disease combined with history of life-threatening gastrointestinal bleeding might provide arguments for CABG in certain patients in order to avoid contrast-associated nephropathy necessitating permanent dialysis and recurrent bleeding from the need of DAPT following DES. It is therefore, imperative, that one seeks expert opinion and has a candid discussion with patients regarding risks and benefits before committing them to a certain reperfusion therapy.

After the Initial Presentation:

Even though the patient presentation does not endorse significant angina, his clinical manifestation is concerning for STEMI. Given the elective nature of his surgery, the case was canceled. He was given morphine for symptomatic relief, and an esmolol infusion was started to decrease myocardial demand by slowing his heart rate. After obtaining an emergent cardiology consultation for STEMI, this patient underwent coronary artery angiography which revealed an in-stent restenosis of his prior RCA stent and a newly >80% occluded LAD.

6. What is in-stent restenosis (ISR)?

It is important to distinguish ISR from stent thrombosis. ISR is the result of arterial damage with subsequent neointimal tissue proliferation that leads to >50% stenosis in the diameter [14]. The need for repeat revascularization within 30 days after the initial stent deployment most likely suggests stent thrombosis since the time frame is too short for the narrowing and/or occlusion of the targeted vessels to be caused by neointimal tissue. Stent thrombosis typically presents with MI while the incidence of MI from ISR is much lower since restenosis only implies reduction in the coronary arterial lumen diameter, instead of complete occlusion. As a result, traditionally, ISR is thought to be a

relatively benign entity but more recent studies have suggested that these patients can and will frequently present with acute MI [15, 16].

The optimal treatment for DES restenosis is still under investigation given the various etiologies for ISR (neoatherosclerosis, drug resistance, stent underexpansion, residual uncovered atherosclerotic plaques, etc.). The most popular modality is repeat DES or drug-coated balloon angioplasty, provided that the anatomical features of ISR are favorable for such intervention, since they provide the best clinical and angiographic results [17, 18]. However, the success rate for retreatment differs significantly depending on the clinical scenario, and therefore, it is imperative to recognize that at some point, CABG should be considered as a treatment option, especially in complex cases (e.g., multivessel DES with multivessel diffuse ISR) [19].

This patient's STEMI is most likely from the combination of his newly occluded LAD and his ISR with prior RCA stent (clopidogrel was held for 7 days). That is, he has both type 1 and type 4c MI. It is important to recognize that a patient treated with a new DES for ISR should be considered high risk, and DAPT should be continued indefinitely unless a serious complication occurs, upon which time, an expert consultation should be sought in order to balance the risk of bleeding and thrombosis.

7. What are high-risk PCIs?

Unfortunately, there is no universally accepted definition of high-risk PCI, and therefore limited data exist to help guide management to minimize peri-procedural complications. Nevertheless, high-risk PCIs are typically associated with significant hemodynamic instability and technical challenges with a higher possibility of requiring mechanical circulatory support and/or emergent surgical intervention. An example to further categorize high-risk PCIs is as follows [20, 21] (see Table 2.2).

One needs to bear in mind that the list above is not comprehensive, and therefore it should only serve as an example to urge clinicians to seek more detailed risk stratification after consulting expert opinion.

Follow Up of the Case:

Given the new findings, a BMS was deployed into his LAD, and balloon angioplasty to RCA was also performed. BMS was chosen to minimize the duration of DAPT given that this patient might be a candidate for pleuroctomy in the near future, assuming that his clinical condition is stabilized and that he is able to undergo the initial cancer staging after one month of DAPT. He was subsequently transferred to cardiac critical care unit and discharged home after a few

Table 2.2 An example to further categorize high-risk PCIs [20, 21]

Anatomical location	Intervention to an unprotected left main coronary artery or left main equivalent
	Multivessel disease
	Distal left main bifurcation intervention
	Previous CABG, including intervention to a graft, particularly a degenerated graft
	Last remaining coronary conduit
	Duke Myocardial Jeopardy score >8
	Target vessel providing a collateral supply to an occluded second vessel that supplies >40% of the left ventricular myocardium
	Ostial stenosis
	Heavily calcified lesions
	Chronic total occlusions
Hemodynamic criteria	SYNTAX score >33
	Cardiac index <2.2 L/min/m ²
	Pulmonary capillary wedge pressure >15 mmHg
Clinical feature	Mean pulmonary artery pressure >50 mmHg
	Cardiogenic shock occurring within 24 h or at the start of coronary intervention
	Left ventricular systolic dysfunction on presentation (ejection fraction <30–40%)
	Killip class II–IV on presentation or congestive heart failure
	Coronary intervention after resuscitated cardiac arrest within 24 h
	STEMI
	Acute coronary syndrome complicated by unstable hemodynamics, dysrhythmia, or refractory angina
	Prior MI
	Age >70–80 years
	History of cerebrovascular disease, diabetes, renal dysfunction, peripheral arterial disease, or chronic lung disease

days. He was instructed to follow up with his cardiologist within a week after discharge.

8. What is the current guideline for DAPT after PCI?

Table 2.3 reflects the current guideline for DAPT after PCI based on 2005 ACC/AHA publication [13].

For our patient, he should continue clopidogrel 75 mg daily and increase his aspirin to 325 mg daily for at least one month given the new BMS to his LAD. The decision as to whether or not hold clopidogrel prior to his elective cancer staging surgery has to be revisited.

9. What is the implication of DAPT in the perioperative setting?

Since DAPT has been proven to be superior in terms of preventing cardiovascular events after PCI to either aspirin alone, or clopidogrel alone, or even combination of aspirin and warfarin, the decision to withhold DAPT needs to be made individually [26]. At the same time, despite multiple clinical practice guidelines, the management of perioperative

DAPT continues to evolve [27]. The risk of major adverse cardiovascular events and stent thrombosis is highest in the first year after implantation with mortality up to 45% [28]. During that first year, the endothelialization typically takes 4–6 weeks for BMS and 6–12 months for DES [29]. Early withdraw of antiplatelet agents is the main determinant for ischemic complication and the complication rate is the highest when the stent implantation is <30 days [30]. As a result, it is recommended that elective surgery should be postponed for a minimum of 4–6 weeks after BMS and 6 months after DES (preferably 12 months).

Aspirin should be continued throughout the perioperative period. The only possible exception is closed space surgeries such as intracranial surgery, spinal surgery, and posterior eye chamber surgery. For those who require semi-elective surgery such as cancer staging or diagnosis, a delay of 12 months is not ideal. As a result, timed transfusion of platelets can be considered. For example, the last dose of aspirin and clopidogrel is given 12–24 h before surgery followed by 2 pools of platelet concentration given 1–2 h immediately before surgery. The duration of holding DAPT should be minimized and ideally, aspirin should be restarted

Table 2.3 The current guideline for DAPT after PCI based on 2005 ACC/AHA publication [13]

Aspirin	Pre-PCI: Aspirin (either 75 or 325 mg) should be continued on patients who are on chronic daily aspirin. Of note, a daily dose of 75 mg of aspirin has similar cardiovascular outcomes to 325 mg but with fewer bleeding complications [22–24]
	Pre-PCI: Aspirin (300 mg or 325 mg) should be given at least 2 h and preferably 24 h for patients who are not on chronic daily aspirin
	Post-PCI: Aspirin 325 mg daily should be given <ul style="list-style-type: none"> – 1 month after bare-metal stent – 3 months after sirolimus-eluting stent – 6 months after paclitaxel-eluting stent After the above-specified duration, chronic daily aspirin (75 mg to 162 mg) should be continued indefinitely
Clopidogrel	Pre-PCI: A loading dose of clopidogrel 300 mg should be given preferably at least 6 h prior to procedure if feasible [25]
	Post-PCI: Clopidogrel 75 mg should be given <ul style="list-style-type: none"> – at least one month after bare-metal stent (unless the patient is at increased risk for bleeding, then it should be given for a minimum of 2 weeks) – 3 months after sirolimus stent – 6 months after paclitaxel stent Ideally, the duration for clopidogrel should be extended to 12 months in patients who are not at high risk of bleeding In patients with clinical features associated with stent thrombosis (i.e., renal insufficiency, diabetes, or procedural characteristics, such as multiple stents or treatment of a bifurcation lesion), it is reasonable to extend clopidogrel beyond 1 year
	Post-PCI: In patients whose subacute thrombosis may be lethal (e.g., unprotected left main, last patent coronary vessel), it is reasonable to consider platelet aggregation study. If <50% inhibition of platelet aggregation is demonstrated, it is reasonable to increase the dose of clopidogrel to 150 mg given clopidogrel resistance is a significant problem

6 h postoperatively and clopidogrel 24–48 h (\pm loading dose of 300 mg) [31]. Of note, this regimen is not valid for newer antiplatelet agents such as prasugrel or ticagrelor.

In cardiac surgery, it is recommended to hold clopidogrel for at least 5 days but the data concerning non-cardiac surgery are limited and conflicting [13]. Therefore, other “bridging” therapies (such as eptifibatide) should also be considered in high-risk patients since DAPT does result in a significant increase in bleeding, transfusion, mechanical ventilation, length of hospital stay, and surgical re-exploration [28, 32–34].

Similar to clopidogrel, prasugrel also binds irreversibly to the platelet P2Y₁₂ receptor but with a more rapid, potent, and consistent platelet inhibition at the cost of increased risk of bleeding [35, 36]. As a result, prasugrel has a more limited use in the perioperative setting.

Unlike clopidogrel, ticagrelor binds reversibly to platelet P2Y₁₂ receptor and is able to achieve a greater inhibition of platelet aggregation compared to clopidogrel without significant difference in the rates of major bleeding [37, 38]. The major advantage of ticagrelor is its short half-life (6–13 h) and reversibility [39]. In the perioperative setting, one only needs to hold ticagrelor for 1 day.

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Anesthesiology

Clinical Case Reviews

Aglio, L.S.; Urman, R.D. (Eds.)

2017, XV, 493 p. 19 illus., 13 illus. in color., Softcover

ISBN: 978-3-319-50139-0