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An Updated Protocol for Evaluating Chest Pain and Managing Acute Coronary Syndromes

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Abstract

Clinical pathways can optimize care both across and within institutions, but regular updates to these pathways based on new clinical trials, professional guidelines, and Food and Drug Administration approvals are essential. Herein we describe the most recent revisions to the New York-Presbyterian Hospital (Columbia University Medical Center and Weill Cornell Medical Center) clinical pathway for acute coronary syndromes and chest pain, which incorporates novel data regarding the timing and administration of P2Y₁₂ inhibition (including the intravenous P2Y₁₂ inhibitor cangrelor) and the appropriateness of prolonged (>1 year) dual antiplatelet therapy for the secondary prevention of ischemic events.

Keywords

acute coronary syndromes; antiplatelet therapy; percutaneous coronary intervention

Because of the life-threatening nature of an acute coronary syndrome (ACS) and the frequency with which patients present for evaluation of a suspected ACS, clinicians from a wide range of disciplines must be capable of recognizing, assessing, and treating this condition. New York-Presbyterian Hospital is a large, tertiary-care center that cares for thousands of patients with ACS each year. To standardize care according to the latest evidence and guidelines, we publish and regularly update a clinical pathway that guides providers through the evaluation of chest pain and management of ACS.

The last update to this algorithm, published in 2012, addressed the need for more potent P2Y₁₂ inhibition with ticagrelor, removed warnings about the interaction between clopidogrel and proton pump inhibitors, and eliminated a recommendation for platelet function testing prior to percutaneous coronary intervention (PCI).¹

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DISCLOSURES

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Since that update, there have been numerous changes and innovations in the management of ACS. First, several trials have examined the optimal timing of initial P2Y₁₂ inhibition. Second, the United States Food and Drug Administration (US FDA) has approved cangrelor, a rapid-acting intravenous P2Y₁₂ inhibitor, based on clinical trials examining its use in patients undergoing PCI for various indications. Finally, there have been several studies (and an ACC/AHA guideline update) regarding the role for prolonged dual-antiplatelet therapy (DAPT) for the secondary prevention of ischemic events following an ACS. Herein we describe the specific ways in which the protocol has been updated to address these new data, along with the rationales for each change.

P2Y₁₂ INHIBITORS: PROBLEMS WITH THE STATUS QUO

The platelet P2Y₁₂ receptor is central to platelet activation that underlies coronary atherothrombosis during an ACS.² Inhibitors of the P2Y₁₂ receptor have been cornerstones of ACS management since the CURE trial demonstrated that the addition of clopidogrel to aspirin significantly reduced the composite rate of cardiovascular death, recurrent myocardial infarction (MI), or cerebrovascular accident (CVA).³ Although clopidogrel was better tolerated than ticlopidine, an earlier P2Y₁₂ receptor antagonist with rare but serious hematologic complications, it had several shortcomings of its own, including a relatively slow onset of action, interaction with certain proton pump inhibitors, and reduced conversion to its active metabolite among patients with certain *CYP2C19* variants.

The subsequent introduction of prasugrel and then ticagrelor eliminated some of these issues while also providing superior protection from recurrent ischemic events.^{4,5} With both agents, however, such protection came at the cost of increased bleeding. In the TIMI-TRITON 38 trial,⁴ which compared prasugrel with clopidogrel in patients with ACS, prasugrel significantly increased the rate of non-coronary artery bypass grafting (CABG)-related TIMI major bleeding (intracranial bleeding, hemorrhage with decrease in hemoglobin ≥ 5 g/dL, or bleeding that causes death within 7 days) during 15 months of follow-up (2.4% vs. 1.8%, $P=0.03$), with a relative excess of fatal bleeding (0.4% vs. 0.1%, $P=0.002$) and no significant difference in all-cause mortality. In the PLATO trial,⁵ which compared ticagrelor with clopidogrel in patients with ACS, ticagrelor also increased non-CABG-related TIMI major bleeding during the 12-month follow-up period (2.8% vs. 2.2%, $P=0.03$), but did not cause more fatal bleeding. Moreover, use of ticagrelor decreased all-cause mortality (4.5% vs. 5.9%, $P<0.001$).

The increased efficacy of both prasugrel and ticagrelor over clopidogrel reflects more rapid and potent inhibition of platelet aggregation. In the ONSET/OFFSET study, patients on stable doses of aspirin were randomized to loading doses of ticagrelor (180 mg) or clopidogrel (600 mg) and then underwent frequent blood draws. Platelet inhibition was greater with ticagrelor at 0.5, 1, 2, 4, 8, and 24 hours after loading. Moreover, ticagrelor required only 2 hours to achieve maximal platelet inhibition, whereas clopidogrel required 8 hours.⁶ Meanwhile, the TIMI PRINCIPLE-44 study randomized patients planned for elective PCI to receive loading doses of clopidogrel (600 mg) or prasugrel (60 mg). Thirty minutes after a loading dose, the mean inhibition of platelet aggregation was 30.8% in the

prasugrel group and 4.9% in the clopidogrel group; by 2 hours, the values had risen to 64.5% and 20.3%, respectively.⁷

Of note, the efficacy of all oral agents is delayed in patients with ACS, particularly those with ST-segment elevation myocardial infarction (STEMI), as high sympathetic tone inhibits gastrointestinal motility and thereby slows medication absorption. In one trial, the pharmacokinetics of clopidogrel were markedly altered in patients with STEMI compared with normal controls, with prolonged time-to-maximum concentrations for the drug and its metabolites; consequently, inhibition of platelet aggregation was both reduced and delayed.⁸ Both ticagrelor and prasugrel also appear to have delayed effects in patients with STEMI.⁹ In addition, the administration of morphine and other opioids appears to further reduce the efficacy of these agents, likely by slowing gastric emptying.¹⁰

All oral P2Y₁₂ inhibitors also have a slow offset, causing several days of platelet inhibition following their last dose. This long-lasting effect provides a safety margin to patients who occasionally forget to take their medications but becomes problematic when an urgent surgical procedure is required. A prime example is the patient with non-ST-segment elevation acute coronary syndrome (NSTEMI) who receives an oral P2Y₁₂ inhibitor prior to angiography but is then discovered to have severe, 3-vessel coronary artery disease that warrants CABG. In such cases, there are 2 options: (1) perform CABG while the patient's platelets remain inhibited, accepting the increased risk of bleeding, or (2) delay the patient's surgical procedure for several days while the effect of the P2Y₁₂ inhibitor washes out and platelets regain normal function. Between 5% and 15% of patients presenting with an ACS will require CABG during the index hospitalization, with the rate depending on both case mix and institutional practice patterns.

Given the foregoing, the optimal timing of the P2Y₁₂ inhibitor remains controversial. Although a preload (ie, loading dose given prior to angiography) provides better platelet inhibition at the time of PCI, potentially averting events such as stent thrombosis, it also increases the risk of procedure-related bleeding and complicates the management of patients who require urgent CABG.¹¹ As a result, there is wide variation in practice regarding the role of preloading with P2Y₁₂ inhibitors, even though societal guidelines favor the practice.¹² A recent examination of hospital records for nearly 40,000 patients throughout the United States found that P2Y₁₂ inhibitors were given to only 38% of patients with STEMI and 32% of patients with NSTEMI prior to cardiac catheterization.¹³

Several trials have attempted to clarify the optimal timing for P2Y₁₂ inhibition. A large meta-analysis suggested that clopidogrel preloading reduced both major cardiac events (MI, CVA, urgent revascularization) and all-cause mortality in patients with STEMI, but did not affect mortality in patients with NSTEMI.¹⁴ Meanwhile, the ACCOAST trial¹⁵ randomized patients with NSTEMI to a loading dose of prasugrel either at diagnosis or just prior to PCI, if indicated. Preloading did not affect ischemic endpoints but was associated with higher rates of non-CABG-related TIMI major bleeding at 7 days of follow-up (1.3% vs. 0.5%, $P = 0.003$). The ATLANTIC trial¹⁶ randomized patients with STEMI to receive a loading dose of ticagrelor in the ambulance or in the hospital (but still prior to angiography). Prehospital loading (which occurred, on average, 31 minutes earlier than hospital loading)

had no effect on pre-PCI resolution of ST-segment elevation or pre-PCI TIMI 3 flow in the infarct artery but was associated with a reduction in the secondary endpoint of definite stent thrombosis at 24 hours (0% vs. 0.8%, $P=0.008$) and 30 days (0.2% vs. 1.2%, $P=0.02$). There was no significant effect on bleeding rates.

Together these studies suggest that earlier loading with an oral P2Y₁₂ inhibitor provides only limited protection against ischemic events, especially in patients with NSTEMI. Since a significant minority of these patients will subsequently require CABG (and will incur delays to surgery if a preload has been given), and because a rapidly acting intravenous P2Y₁₂ inhibitor has recently been approved for use (see below), we have updated our protocol to advise against oral agent preloading in patients with NSTEMI when a relatively rapid, early invasive strategy is planned. We continue to recommend preloading patients with STEMI because a much smaller proportion of patients requires CABG. Moreover, this population has the slowest gastrointestinal absorption of oral medications, making a delayed loading strategy more likely to leave them vulnerable during the immediate post-PCI period as the effects of intravenous medications wane.

ROLE OF CANGRELOR IN ACS

The US FDA recently approved the use of cangrelor, a rapidly acting and reversible P2Y₁₂ inhibitor, specifically “as an adjunct to PCI ... in patients who have not been treated with a P2Y₁₂ inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.”^{16a} This approval was based on data from the 3 CHAMPION trials,^{17–19} which compared cangrelor with clopidogrel in patients undergoing PCI. The largest such trial, known as CHAMPION-PHOENIX¹⁸ randomized patients undergoing PCI to (1) intraprocedural cangrelor followed by a 600 mg clopidogrel load postprocedure or (2) clopidogrel alone, with the timing (pre- or post-PCI) and dose (300 or 600mg) determined by institutional practice. Patients receiving cangrelor had a lower rate of a composite outcome (death, MI, ischemia-driven revascularization, and both intra- and postprocedural stent thrombosis) at 48 hours (4.7% vs. 5.9%, $P=0.005$), primarily due to lower rates of stent thrombosis and MI. Subgroup analyses demonstrated similar effects in patients receiving 300 or 600 mg of clopidogrel either before or after PCI. There was no significant increase in major bleeding although minor bleeding (mostly hematomas) was more common with cangrelor.

The CHAMPION trials had several limitations that were extensively discussed at an FDA panel meeting; specifically, cangrelor was not compared with the newer P2Y₁₂ inhibitors, and the control group was not given consistent P2Y₁₂ receptor inhibition prior to PCI. Nonetheless, cangrelor provides markedly greater platelet inhibition than clopidogrel without increasing major bleeding. Although cangrelor may not offer significant benefits over an oral P2Y₁₂ inhibitor that is given hours before PCI, it is useful for patients with extenuating circumstances that prevent timely oral agent loading and, because of its rapid onset, permits deferral of the decision to administer a P2Y₁₂ inhibitor until after the completion of coronary angiography. As a result, patients who actually require CABG can proceed to surgery without delay, and patients who do not require any revascularization may, in some circumstances, avoid P2Y₁₂ inhibition altogether. Therefore, we have amended our

algorithm to state that patients with NSTEMI who are not already receiving an oral P2Y₁₂ inhibitor can receive cangrelor or an oral P2Y₁₂ inhibitor load prior to PCI.

Given the rapid offset of cangrelor, patients who receive this agent must be promptly transitioned to an oral P2Y₁₂ inhibitor. Pharmacodynamic studies demonstrate that ticagrelor can be safely started at any time before, during, or after a cangrelor infusion without significant drug interaction.²⁰ In contrast, clopidogrel²¹ and prasugrel^{22,23} are less effective when coadministered with cangrelor due to competitive inhibition of these agents' short-lived active metabolites by cangrelor at the P2Y₁₂ receptor. Therefore, as recommended by the cangrelor package insert, these agents should not be dosed until the time that the cangrelor infusion is discontinued (usually ~2 hours post-PCI). Unfortunately, this results in a transition period (especially for clopidogrel) during which platelet inhibition is suboptimal. On the basis of these issues, we recommend ticagrelor as the oral agent of choice when transitioning from cangrelor, particularly for higher-risk ACS patients who would benefit from potent P2Y₁₂ inhibition and do not have bleeding-related contraindications. In patients with NSTEMI, ticagrelor should be administered as soon as it has been determined that PCI will be performed.

OPTIMAL DURATION OF DUAL ANTIPLATELET THERAPY

Based on the heightened risk of recurrent ischemic events following an ACS, the standard recommendation until recently had been to continue DAPT with aspirin and a P2Y₁₂ inhibitor for 1 year after an ACS regardless of stent type.¹²

Several recent trials have examined the effects of further extending DAPT in high-risk patients.^{24–26} Among these, the DAPT trial²⁶ was the largest, randomizing nearly 10,000 patients treated with drug-eluting stents for various indications (about 40% for ACS). Patients who tolerated 1 year of DAPT (clopidogrel or prasugrel) without cardiovascular or cerebrovascular events, repeat revascularization, or moderate-to-severe bleeding were randomized to 18 more months of DAPT or to aspirin alone. Patients who continued DAPT had a lower rate of stent thrombosis (0.4% vs. 1.4%, $P < 0.001$) and a lower rate of a composite outcome of death, MI, and CVA (4.3% vs. 5.9%, $P < 0.001$) but a higher rate of moderate or severe bleeding (2.5% vs. 1.6%, $P = 0.001$). The DAPT group had a slightly higher mortality rate (2.0% vs. 1.5%, $P = 0.05$); however, there were no differences in rates of cardiac death, severe bleeding, or fatal bleeding, though these events were rare. In a subgroup analysis of patients who presented with MI, continued DAPT was associated with a greater reduction in ischemic events and lower absolute rates of bleeding than in patients who underwent elective PCI, with a neutral effect on mortality.²⁷

The PEGASUS-TIMI 54 trial²⁸ explored the efficacy of longterm DAPT with ticagrelor among patients who had survived MIs 1–3 years earlier, regardless of whether PCI was performed, and were “high risk” because of one of the following: age >65 years, diabetes mellitus, multiple prior MIs, multivessel coronary artery disease (CAD), and chronic kidney disease. Unlike in the DAPT trial, most patients had already transitioned from DAPT to aspirin monotherapy. Patients treated with aspirin were randomized to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo and followed for 36 months. Patients

were excluded if they required anticoagulants or had a history of stroke, intracranial bleeding or risk factors (eg, intracranial mass or vascular malformation), GI bleeding within the prior 6 months, or surgery within the past 30 days. Long-term ticagrelor use reduced the rate of a composite outcome of cardiac death, MI, and CVA at 3 years (7.85% for 90 mg, 7.77% for 60 mg, 9.04% for placebo); however, it also increased the rate of TIMI major bleeding (2.60% for 90 mg, 2.30% for 60 mg, 1.06% for placebo). There was a neutral effect on all-cause mortality with all 3 regimens. There were no statistically significant differences between the 2 ticagrelor doses although the bleeding rate was numerically lower with the 60 mg dose.

Overall these studies indicate that in unselected patients, prolonged DAPT therapy reduces recurrent ischemia at the cost of increased bleeding, with a neutral or even possibly harmful effect on overall mortality (in the case of thienopyridines). Nonetheless, patients at high risk of recurrent ischemia but at low risk of bleeding would likely derive benefit from prolonged DAPT. Similarly, patients with an ACS may represent a population with higher risk of recurrent ischemic events and a lower risk of bleeding.²⁷ Alternative ways to individualize risk have been devised, such as the DAPT score.²⁹

We have updated our algorithm to advise clinicians that long-term DAPT (with ticagrelor preferentially dosed at 60 mg) may be appropriate in high-risk ACS patients. This recommendation is consistent with the recent update to the recent ACC/AHA guideline-focused update on DAPT duration, in which extended duration DAPT (>1 year) in patients with ACS is afforded a Class IIb recommendation.³⁰

CONCLUSIONS

Since the last publication of our chest pain algorithm, there have been numerous studies reassessing the optimal pharmacotherapy of patients with ACS. Among the many advances have been new trials on cangrelor, an intravenous P2Y₁₂ inhibitor, and prolonged DAPT, which have prompted changes in our algorithm. The algorithm is given below in its entirety and is also available in abbreviated form as a clinician pocket card (Fig. 1).

ALGORITHM INITIAL ASSESSMENT

Vital signs. Temperature, pulse, respiratory rate, blood pressure (both arms simultaneously), O₂ saturation

12 lead EKG (within 5 minutes of triage).

If ST elevation in II, III, or AVF, check right-sided EKG leads

If anterolateral ST depressions, check posterior EKG leads

History and physical (focused)

Cardiac monitor

Oxygen therapy. 2 liters/min via nasal cannula, or as clinically indicated

IV access (16–20 gauge)

Blood tests CBC, basic metabolic panel, troponin, brain-type natriuretic peptide (BNP), creatine phosphokinase (CPK) (including MB isoform), prothrombin time (PT), activated partial thromboplastin time (PTT), lipid profile, liver profile, Mg⁺⁺

CLINICAL STRATIFICATION AND MANAGEMENT

Level 1: ST ↑ Acute coronary syndrome (STEMI)

Definition—Chest pain at rest >20 minutes and:

ST ↑ 1 mm in 2 contiguous leads, OR

New (or not known to be old) left bundle branch block (LBBB), OR

True posterior MI with anterolateral ST depression and ongoing chest pain

Initial Treatment—*Immediate primary percutaneous coronary intervention*. 24 hours per day, 7 days per week. In exceptional cases where primary PCI cannot be performed, consider tenecteplase bolus. All delays to cath lab need to be clearly documented as follows “Delay to the cath lab secondary to”

Aspirin. nonenteric-coated, 325 mg chewed

Unfractionated heparin. bolus (without a drip), 60 Units/kg (max 4000 Units).

P2Y₁₂ antagonist. give PRIOR to catheterization unless there are contraindications (see below):

First-line agent: ticagrelor (Brilinta) 180 mg loading dose (regardless of whether the patient was already taking clopidogrel, prasugrel, or ticagrelor) unless contraindications present. Ticagrelor is the only P2Y₁₂ inhibitor with an FDA approved crushing option for administration.

Second-line agent: prasugrel (Effient)—60 mg loading dose. Third-line agent: clopidogrel (Plavix)—600 mg PO loading dose

Nitrates. Do not give nitrates to hypotensive patients (systolic blood pressure [SBP] <100 mm Hg). Sublingual nitroglycerin (SL NTG) may be given as front-line therapy to exclude unstable angina and for pain relief in patients who are not hypotensive. IV NTG may be used as needed for ischemic pain in patients who are not hypotensive. Titrate to target SBP.

Nitrates must not be administered if the patient has taken phosphodiesterase inhibitors such as sildenafil citrate (Viagra), tadalafil (Cialis), and vardenafil hydrochloride (Levitra) within 48 hours. Avoid nitrates in patients with ST-segment elevation in II, III, or AVF, especially if there is concern for right ventricular infarct.

P2Y₁₂ antagonist contraindications

Contraindications to ticagrelor

AND prasugrel

Known moderate or severe liver disease,

known hemoglobin <10 g/dL, or known platelet count <100,000 cells/mm³, major bleed within 2 months, major surgery within 1 month, oral anticoagulation therapy that cannot be stopped, fibrinolytic therapy planned or given within the previous 24 hours; will refuse blood transfusions

Contraindications to ticagrelor (NOT to prasugrel)	Second degree or greater heart block concomitant therapy with reverse transcriptase inhibitors (eg, for the treatment of HIV infection), strong CYP3A inhibitors (eg, ketoconazole, clarithromycin), CYP3A substrates (eg, cyclosporine, quinidine), or strong CYP3A inducers (eg, rifampin/rifampicin, phenytoin)
Contraindications to prasugrel	Dialysis; prior transient ischemic attack (TIA) or cerebrovascular accident (CVA); age >75; weight <60 kg
No P2Y ₁₂ antagonists should be given if the patient is actively bleeding.	

Beta-blocker. It is reasonable to administer IV beta-blockers promptly to STEMI patients without contraindications, especially if a tachyarrhythmia or hypertension is present. DO NOT administer betablockers if hypotension, pulmonary edema, severe bradycardia, heart block, asthma, or severe COPD is known/present). A recommended regimen is IV metoprolol 5 mg given over 2 minutes, repeat every 5 minutes for a total of 3 doses (15 mg). Use with caution in patients with ST-segment elevation in II, III, or AVF.

Level 2: Non ST ↑ Acute Coronary Syndrome (Unstable Angina and NSTEMI)

Definition—Chest pain consistent with ischemia at rest 10 minutes with:

ST ↓ 0.5 mm, or

ST ↑ 0.6 mm to <1 mm (or >1 mm which resolved in <30 minutes), or TW ↓ >1 mm, or Positive troponin, or

Unstable angina history in a patient with CAD risk factors

Initial Treatment—*Aspirin*. nonenteric-coated, 325 mg chewed followed by 81 mg daily beginning the following day.

Unfractionated heparin. bolus 60 Units/kg (max 5000 Units) followed by weight-based drip. Avoid enoxaparin (Lovenox) in patients who are candidates for percutaneous coronary intervention (PCI).

P2Y₁₂ antagonist. DO NOT LOAD at presentation UNLESS the patient is already on one of these agents OR an early invasive strategy is NOT planned.

For patients already taking P2Y₁₂ antagonists prior to admission: For patients with anticipated delay to the cath lab (>24 hours): preload with an oral P2Y₁₂ inhibitor as follows:

Home Medication	Use
Clopidogrel (Plavix)	Full loading dose of ticagrelor (Brilinta)
Prasugrel (Effient)	Continue patient's maintenance dose rather than switching. Do not reload
Ticagrelor (Brilinta)	Continue 90 mg PO bid

First-line agent: ticagrelor 180 mg PO followed by 90 mg PO bid. Second-line agent (if contraindication to ticagrelor): clopidogrel 600 mg PO followed by 75 mg PO qd.

Beta-blocker (IV or PO). titrate to HR and SBP (with contraindications as above in level 1 protocol).

Nitrates. Do not give nitrates to hypotensive patients (SBP <100 mm Hg). SL NTG may be given as front-line therapy to exclude unstable angina and for pain relief in patients who are not hypotensive. IV NTG may be used as needed for ischemic pain in patients who are not hypotensive. Titrate to target SBP. Nitrates must not be administered if the patient has taken phosphodiesterase inhibitors such as sildenafil citrate (Viagra), tadalafil (Cialis), and vardenafil hydrochloride (Levitra) within 48 hours. Avoid nitrates in patients with ST-segment elevation in II, III, or AVF, especially if there is concern for RV infarct.

PCI. Call an immediate cardiology consult for potentially emergent cardiac catheterization if the patient has any of the following: severe refractory chest pain, hemodynamic instability, acute heart failure, refractory ventricular arrhythmia, global ischemia (diffuse ST depression with ST elevation in AVR).

Pursue an early invasive (within 24–48 hours) strategy in patients thought to have a primary coronary event associated with elevated troponin levels, new ST-T wave changes, and/or 2 of the following: age ≥65, ≥3 CAD risk factors (hypertension, hyperlipidemia, diabetes, smoking, significant family history), prior MI/CABG/PCI, recurrent chest pain, aspirin use in last 7 days, low left ventricular ejection fraction (LVEF).

Pursue medical management in other patients unless there are signs of recurrent ischemia that warrant invasive assessment.

Antiplatelet therapies in the cardiac catheterization laboratory. Because the majority of patients with NSTEMI/ACS will NOT have received a P2Y₁₂ antagonist prior to diagnostic catheterization, close attention will need to be paid to the antiplatelet regimen used in the catheterization laboratory if PCI is to be performed. The following are potential options for antiplatelet therapies administered in the cardiac catheterization laboratory for patients undergoing PCI:

Cangrelor 30 µg/kg IV bolus infused over 1 minute before PCI. Immediately follow bolus injection with 4 µg/kg/min IV infusion; continue for at least 2 hours and for a maximum of 4 hours (including the duration of PCI). Following stent placement, cangrelor-treated patients must be transitioned to oral P2Y₁₂ inhibitor. To initiate oral therapy, choose from one of the following loading-dose regimens described below:

Ticagrelor	180 mg PO crushed given at any time before, during, or after discontinuation of the cangrelor infusion (the earliest possible time of administration is preferred to avoid a gap in platelet inhibition). Because ticagrelor can be given before, during, or after the cangrelor infusion, it is the preferred oral agent to pair with cangrelor
Prasugrel	60 mg PO given immediately after discontinuing cangrelor; DO NOT administer prasugrel prior to cangrelor discontinuation (because of drug interaction). If prasugrel was given before or during cangrelor, a second loading dose should be given at the time of cangrelor discontinuation
Clopidogrel	600mg PO given immediately after discontinuing cangrelor; DO NOT administer clopidogrel prior to cangrelor discontinuation (because of drug interaction). If clopidogrel was given before or during cangrelor, a second loading dose should be given at the time of cangrelor discontinuation

If cangrelor is NOT used, load with an oral P2Y₁₂ inhibitor PRIOR to PCI using the doses listed above.

For high-risk patients at lower risk of bleeding in whom cangrelor is NOT used, operators can consider using an intravenous glycoprotein IIb/IIIa inhibitor (tirofiban, abciximab, or eptifibatide), administered as a weight-based bolus (with renally adjusted infusion). Continuance of the infusion beyond the PCI is at the operator discretion, but will likely be associated with a greater risk of bleeding.

Anticoagulation therapies in the cardiac catheterization laboratory. Bivalirudin or unfractionated heparin at the discretion of intervention- alist based on bleeding and ischemic risk of the patient. Bivalirudin is preferred for patients at greater risk for bleeding complications.

LEVEL 3: NORMAL OR NONDIAGNOSTIC EKG AND/OR ATYPICAL CHEST PAIN WITHOUT ALTERNATIVE EXPLANATION

Treatment

ASA. 325 mg, chewed

Beta-blockers

Nitrates. (as needed)

Troponins. (0, 4, and 8 hours from time of admission), CPKs, and serial EKGs.

Nuclear stress study, stress echo, or CTA. if negative troponins at 0, 4, 8 hours and no ischemic EKG changes.

Prior to stress test, NPO for 4 hours, no caffeine for 12–24 hours, and hold beta-blockers if possible.

Consider outpatient cardiac evaluation for patients at low risk for ACS.

Level 4: Normal or Nondiagnostic EKG With Atypical Chest Pain

Definition—Pain not consistent with an acute coronary syndrome, and/or alternative explanation for chest pain has been established, and/or age less than 30 years.

Management—Consider discharge with follow-up evaluation.

Cocaine-Induced Chest Pain—Follow above clinical pathways except: beta-blockers are relatively contraindicated, and benzodiazepines may be helpful.

SECONDARY PREVENTION AFTER ALL ACUTE CORONARY SYNDROMES

Aspirin 81 mg PO daily indefinitely, unless coronary arteries were normal and ACS was ruled out.

P2Y₁₂ antagonist

If PCI was performed for an ACS, or no PCI was performed but diffuse coronary artery disease was present, use ticagrelor (preferred), prasugrel, or clopidogrel for a minimum of 1 year. The decision to use after 1 year should be based on the relative risk of ischemia versus bleeding.

Ticagrelor (Brilinta) should be continued at 90 mg PO bid (60 mg PO bid preferred after 1 year).

Prasugrel (Effient) should be continued at 10 mg PO qd (or 5 mg PO qd if body weight <60 kg or age >75 years).

Clopidogrel (Plavix) should be continued at 75 mg PO daily.

If CABG is necessary for a patient already treated with a P2Y₁₂ antagonist, defer surgery if possible to allow washout for 5 days (for ticagrelor or clopidogrel) or 7 days (for prasugrel). After surgery, once the patient is stable, all major lines have been removed, and no bleeding is evident, the patient should be restarted on clopidogrel 75 mg qd for 1 year. Ticagrelor or prasugrel may be considered.

If catheterization demonstrated normal or near-normal coronary arteries and the final diagnosis is not ACS, all P2Y₁₂ antagonists should be discontinued.

Beta-blocker. consider carvedilol if LVEF <40%.

High-dose statin. atorvastatin (Lipitor) 80 mg daily or, if intolerant, rosuvastatin (Crestor) 40 mg daily, with long-term target LDL <70. *ACE inhibitor.* consider valsartan if intolerant.

Aldosterone antagonists. if LVEF <40 % and clinical symptoms of CHF (closely monitor K⁺ and serum Cr).

Warfarin (Coumadin). in patients with LV thrombus, apical dyskinesia, atrial fibrillation, or anterior wall MI with significant wall motion abnormality. If a patient has received a coronary stent, and thus requires an P2Y₁₂ antagonist for at least 1 year, and also requires oral anticoagulation, aspirin and clopidogrel should be used. Ticagrelor and prasugrel should not be used in combination with oral anticoagulants. Warfarin is preferred over other oral anticoagulants in this setting and should be used at the lowest possible dosage for the particular indication while the patient is on all 3 medications.

Nitrates. (including sublingual prn) for any patient with recurrent angina or ischemia after treatment for ACS.

Diet

Exercise

Smoking cessation

Referral to cardiac rehabilitation

Annual influenza vaccination

Avoidance of NSAIDs

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B LEVEL 2: NSTEMI/UA PROTOCOL

Aspirin 325mg, chewed, non-enteric coated	STAT Medications	Heparin Bolus 60 units/kg, max. 4000 units Drip x 48 hours or until PCI (aPTT 60-80)
Nitrates Sublingual tab for angina if NOT hypotensive and NO use of PDE-5 inhibitor (i.e., for erectile dysfunction or pHTN) within past 48 hours. Use IV drip or paste for hypertensive patients.		Beta Blocker Metoprolol 5mg IV for hypertension or tachycardia, can repeat q2m x3. Do NOT give if hypotension, pulmonary edema, bradycardia, heart block, asthma/COPD, cocaine, STE in II/III/aVF

Determine Need for / Timing of Cardiac Catheterization

Emergent	Severe refractory chest pain Refractory ventricular arrhythmia	Hemodynamic instability Diffuse ST depressions with ST elevation in aVR	Acute heart failure
Early Invasive (24-48h)	Likely primary coronary event with + troponin, new ST-T wave changes, or ≥2 of the following: • Age ≥ 65 years • Recurrent chest pain • ≥3 CAD risk factors* • Aspirin use in last 7 days * Risk factors include hypertension, hyperlipidemia, diabetes, smoking, and family history of premature CAD		
Conservative	Patients not meeting criteria for emergent or urgent catheterization.		

Determine Need for / Dose of P2Y₁₂ Inhibitor

Patient actively taking P2Y₁₂ inhibitor already Yes No	Yes	Home Ticagrelor: continue 90mg BID Home Prasugrel: continue 10mg daily Home Clopidogrel: switch to ticagrelor, load with 180mg (if no contraindication)
	No	DO NOT DOSE before angiography. In lab, patient can receive pre-PCI cangrelor 30mcg/kg bolus then 4 mcg/kg/min infusion (min. 2 but not >4 hrs). If cangrelor used, give crushed ticagrelor load as soon as appropriate (before, during, or after infusion). Give prasugrel or clopidogrel load only AFTER infusion. If cangrelor not used, give pre-PCI ticagrelor or prasugrel load (crushed) or clopidogrel load. For high-risk patients not receiving cangrelor, GpIIb/IIIa inhibitor bolus may be given.
Patient planned for early invasive strategy Yes No	Yes	
No		Load ticagrelor 180mg or clopidogrel 600mg (if contraindications to ticagrelor)

Medications for Secondary Prevention (see STEMI protocol)**LEVEL 3: POSSIBLE ACS PROTOCOL**

Medications Aspirin 325mg Beta blocker Nitrates as needed for chest pain	Diagnostic Evaluation Serum troponin levels at 0, 4, 8 hours If ruled out for ACS, perform stress test (nuclear or echo) or coronary CT angiogram; outpatient if low risk.
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FOR ALL PATIENTS

Recommend diet, exercise, smoking cessation, annual influenza vaccination, pneumococcal vaccination.
If ACS definite or likely, refer for cardiac rehabilitation and recommend NSAID avoidance.

DISCLAIMER The assigned chest pain level is not a final diagnosis and does not substitute for clinical judgment. After further evaluation, some patients initially assigned an ACS Level will be found to have an alternate or concurrent diagnosis, such as aortic dissection or aneurysm, myopericarditis, or pulmonary emboli. Similarly, all ACS levels can progress or regress to other ACS levels or another serious condition throughout admission.

FIGURE 1.

A pocket card for clinicians with an abbreviated version of our algorithm (A: front; B: back)