2015 Louisville Symposium on Heart Disease in Women:

A case for Medical management

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CASE 1: Coronary Artery Disease

Presentation

- 81 year-old woman presented to the ER with worsening chest pain
  - Similar pain to her usual “angina” but not relieved with nitro
  - Pain started when she was making dinner
  - She rated the pain as 8/10
  - Denies radiation to the arm or jaw

- She worked as a school teacher, lives alone, still drives, dances three times per week, and takes care of her younger sister who has congestive heart failure
- She does not smoke or use alcohol

Past Medical History

- Hypertension
- Hyperlipidemia
- Breast cancer s/p mastectomy 15 years ago
- Left hip replacement 3 years ago

Presentation in the Emergency Room

- HR 72, BP 135/89, Respirations 18, Saturations 100% 2L NC
- Troponin 0.02
- EKG with Sinus Rhythm, 1st Degree AV Block

20-JUL-1932 (82 yr)
Female Caucasian

Room:58515
Loc:231

Vent. rate	76	BPM
PR interval	232	ms
QRS duration	96	ms
QT/QTc	410/461	ms
P-R-T axes	87 -61	24

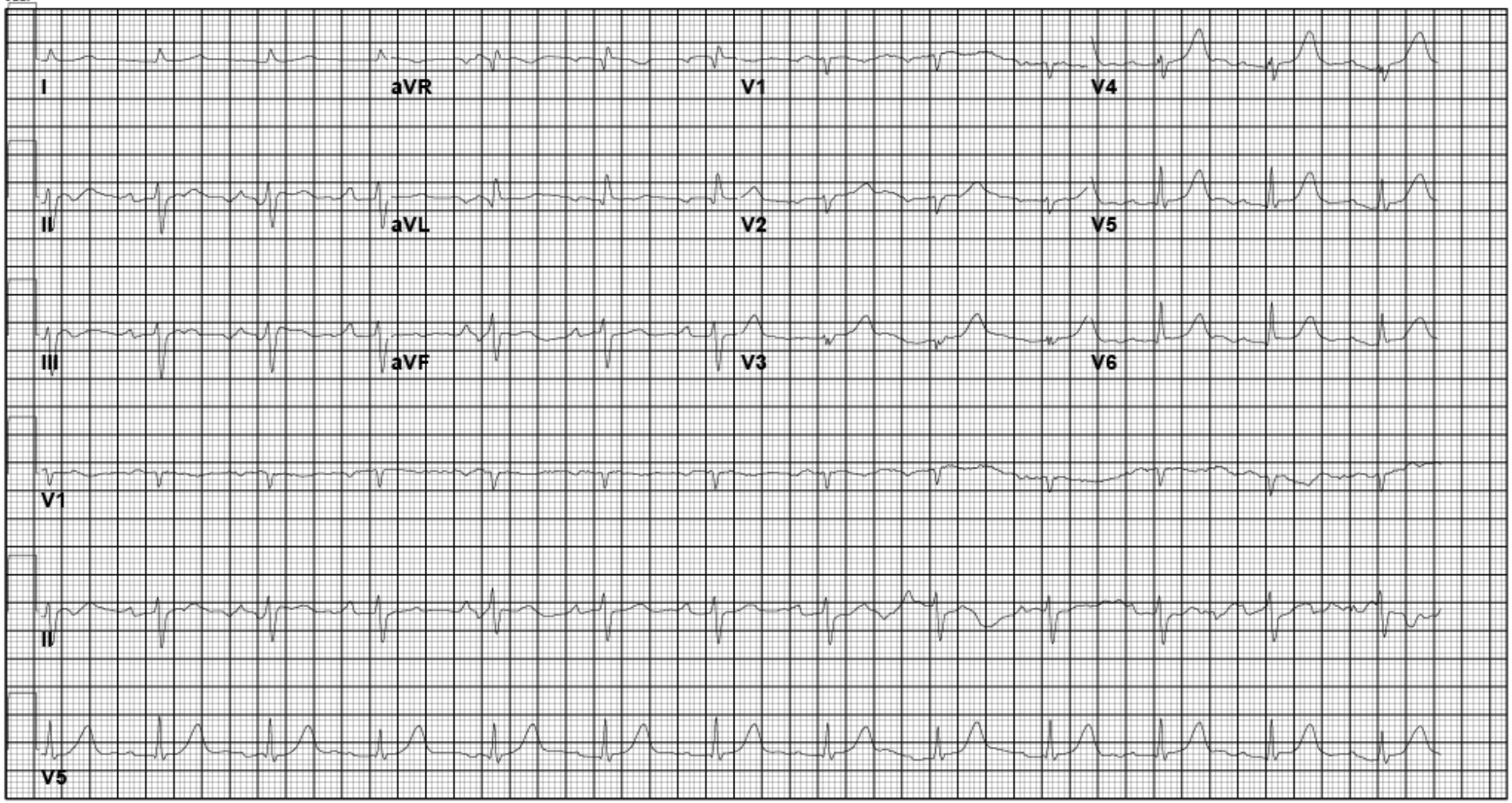
Sinus rhythm with 1st degree A-V block
Left axis deviation
Low voltage QRS
Cannot rule out Anterior infarct , age undetermined
Abnormal ECG
When compared with ECG of 04-FEB-2015 06:14,
PR interval has increased

Technician:MARIAH WALKER
Test ind:

Referred by: NONE PHY

Unconfirmed

JH:



Echocardiogram (Video of ECHO included)

- EF 50%
- Mild to moderate Mitral Regurgitation
- Atrial Fibrillation

Cardiac Catheterization (Images will be included)

- 2 vessel Coronary Artery Disease
  - LM 40%
  - LAD 80%
  - Left CX luminal irregularities
  - RCA proximal 70%, Distal 99%
- Heavily Calcified Aorta

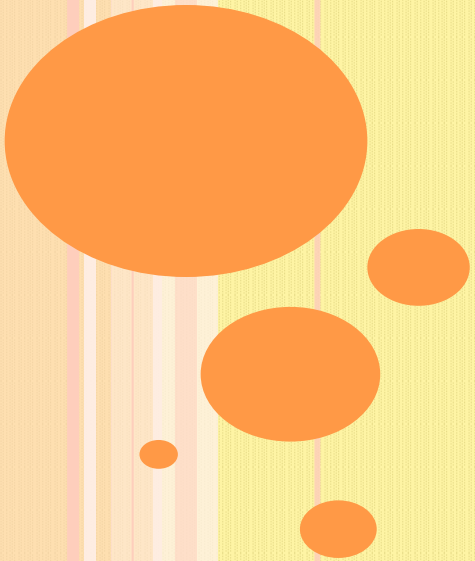
Additional Considerations

- Frailty – Fails only 0 of 4
  - Walk test: 5.3 seconds
  - Katz Activities of Daily Living: 6/6
  - Albumin: 3.8 g/dL
  - Grip strength: 18
    - (Note: cutoff for walk test is >7, normal Alb 3.5, Grip strength cutoff is <17
- Other data
  - Height 165 cm
  - Weight 51 kg
  - BMI 18.7
  - Cr 0.75
  - Hgb 13.9
  - Plt 206
  - HgA1C 6.0

STS Risk

- Risk of Mortality: 2.751 %
- Morbidity of Mortality: 12.176%
- Short Length of Stay: 33.501%
- Stroke 1.332%
- Prolonged Ventilation 7.499%
- DSW Infection 0.122%
- Renal Failure 1.702%
- Reoperation 5.705%

Do women have a different heart?



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The answer is YES!

More atypical sxs
Generally older
Greater delays to presentation
Higher prevalence of HTN
Higher risk of bleeding

Women are less likely to get an EKG early in the ED!

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Approach to diagnosis and Rx of women should be the same but additional diagnoses must be considered even more:

Stress(Takotsubo cardiomyopathy)

Aortic Dissection

Myocarditis

Elderly Population_

60-65% MIs occurs in people >65 years old
33% in people >75 yo
80% of all deaths are related to MI in patients >65 yo

Patients >75 years old_

People >75 years are more likely to have NSTEMI than STEMI
Atypical presentations e.g. syncope, weakness, confusion
Higher in-hospital mortality, 19% vs. 5%
More bleeding and recurrent MI
More CHF with MI(40% vs. 14%)
Beta Blockers, PCI and CABG less utilized although could be beneficial
ACC/AHA recommends same Rx for elderly with some cautions:

- Pts. physical and mental health and life expectancy to be taken into account
- They are more prone to hypotension due to altered pharmackkinetics
- Calculate creatinine clearance in all pts. > 75 years

Goals of Rx_

Relief of ischemic pain
Treat HTN
Treat tachycardia
Risk estimation
Antithrombotic Tx(Anti coagulants and antiplatelets)
Prevent arrhythmias
Long term Rx(statins, anticoagulation for LV thrombus and afib, ACEI)

Treatment in the ED_

Rapid evaluation, preferably within 10 minutes
IV access and quick blood work
Assessment of ABC
Quick and focused H&P
12 lead EKG, repeat in 10 minutes
Crash cart at bedside
Cardiac monitoring
Oxygen to keep sats >90%

Treatment in the ED

ASA 162-325 mg oral or rectally
For patients not going for invasive strategy give Ticagrelor 180 mg and 2B3A agents(eptifibatide or Tirofiban in high risk patients.
Nitrates and MSO4(unless contra indicated)
NTG s/l 0.4 mg q 5 mins x3
MSO4 2-4 mg IV with increments to 2-8 mg q 5-15 mins(CRUSADE showed adverse outcomes possibly by interfering with the anti platelet activity of the P2Y12 blockers)
Atorvastatin 80 mg orally(PROVE IT-TIMI 22 and MIRACL trials)
Beta Blockers within 24 hours. Aetenolol or Metoprolol, IV(Hold in unstable patients;COMMIT and CCS2 trials)
UFH or LMWH:(enoxaparin 1mg/kg q 12 or Fondapainux 2.5 mg s/q every 24 h(Cr. Clearance >30)
Potassium and Magnesium: Maintain the serum potassium concentration above 4.0 meq/L and a serum magnesium concentration above 2.0 meq/L (2.4 mg/dL or 1 mmol/L)

Initial Med Therapy

Patients with unstable angina (UA) or acute non-ST elevation myocardial infarction (NSTEMI) should be treated with an early medical regimen similar to that used in an acute ST elevation MI (STEMI) with one exception: There is no evidence of benefit (and possible harm) from fibrinolysis.

Drug metabolism is more likely to be reduced in elderly patients, particularly with regard to drugs that are excreted by the kidney. Dose adjustment is necessary with glycoprotein IIb/IIIa inhibitors and unfractionated or low molecular weight heparin, but not with aspirin and clopidogrel

Trials of conservative versus early invasive therapy in unstable angina and non-ST elevation myocardial infarction

INTRODUCTION — There is at present no accurate method of predicting which patients with unstable angina (UA) will progress to myocardial infarction (MI) and which patients will stabilize on medical therapy alone. Similarly, it is unclear which patients would benefit from revascularization among patients with a non-ST segment elevation (non-Q wave) MI (NSTEMI), which cannot be distinguished from UA until serum enzymes show evidence of an acute infarction.

Given these uncertainties in predicting the response to therapy and prognosis, two diagnostic approaches have evolved: conservative versus early invasive therapy. The latter involves prompt catheterization of all patients with UA or NSTEMI after the initiation of medical therapy, usually within 4 to 48 hours of admission.

CONSERVATIVE APPROACH —

The conservative strategy begins with rapidly intensifying medical therapy consisting of aspirin, clopidogrel, intravenous heparin or low molecular weight heparin, an intravenous beta blocker, and intravenous nitroglycerin for symptoms. For patients not undergoing percutaneous coronary intervention, the benefit of a glycoprotein IIb/IIIa inhibitor is primarily seen in those at high risk of further cardiac events. This includes patients with elevated levels of troponin I or T patients with a TIMI risk score ≥4, and patients with continuing ischemia or other high-risk features.

Patients who become asymptomatic on this regimen are given several days to "cool off," intravenous medications are discontinued, and, if the patient is still symptom free, exercise testing is performed, most often with some form of myocardial imaging (nuclear or echocardiography). Persistence of symptoms, symptom recurrence, or a positive stress test lead to prompt cardiac catheterization.

CONSERVATIVE APPROACH —

The advantage of the conservative strategy is that it limits the use of cardiac catheterization, which probably reduces the incidence of unnecessary revascularization. The main disadvantage is prolonged length of hospitalization that frequently involves the use of expensive coronary care unit beds and some diagnostic uncertainty associated with noninvasive testing of coronary disease.

CLINICAL TRIALS

The relative merits of these two approaches have been tested in a number of randomized trials, most of which included patients with both unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI). Among patients in the early invasive arm, the following general observations were made in the large FRISC II and TACTICS-TIMI 18 trials:

- *Coronary angiography revealed either normal vessels or no vessel with ≥50 percent stenosis in 13 to 14 percent. In TACTICS-TIMI 18, this was more likely to occur in women than men (17 versus 9 percent).* Possible mechanisms for myocardial ischemia in the absence of significant epicardial coronary disease include rapid clot lysis, vasospasm, and coronary microvascular disease.
- Early revascularization was performed in 61 to 71 percent.
- Among patients undergoing early revascularization, coronary artery bypass graft surgery (CABG) was performed in 33 to 42 percent of patients, most often for three vessel or left main disease.

TIMI IIIB TRIAL

E

FFECTS OF TISSUE PLASMINOGEN ACTIVATOR AND A COMPARISON OF EARLY INVASIVE AND CONSERVATIVE STRATEGIES IN UNSTABLE ANGINA AND NON-Q-WAVE MYOCARDIAL INFARCTION. RESULTS OF THE TIMI IIIB TRIAL. THROMBOLYSIS IN MYOCARDIAL ISCHEMIA. CIRCULATION 1994; 89:1545.

TIMI IIIB was a randomized, double-blinded trial of therapeutic strategies and thrombolysis in patients with UA and NSTEMI. TIMI IIIB randomly assigned 1473 patents seen within 24 hours of an episode of rest angina in a 2x2 factorial design to alteplase or placebo, and to a conservative or early invasive approach. All patients were treated with a standard anti-ischemic regimen including intravenous heparin and aspirin.

- Patients in the conservative arm underwent catheterization only if they developed evidence of recurrent ischemia, including recurrent chest pain with electrocardiographic changes, prolonged ST segment depressions on ambulatory Holter monitoring, or a positive predischarge exercise test.

- Patients assigned to the early invasive strategy underwent cardiac catheterization and angiography within 18 to 48 hours, followed by revascularization by balloon angioplasty or CABG if indicated.

There was no significant difference in the rates of death and nonfatal MI between invasive and conservative therapy at six weeks (7.5 versus 8.2 percent) or one year (10.8 versus 12.2 percent). The frequency of death, MI, or a positive exercise test at six weeks was also similar in the two groups, except for patients over age 65, who had a significant benefit from invasive therapy (8 versus 15 percent).

Patients assigned to the invasive strategy had significant reductions in initial hospital stay (10.2 versus 10.9 days), the rate of rehospitalization at six weeks and at one year (26 versus 33 percent), and the number of antianginal medications required.

The lack of major benefit in TIMI IIIB may have been related to the high crossover to invasive therapy in the conservative group. Of the 733 patients assigned to the conservative approach, revascularization was performed in 58 percent by one year.

VANQWISH TRIAL

Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. N Engl J Med 1998; 338:1785.

The VANQWISH trial randomly assigned 920 patients with an NSTEMI to an early invasive strategy (coronary angiography followed by revascularization as dictated by anatomic findings) 72 hours after the last episode of chest pain or an early conservative strategy with angiography and revascularization only if there were spontaneous ischemia associated with ST segment changes or if a thallium stress test suggested the presence of residual ischemia (e.g. ST segment depression ≥2 mm, redistribution defects in two or more different territories, or one redistribution defect associated with increased lung uptake of thallium).

There was no benefit from the invasive approach, which was only performed in 44 percent of patients in this arm. To the contrary, at the time of hospital discharge, the primary end point of death or nonfatal MI occurred significantly more frequently in the invasive group (7.8 versus 3.2 percent). Both the primary end point and mortality were still increased in the invasive group at one year but not at two years. Subset analysis revealed that the two approaches were associated with similar outcomes except for three groups of patients who clearly did worse with early invasive therapy:

- *Those who received thrombolysis*
- *Those without ST segment depression*
- *Those without a prior MI*

• FRISC II TRIAL

Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Lancet 1999; 354:708.

In the FRISC II trial, 2457 patients with unstable coronary disease were randomly assigned after 48 hours to an invasive (catheterization followed by revascularization within seven days) or noninvasive approach (angiography for a positive exercise test, refractory or severe angina, or MI). All patients were treated with aspirin, beta blockers, and low molecular weight heparin until revascularization in the invasive group or for at least five days in the noninvasive group. At six months, the following outcomes were observed:

● *The rate of death or MI was significantly lower in the invasive group* (9.4 versus 12.1 percent in the noninvasive group); *the difference was primarily due to a lower rate of MI* (7.8 versus 10.1 percent), while the *difference in mortality was not significant at six months* (1.9 versus 2.9 percent) *but was significant at one year* (2.2 versus 3.9 percent). *The invasive approach was also associated with a 50 percent reduction in angina and the need for readmission.*

● The greatest benefit with invasive therapy was seen in high risk patients who had ST depression on the electrocardiogram and/or biochemical markers of myocardial damage. Patients with both findings had a marked reduction in death or MI at one year (13.2 versus 22.1 percent). The benefit was primarily seen in patients with more marked or more widespread ST segment depression, particularly if associated with T wave abnormalities in ≥6 leads.

A possible explanation for the prognostic importance of these findings was their more frequent association with three vessel and left main disease (46 versus 22 percent in those with and without ST depression; and 49 versus 17 percent in patients with both ST depression and elevated troponins compared to those with neither finding).

The reduction in the rate of the combined end point of death or MI was sustained at one year. The differences in each end point considered separately (death or MI) were both independently significant. At five years, there was still a significant reduction in the composite end point (19.9 versus 24.5 percent), *but the benefit was limited to men and the mortality benefit was no longer significant*.

TACTICS-TIMI 18 TRIAL

C
ANNON CP, WEINTRAUB WS, DEMOPOULOS LA, ET AL. COMPARISON OF EARLY INVASIVE AND CONSERVATIVE STRATEGIES IN PATIENTS WITH UNSTABLE CORONARY SYNDROMES TREATED WITH THE GLYCOPROTEIN IIB/IIIA INHIBITOR TIROFIBAN. N ENGL J MED 2001; 344:1879.

The role of an invasive strategy in patients receiving tirofiban was evaluated in the TACTICS-TIMI 18 trial, which randomly assigned 2220 patients presenting with UA or an NSTEMI to an invasive strategy (catheterization within 4 to 48 hours and revascularization with angioplasty or CABG if feasible) or conservative medical therapy; all patients received aspirin, beta blockers, heparin, and tirofiban for 48 to 108 hours.
Normal vessels were more likely to occur in women than men (17 versus 9 percent).

At six months, the primary end point (death, MI, rehospitalization for an acute coronary syndrome [ACS]) was significantly lower with an invasive strategy (15.9 versus 19.4 percent for conservative approach, odds ratio 0.78). This benefit was due to reductions in MI or rehospitalization for an ACS; *there was no mortality benefit from invasive therapy at either 30 days (2.2 versus 1.6 percent) or six months (3.3 versus 3.5 percent).*

The reduction in the primary end point with the invasive approach was seen only in those patients who had an elevation of serum troponin I concentration (≥0.1 ng/mL) upon presentation to the hospital (15 versus 25 percent for a conservative approach), even if the elevation was only minimal (0.1 to 0.4 ng/mL) (4.4 versus 16.5 percent). *No improvement was noted with the invasive approach in those with serum troponin I concentrations below 0.1 ng/mL.*

A substudy from TACTICS-TIMI 18 suggested that an invasive approach may be beneficial in women who have elevations of C-reactive protein (CRP) or brain natriuretic peptide (BNP) as well as troponins.

RITA 3 TRIAL

Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. Lancet 2002; 360:743.

RITA 3 compared early angiography and revascularization with conservative therapy in 1810 patients with a non-ST elevation ACS. All patients were eligible for either approach, and all received optimal medical therapy, including enoxaparin as the antithrombin. Exclusion criteria included new Q waves, CK or CK-MB twice the upper limit of normal at randomization, MI within the previous month, percutaneous coronary intervention (PCI) within the previous year, and CABG at any time. The following findings were noted:

- At four months, an early invasive strategy was associated with a lower rate of the coprimary end point of death, nonfatal MI, or refractory angina (9.6 versus 14.5 percent, odds ratio 0.66, 95% CI 0.51-0.85); *this benefit was entirely due to a reduction in refractory angina (defined as an episode of angina with new ischemic electrocardiographic changes*) and persisted at one year.

- *At one year, there was no difference between the two groups in the coprimary end point of death or nonfatal MI* (7.6 versus 8.3 percent, risk ratio 0.91, 95% CI 0.67-1.25). However, symptoms of angina were improved in the interventional group and there was a significant reduction in MI at one year (9.4 versus 14.1 percent) if the new American College of Cardiology/ European Society of Cardiology definition of MI, which includes elevated serum troponins, was used.

- *In contrast to the equivocal benefit at one year, prespecified follow-up at a median of five years revealed that the interventional group had significant reductions in death or nonfatal MI* (16.6 versus 20.0 percent, odds ratio 0.78, 95% CI 0.61-0.99) and in cardiovascular death or nonfatal MI (12 versus 15 percent, odds ratio 0.74, 95% CI 0.56-0.97). *The benefits were primarily seen in patients at highest risk* (29.2 versus 48.5 percent, odds ratio 0.44, 95% CI 0.25-0.76).

The benefits of an early invasive strategy were similar and of the same magnitude at five-year follow-up in both the RITA 3 and FRISC II trials.

ICTUS TRIAL

de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. N Engl J Med 2005; 353:1095.

The ICTUS trial included 1200 patients with a non-ST elevation ACS who had chest pain, an elevated serum cardiac troponin T, and either electrocardiographic evidence of ischemia or a documented history of coronary disease. The patients were randomly assigned to an early invasive strategy or a selectively invasive strategy in which angiography was performed only for refractory angina, hemodynamic or arrhythmic instability, or significant ischemia on the predischarge exercise stress test. All were treated with aspirin, enoxaparin, and, at the time of PCI, abciximab, and clopidogrel and intensive statin therapy were recommended.

Catheterization (98 versus 53 percent) and revascularization (76 versus 40 percent) were more likely to be performed in the early invasive group during the initial hospitalization. The median time to revascularization was 23 hours with the early invasive strategy and 11.8 days with the selective invasive strategy.

The primary end point was a composite of death, nonfatal MI, or rehospitalization for angina within one year. *The trial failed to show a benefit from an early invasive strategy as illustrated by the following observations:*

- *There was no difference in the incidence of the primary end point* (22.7 versus 21.2 percent with the selective strategy). Although all patients had an elevated serum cardiac troponin T concentration, the presence of additional high-risk features (eg, older age, ST segment depression, or a more marked elevation in serum cardiac troponin T) did not predict a better outcome with an early invasive strategy in contrast to other studies' trials above.

- *There was a significant increase in MI with an early invasive strategy (mostly periprocedural*); although a less stringent CK-MB elevation was required, the increase in MI persisted when using the definitions from FRISC II or TACTICS-TIMI 18.

- Rehospitalization was significantly less common with an early invasive strategy (7.4 versus 10.9 percent).

- *After five years of follow-up, the rates of death and MI remained similar in the two groups of patients*.

Effect in women —

A separate issue is whether the benefit of an early invasive approach in appropriately selected patients applies to women. In FRISC II and RITA 3, the favorable effect of early invasive therapy was seen only in men and, in FRISC II, this difference was persistent at five years. However, three other observations found that women benefit from an early invasive therapy:

- In TACTICS-TIMI 18, the benefit of early invasive therapy was equivalent in women and men overall and in patients with elevated troponin T.

- A prospective study evaluated 1450 consecutive patients (29 percent women) with a non-ST elevation ACS treated with very early revascularization primarily by PCI with stenting. Women had better outcomes, as the primary end point, death, or nonfatal MI at 20 months occurred significantly less often in women (adjusted hazard ratio 0.51 compared to men). This may have been due at least in part to lower baseline risk, since women were less likely to have had a previous MI or three vessel disease (29 versus 42 percent).

- A post-hoc analysis from the CURE trial of clopidogrel therapy in non-ST elevation ACS found that women, compared to men, were less likely to undergo an invasive strategy and were more likely to develop refractory ischemia and to be rehospitalized for chest pain (16.6 versus 13.9 percent). This increase in risk was most prominent in women at high risk (as determined from the TIMI risk score).

EFFECT IN WOMEN —

The factors responsible for these conflicting findings are not well understood. *A possible contributing factor is that women in FRISC II and RITA 3 were at lower risk; in such patients, the benefit from revascularization would be less and the procedural risk might be a more important determinant of outcome*. Consistent with this hypothesis are the following observations:

- *In TACTICS-TIMI 18, women with low TIMI risk scores (0 to 2) or no elevation in serum troponin T had a nonsignificant trend toward a worse outcome with early invasive therapy; men with these features had no benefit but no suggestion of harm. Compared to men, women who underwent PCI had a significantly higher risk of major bleeding (8.3 versus 2.9 percent).*

- *In FRISC II, the excess risk in women was due to a high mortality rate with CABG.* In contrast, the peri-CABG mortality was not so high in TACTICS-TIMI 18 and the above observational study, which contributed to the beneficial effect of early intervention. Any increase in CABG risk in women is largely related to comorbid conditions.

A related issue is that the optimal approach to accurate assessment of risk in women may differ from that in men. This was suggested by an analysis from TACTICS-TIMI 18, which found that women were more likely to have elevations of CRP and BNP, and less likely to have elevations of troponins and CK-MB, than men, despite similar levels of risk. When a multimarker approach incorporating CRP, BNP, and troponins was used, *women with any positive marker benefited from an invasive strategy, while those with no positive markers benefited from a conservative strategy*.

Effect in the elderly —

Selected elderly patients may derive a greater benefit from an invasive strategy than younger patients, although with an increased risk of bleeding complications.

This was suggested by an analysis from TACTICS-TIMI 18. Of the 2220 trial participants, 962 (43 percent) were ≥65 years of age. Elderly patients were more likely to have a TIMI risk score ≥3 than younger patients (91 versus 63 percent). In an analysis by age, the following findings were noted:

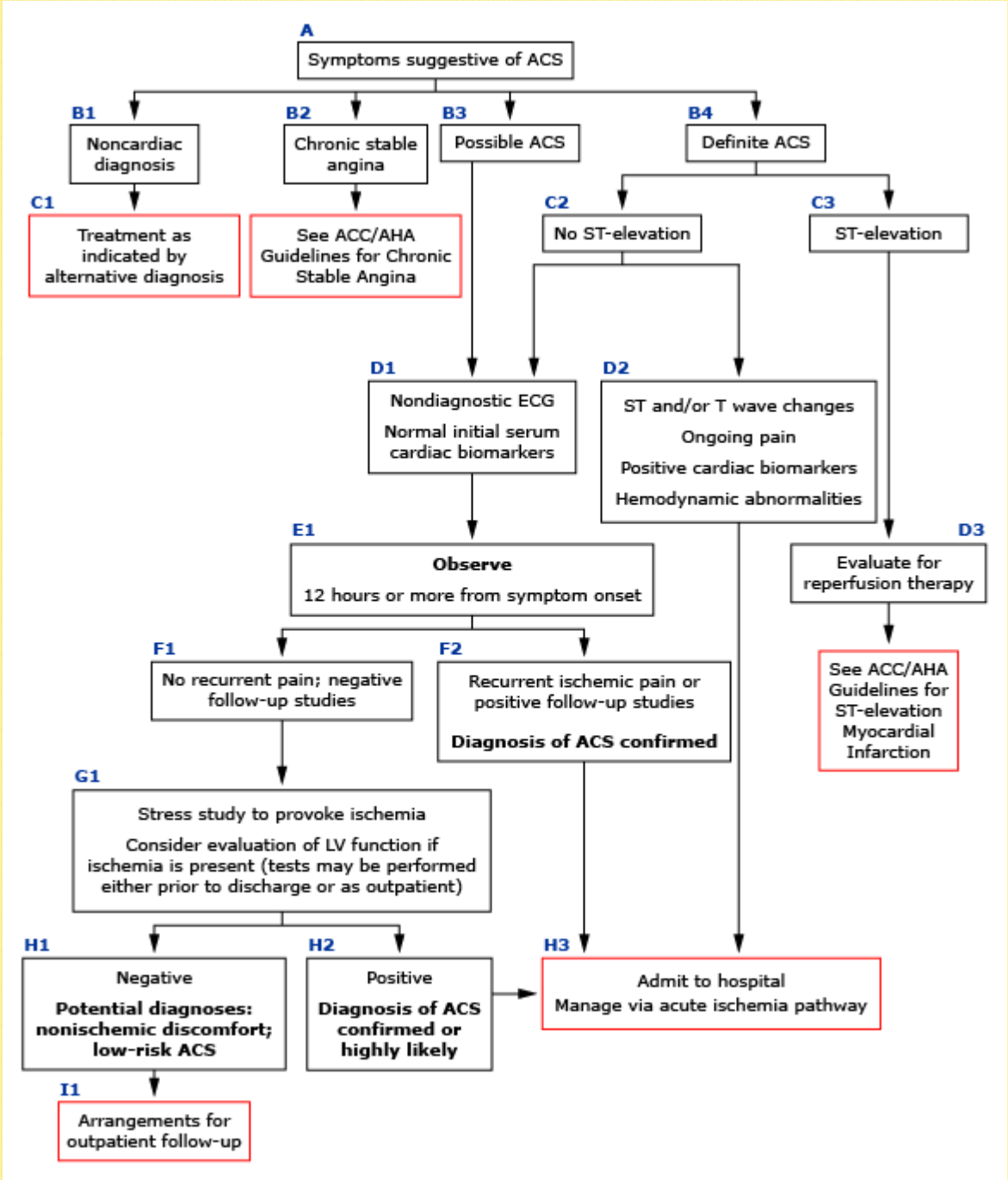
- Among patients ≥65 years of age, an early invasive strategy compared to a conservative strategy significantly reduced the incidence of death or MI at 30 days (5.7 versus 9.8 percent) and six months (8.8 versus 13.6 percent). In contrast, the benefit of an invasive strategy was not significant for younger patients at 30 days (3.9 versus 4.9 percent) or six months (6.1 versus 6.5 percent).

- Among patients >75 years of age, the advantage of an early invasive strategy in reducing the incidence of death or MI at six months was even more marked (10.8 versus 21.6 percent).

- *Among patients >75 years of age, an early invasive strategy significantly increased the frequency of major bleeding during the index hospitalization (16.6 versus 6.5 percent).*

One limitation of this analysis is that the study excluded patients with major comorbidities, including a history of stroke, renal dysfunction, bleeding disorder, or clinically important systemic disease. Patients with severe heart failure, cardiogenic shock, or secondary angina were also excluded. As a result, the findings may not be applicable to some higher-risk elderly patients.

Algorithm


A
Symptoms suggestive of ACS
B1
Noncardiac diagnosis
B2
Chronic stable angina
B3
Possible ACS
B4
Definite ACS
C1
Treatment as indicated by alternative diagnosis
See ACC/AHA Guidelines for Chronic Stable Angina
C2
No ST-elevation
C3
ST-elevation
D1
Nondiagnostic ECG
Normal initial serum cardiac biomarkers
D2
ST and/or T wave changes
Ongoing pain
Positive cardiac biomarkers
Hemodynamic abnormalities
E1
Observe
12 hours or more from symptom onset
D3
Evaluate for reperfusion therapy
F1
No recurrent pain; negative follow-up studies
F2
Recurrent ischemic pain or positive follow-up studies
Diagnosis of ACS confirmed
See ACC/AHA Guidelines for ST-elevation Myocardial Infarction
G1
Stress study to provoke ischemia
Consider evaluation of LV function if ischemia is present (tests may be performed either prior to discharge or as outpatient)
H1
Negative
Potential diagnoses: nonischemic discomfort; low-risk ACS
H2
Positive
Diagnosis of ACS confirmed or highly likely
H3
Admit to hospital
Manage via acute ischemia pathway
I1
Arrangements for outpatient follow-up

Anti-ischemic and analgesic therapy

Oxygen —Recommend supplemental oxygen for patients with an arterial saturation less than 90 percent, patients in respiratory distress, or those with other high risk features for hypoxemia . There are no convincing data to suggest its use in normoxic patients and there is a remote risk of inducing hyperoxia and vasoconstriction in that patient population .

The role of supplemental oxygen in patients without hypoxia has not been well studied. A 2013 Cochrane review evaluated four trials of 430 patients with presumed MI who were randomly assigned to supplemental oxygen or room air. Enrolled patients were either hypoxic or normoxic. The study found no significant difference in mortality (pooled relative risk 2.05, 95% CI 0.75-5.58 in an intention-to-treat analysis and 2.11, 95% CI 0.78-5.68 among those with confirmed MI). No subgroup analysis was performed on those with normoxia.

Anti-ischemic and analgesic therapy

Nitroglycerin — Sublingual nitroglycerin is administered to patients presenting with ischemic type chest pain, followed by intravenous nitroglycerin in patients with persistent pain after three sublingual nitroglycerin tablets, hypertension, or heart failure.

Nitrates must be used with caution or avoided in settings in which hypotension is likely or could result in serious hemodynamic decompensation, such as right ventricular infarction or severe aortic stenosis. In addition, nitrates are contraindicated in patients who have taken a phosphodiesterase inhibitor for erectile dysfunction within the previous 24 hours.

Anti-ischemic and analgesic therapy

Morphine — For patients with pain due to myocardial ischemia, morphine may be given for the relief of chest pain or anxiety. We give intravenous morphine sulfate at an initial dose of 2 to 4 mg, with increments of 2 to 8 mg repeated at 5- to 15-minute intervals.

However, we usually reserve its use for patients with an unacceptable level of pain due to observational evidence of worse outcomes in patients receiving the drug. In a study of 57,039 patients enrolled in the CRUSADE Initiative, a nonrandomized, retrospective observational registry of patients with non-ST elevation ACS, those treated with morphine (29.8 percent) had a higher adjusted risk of death than those not (odds ratio 1.48, 95% CI 1.33-1.64) [20].

While the mechanism(s) by which morphine might be associated with decreased survival is not known, at least two studies have raised the possibility that it acts by interfering with the antiplatelet effect of the $P2Y_{12}$ receptor blockers:

- In a study of 24 healthy subjects who received a loading dose of 600 mg of clopidogrel and either 5 mg of intravenous morphine or placebo, morphine significantly delayed clopidogrel resorption and reduced the area under the curve levels of its active metabolite by 52 percent [21]. Platelet inhibition, as measured by multiple tests, was less pronounced in those given morphine.
- In a study of 50 patients with STEMI undergoing primary percutaneous coronary intervention who were randomly assigned to either prasugrel or ticagrelor, morphine was an independent predictor of high residual platelet reactivity at two hours (odds ratio 5.29, 95% CI 1.44-19.49) [22].

After Stabilization

The following interventions are beneficial in the majority of patients with NSTEMI or unstable angina who have undergone early interventions:

- Beta blockers
- Statins
- Aggressive management of recurrent myocardial ischemia or reinfarction
- Angiotensin converting enzyme inhibitors in patients with diabetes, heart failure, a left ventricular ejection fraction <40 percent, and hypertension.
- Long-term risk stratification with assessment of left ventricular function and either diagnostic coronary arteriography or pre-discharge stress testing.

The major modifiable risk factors for coronary artery disease (smoking, hypertension, diabetes, and dyslipidemia) need to be evaluated and corrected as necessary. A long-term plan for their control needs to be discussed with the patient; referral to an outpatient cardiac rehabilitation program is useful for this purpose.

Risk Factor Modification

Risk factor modification using behavioral/lifestyle changes such as dietary modification, increase in activity level, and smoking cessation are associated with better outcomes after acute coronary syndromes (ACS). Patient education should be given at the time of discharge and referral to a cardiac rehabilitation program should be made.

Hypertension — Hypertension should be treated in patients who have had a non-ST elevation ACS.

Glycemic control

Smoking cessation — Smoking cessation reduces the risk of recurrent coronary events. The 2014 American College of Cardiology/American Heart Association guideline on the management of patients with non-ST elevation ACS recommended education about smoking cessation during hospitalization and referral to a smoking cessation program or outpatient cardiac rehabilitation program where nicotine replacement therapy and bupropion are available . The guidelines recommended against the initiation of nicotine replacement during hospitalization, in part due to concerns about its effect on blood pressure and heart rate. However, the issue of whether nicotine replacement can be started during hospitalization has not been well studied and there is some evidence of lack of harm with transdermal nicotine replacement. We suggest that cautious initiation of nicotine replacement can be considered during hospitalization for those patients with ACS in whom the benefits appear to outweigh the risks.

Risk Factor Modification

Diet — Good dietary habits and use of a prudent diet can reduce the risk of coronary heart disease.

Exercise —An increase in activity level in patients with established cardiovascular disease is associated with better outcomes.

Stress management — Psychosocial stress factors are associated with a poor long-term prognosis, and reducing emotional stress may improve outcomes.

Cardiac rehabilitation — Multifactorial cardiac rehabilitation can produce significant long-term reductions in both total and cardiovascular mortality.

PROGNOSIS

Patients presenting with a non-ST elevation myocardial infarction have a lower in-hospital mortality than those with an ST elevation myocardial infarction, but a similar or perhaps worse long-term outcome.

PREPARING FOR DISCHARGE

The optimal duration of hospitalization for patients with non-ST elevation acute coronary syndrome (ACS) who have been revascularized with percutaneous coronary intervention (PCI) has not been defined. The employment of early angiography and revascularization has led to shorter hospitalizations for patients and the use of stenting and potent antiplatelet therapy in the periprocedural period has led to a reduction in recurrent ischemic events. On the other hand, potent antiplatelet and antithrombotic therapies are associated with an increased risk of major bleeding, which may complicate and lengthen hospitalization.

Prior to discharge, the patient should undergo risk stratification. Other components of predischarge planning include counseling about changes in lifestyle and appropriate medical therapy to reduce the risk for further ischemic episodes.

PREPARING FOR DISCHARGE

Ambulation — The first major step in the transition from acute care to hospital discharge in patients with non-ST elevation ACS is ambulation. The proper timing of ambulation is patient and institution dependent and requires balancing the risk of bleeding after coronary intervention with the deleterious effects of deconditioning that can be induced by prolonged bed rest. We suggest the following approach:

Among patients who have not undergone revascularization, progressive ambulation can be started when the patient is hemodynamically stable without attendant complications for three to six hours after the peak of the cardiac marker rise.

Chronic anticoagulation:

Long-term risk stratification — Patients with a non-ST elevation ACS should undergo further risk assessment prior to discharge.

PREPARING FOR DISCHARGE

Stress testing — Predischarge stress testing to detect residual ischemia is generally **not** performed in patients who have undergone PCI or coronary artery bypass graft surgery and have been **fully** revascularized (eg, single vessel disease and successful PCI). Such patients often undergo exercise testing a few weeks or more after discharge as part of a cardiac rehabilitation program or for activity counseling.

In contrast, patients who have undergone partial revascularization or no revascularization are candidates for predischarge low level stress testing, usually with exercise.

For patients with symptomatic ischemia on post-infarct stress testing, the following approach is suggested:

- Coronary angiography followed by revascularization if appropriate is performed in patients with noninvasive evidence suggesting a moderate to large amount of myocardium at risk. Examples include ischemia during stage I or II of the Bruce protocol, a hypotensive blood pressure response or symptoms of pulmonary congestion, more than 2 mm of ST segment depression, or imaging studies suggesting involvement of either a large portion of the anterior wall or showing multiple areas of ischemia.
- Patients with only mild ischemia can be continued on medical therapy alone, but patient preference may be important.

PREPARING FOR DISCHARGE

Evaluation of LV function — Assessment of resting left ventricular function is an important part of risk stratification in patients with a non-ST elevation ACS [1]. Patients with left ventricular systolic dysfunction have increased mortality at long-term follow-up and more than a 50 percent probability of having multivessel coronary disease [17].

In the absence of a specific indication (eg, heart failure or suspected mechanical complication), the left ventricular ejection fraction (LVEF) is usually measured before discharge.

Multiple imaging techniques for assessing left ventricular function are available and each has equivalent prognostic value in the post-MI patient. In general, echocardiography should be used for routine assessment of LVEF after a non-ST elevation ACS.

PREPARING FOR DISCHARGE

Pharmacologic therapy — In most cases, the inpatient anti-ischemic medical regimen used during hospitalization (other than intravenous nitroglycerin) should be continued after discharge and the antiplatelet/ anticoagulant medications should be changed to an outpatient regimen. The goals for continued medical therapy after discharge relate to potential prognostic benefits; treatment of major risk factors such as hypertension, smoking, hyperlipidemia, and diabetes mellitus; and control of ischemic symptoms if they recur.

Appropriate use of antiplatelet agents, beta blockers, lipid-lowering drugs, and, in selected patients, angiotensin converting enzyme (ACE) inhibitors may reduce six-month mortality by as much as 90 percent compared with patients who receive no appropriate therapy.

PREPARING FOR DISCHARGE

Antiplatelet therapy — In the absence of an absolute contraindication, aspirin is recommended indefinitely in all patients who have had an ACS. Thienopyridine therapy is indicated in all patients after NSTEMI for at least one month and up to a year, irrespective of whether revascularization or stenting occurs.

Nitrates — Long-term nitrate therapy is useful for the treatment of recurrent ischemia or (on occasion) heart failure as long as it does not preclude adequate therapy with agents proven to reduce mortality, such as beta blockers or ACE inhibitors.

All ACS patients should be given a prescription for sublingual or spray nitroglycerin and instructed in its use prior to discharge.

Vaccination — We recommend influenza and pneumococcal vaccination as part of a comprehensive secondary prevention program in adults with coronary and other atherosclerotic vascular diseases. If indicated, we suggest vaccination for these during hospitalization for an ACS. Ventricular arrhythmias —

PREPARING FOR DISCHARGE

Return to activities — Patients should be counseled about return to prior activities before discharge. The majority of patients who remain asymptomatic can probably return to prior nonphysical activities, including work, safely within two weeks, although few data are available.

- Daily physical activity, such as walking, should be encouraged; the intensity of physical activity can be increased according to the cardiac rehabilitation plan.
- When sexual activity can be safely resumed is dependent upon a number of factors, including whether or not the patient has been revascularized and, if not, if there is ischemia on stress testing). An important caveat is that phosphodiesterase-5 inhibitors (sildenafil, vardenafil, and tadalafil) cannot be taken within 24 to 48 hours of a nitrate.
- Driving can begin a week after discharge if the patient is judged to be in compliance with individual state laws
- Since commercial aircrafts are pressurized to 7500 to 8000 feet, air travel should be undertaken only by stable patients (without a fear of flying) within the first two weeks and then only as long as they travel with companions, carry sublingual nitroglycerin, and request airport transportation to avoid rushing.

For patients with a more complicated course, return to usual activities should be delayed by two to three weeks.

DISCHARGE MEDICATIONS

Appropriate medical therapy can reduce the risk of subsequent ischemic events and mortality in patients who have had an acute myocardial infarction (MI). In addition to the interventions discussed in this section, beta blockers, statins, nitrates, and calcium channel blockers may be useful long term.

DISCHARGE MEDICATIONS

ACE inhibitors — Angiotensin converting enzyme (ACE) inhibitors are beneficial after acute ST elevation MI, particularly in patients with an anterior infarct or reduced left ventricular function. There is less information concerning efficacy in non-ST elevation myocardial infarction (NSTEMI) and even less in unstable angina . They are also of benefit in MI patients with hypertension, diabetes, or stable chronic kidney disease . The 2014 American College of Cardiology/American Heart Association guideline on the management of patients with non-ST elevation acute coronary syndrome (NSTE-ACS) recommends ACE inhibitors in these patients with diabetes, a left ventricular ejection fraction (LVEF) <40 percent, hypertension, or stable chronic kidney disease . The guideline also suggests that there may be benefit in all patients after an MI. We recommend that ACE inhibitors be started in-hospital but not necessarily in the first 24 hours as recommended by the guideline.

Caution is required to avoid causing hypotension in the first few hours after the infarction. Concern about concurrent aspirin therapy attenuating the effect of an ACE inhibitor appears largely unwarranted .

DISCHARGE MEDICATIONS

Angiotensin II receptor blockers — An angiotensin II receptor blocker (ARB) is an alternative for patients unable to tolerate an ACE inhibitor (usually due to cough).

An ARB in addition to an ACE inhibitor in the immediate post-MI setting has not been shown to lead to clear benefit.

Aldosterone antagonists — The 2014 ACC/AHA guideline on the management of patients with NSTE-ACS recommends a mineralocorticoid receptor antagonist to all NSTEMI patients who are receiving a therapeutic dose of an ACE inhibitor, have an LVEF ≤40 percent, have heart failure or diabetes mellitus, and are free of significant renal dysfunction or hyperkalemia.

Therapy should be begun before discharge, since a mortality benefit is seen within 30 days.