

Defining the optimal pharmacotherapy of non-ST-segment elevation (NSTE) acute coronary syndromes (ACS): a rapidly moving target

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Acute coronary syndromes (ACS) represent a spectrum of disease, including unstable angina, non ST-elevation myocardial infarction, and ST-elevation myocardial infarction. In patients with cardiovascular disease, ACS represents the most common diagnosis for hospital admission, accounting for nearly 1.5 million hospital admissions in 1999. Similarly, although improvements in medical therapy have resulted in a dramatic decline in mortality from acute myocardial infarction (MI) over the last four decades, MI remains the most common cause of in-hospital death in industrialized nations.

The approach to managing patients with acute coronary syndromes has evolved dramatically over the past decade and, in many respects, represents a rapidly moving target in light of recent advances in pharmacotherapy and catheter-based revascularization. A number of recently-published studies, including the TACTICS Trial [1], the ADMIRAL Trial [2], and the TARGET Trial[3], provide novel information about the relative merits of pharmacologic therapy and invasive intervention. A common theme from these studies is that there is a growing consensus among cardiologists that *combination* therapy with these two modalities may actually provide the best clinical outcomes in ACS patients. *Curr Opin Cardiol* 2001, 16:370–374 © 2001 Lippincott Williams & Wilkins, Inc.

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Unstable angina and non ST-elevation myocardial infarction

Unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI) are two components of the acute coronary syndromes (ACS). These syndromes are currently considered to be conditions with similar pathogenesis and clinical presentations that differ only in severity[4]. The most common cause is thrombus formation secondary to plaque disruption [5]. The presence of markers of cardiac necrosis, such as the I and T subunits of the troponin complex (TnI, TnT) or the MB isoenzyme of creatine kinase (CK-MB), establishes a diagnosis of NSTEMI[4]. Most patients with NSTEMI do not evolve Q waves and are subsequently diagnosed as having non-Q-wave MI (NQMI).

In the treatment of patients with ACS, particularly those with NSTEMI, a fundamental question underlies the debate regarding invasive versus conservative strategies. The American College of Cardiology/American Heart Association Task Force on Practice Guidelines has published recommendations regarding diagnosis and treatment of patients with known or suspected UA/NSTEMI [4]. The acute ischemia pathway presented in these guidelines encompasses both an early invasive strategy and an early conservative strategy. However, the continued technical evolution of stents, and widespread availability and success of catheter-based revascularization has prompted many clinicians to question the need for noninvasive risk stratification of any kind as we enter the third millennium.

The present overview suggests a balanced approach for patients with non-ST segment elevation ACS: an aggressive (“early invasive”) approach for patients with increased risk as manifested by persistent pain, or electrocardiographic or enzymatic changes; and an “ischemia-guided” strategy for patients who do not manifest these signs of increased risk. A “conservative strategy” is defined as including intensive antiplatelet, anti-thrombotic, and anti-ischemic therapy combined with careful clinical assessment and provocative testing (*eg*, myocardial perfusion imaging with use of treadmill exercise or pharmacologic vasodilator stress testing). In these patients, selective catheterization and, if necessary, revascularization are performed only if spontaneous angina occurs or there is objective evidence of stress-induced myocardial isch-

emia. Randomized clinical trials focused on the various treatment approaches will be reviewed.

Studies comparing invasive versus conservative strategies in UA/NSTEMI

TIMI III B (enrollment 1989–1992)

No significant differences in outcome between the invasive and conservative strategies for treating patients with unstable angina and non-Q-wave MI were shown in the Thrombolysis in Myocardial Infarction (TIMI III B) trial, which was published in 1994 [6]. This trial included 1473 patients who were considered to have unstable angina or non-Q-wave MI. Study subjects were randomized using a 2x2 factorial design to compare the following:

Tissue plasminogen activator (TPA) versus placebo as initial therapy

An early invasive strategy (cardiac catheterization, left ventricular angiography, and coronary arteriography 18 to 48 hours after randomization) versus an early conservative strategy (catheterization and angiography only after failure of initial therapy)

The composite end point for the comparison of the two strategies of death, MI, or an unsatisfactory exercise stress test at 6 weeks occurred in 18.1% of patients assigned to the early strategy and 16.2% of those assigned to the invasive strategy. Although the early invasive strategy indicated more rapid relief of angina than the conservative approach, by 6 weeks, anginal status was similar between patients, as was the major clinical outcome of death or MI.

VANQWISH (enrollment 1993–1995)

In the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial [7], which was also conducted during the early 1990s, an unexpected difference was found in outcomes between the two approaches. The study compared early and late clinical outcomes (death or recurrent MI) in 462 patients randomly assigned to the early invasive strategy, with 458 patients who received the early conservative treatment. Patients treated with the routine, early invasive strategy (heart catheterization followed by myocardial revascularization) had significantly worse clinical outcomes during the first year of follow-up than those treated with a conservative strategy (intervention guided by rigorous ischemia management, noninvasive stress testing, and medical therapy). VANQWISH is the largest trial of its kind to test the efficacy of long-term management strategies in patients recovering from non-Q-wave MI. The number of patients who had one of the components of the primary end point was significantly higher in the invasive-strategy group at hospital discharge (36 vs 15 events, $P =$

0.004), at 1 month (48 versus 26 events, $P = 0.012$), and at 1 year (111 versus 85 events, $P = 0.05$).

An overlooked feature of the VANQWISH trial is that patients who remained in the conservative treatment arm and did not cross over to cardiac catheterization in the 44 months of follow-up (52% of this arm) had a remarkably low cardiac event rate; 2 patients (1%) died, and 3 patients (1%) experienced a clinical event at 30-day follow-up review. This low rate of events occurred in patients with high clinical comorbidity and an almost 80% incidence of triple-vessel and left main coronary disease.

An interaction analysis to determine whether any subset of patients benefited with the invasive strategy revealed no evidence of an interaction that supported improved outcomes in the patients with the invasive strategy [4]. In contrast, the ischemia-guided strategy benefited 4 of 10 pre-specified subsets of patients (patients who underwent thrombolysis, those with no prior infarction, those with no ST-segment depression, and those greater than or equal to 60 years).

Whether the results of TIMI III B and VANQWISH are really relevant to the contemporary practice or management of patients with non-ST segment elevation MI remains unclear. Both trials were conducted before a number of important advances that have occurred during the past 2 to 3 years. There has been the advent of stents and the newer catheter-based techniques. The use of glycoprotein IIb/IIIa receptor antagonists has expanded rapidly, based on a number of secondary prevention trials [8–11]. The benefits of low-molecular-weight heparins, particularly enoxaparin, have been convincingly demonstrated [12–14]. Evidence from the Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) trial revealed that hirudin (lepirudin), a direct thrombin inhibitor, may have benefit [15]. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) [16] and the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) [17] trials showed that clopidogrel, a thienopyridine derivative similar to ticlopidine, to be an important adjunctive treatment in the treatment of patients with acute coronary syndromes.

However, the TIMI III B [6] and VANQWISH [7] trials are relevant to risk stratification, because they reveal that both high- and low-risk subsets can be identified. In the VANQWISH trial, only 9% of patients were excluded during the first 48 to 72 hours for symptoms of refractory angina, persistent ischemia, heart failure, or significant ventricular tachyarrhythmia or fibrillation. As discussed, the 30-day event rate of death and MI was remarkably low (1%) with the conservative strategy, despite the high prevalence of clinical comorbidity and angiographic morbidity.

FRISC II (enrollment 1996 to 1998)

The Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) invasive trial [18] showed for the first time, in a subset of patients with unstable angina and non-Q wave infarction, a significant event rate reduction favoring the invasive over the non-invasive strategy at 6 months. In the trial, 2457 patients in 58 Scandinavian hospitals were assigned an early invasive (1222 patients) or noninvasive treatment strategy (1235 patients) with placebo-controlled long-term low-molecular-weight heparin (dalteparin) for 3 months. In the invasive group, 96% of patients received angiography within 7 days; of those, 71% underwent revascularization within 10 days. For the noninvasive group, 10% received angiography within 7 days; of those, 9% went on to undergo revascularization procedures. At 6 months, the rate of death, MI, or both, was 9.4% in the invasive group (113 of 1207 patients) and 12.1% in the noninvasive group (148 of 1226 patients) (risk ratio, 0.78; 95% CI, 0.62 to 0.98; $P = 0.031$).

The results favoring the invasive strategy were not uniformly shown among patient subsets in FRISC II, however. In a substudy examining the influence of troponin levels in study patients, plasma samples for central analyses of troponin T levels were available in 2230 patients; of those, 42% had troponin-negative levels ($<0.1 \mu\text{g/L}$) [19]. The 6-month rate of death or MI was 8.3% in patients assigned to an invasive strategy versus 10.3% in those assigned to a conservative strategy. Although there was a trend toward improvement with the invasive strategy, the difference between groups was not statistically significant.

Similarly, in the evaluation of patients who had ST segment deviations on the admission electrocardiogram (ECG) in FRISC II, 418 patients had no demonstrable ST-T wave changes [20]. The relative risk of an unfavorable outcome—death or MI at 6 months—was actually slightly higher for patients in the invasive group. No significant benefit was shown with the invasive strategy in patients who had isolated T-wave inversion only. The early invasive strategy was not shown to be beneficial in fully 52% of patients who had either no electrocardiographic changes or T wave inversion only. The true benefit of early invasive treatment, when evaluated by electrocardiography, was derived solely from the subset of patients with ST segment depression MI.

In summary, patients who were troponin-negative and those who had no ST-T wave changes or only isolated T wave inversions ($> 50\%$ of all patients) did not benefit from an invasive strategy. There are only observational data and registry data available to show a reduction of death or MI, or refractory ischemia, in NSTEMI patients who underwent PCI within 24 hours of presentation. Thus, much remains to be proven with regard to the

overall benefit of applying an early aggressive invasive strategy in such patients.

TACTICS-TIMI 18 (enrollment 1997–1999)

The Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI 18) trial included 2220 patients with UA/NSTEMI [1]. Inclusion criteria were an accelerating pattern, prolonged or recurrent anginal pain at rest or minimal effort within the previous 24 hours, plus ischemia, electrocardiographic changes, elevated cardiac markers, or a history of prior CAD. Study subjects were immediately treated with aspirin, heparin, and the glycoprotein IIb/IIIa inhibitor tirofiban (administered for 48 to 108 hours). Patients were then randomized to one of the following two groups: catheterization and subsequent PCI/CABG within 4 to 48 hours or conservative strategy with catheterization performed only if there was objective evidence of recurrent ischemia or a positive exercise stress test.

At 6 months, the primary outcome (death, MI, and rehospitalization for acute coronary syndromes) occurred in 15.9% of the invasive-strategy group and 19.4% of the conservative-strategy group (odds ratio, 0.78; $P = 0.025$). The rate of death or MI was also significantly lower in the invasive-strategy group (7.3% versus 9.5%; odds ratio, 0.74; $P < 0.0496$).

Subgroup analysis according to TnT status on admission revealed that the difference between the two strategies was largely due to a reduction in the primary outcome among TnT-positive patients. In this subgroup, the invasive strategy was associated with a primary outcome rate of 14.3% compared with 24.2% for the conservative strategy (odds ratio, 0.52; $P < 0.001$). The two strategies were comparable in their effects on the primary outcome in TnT-negative patients. Patients with an intermediate or high TIMI UA risk score also benefited from an invasive over a conservative strategy. In patients with a low TIMI UA score, the two strategies were comparable.

Thus, compared with earlier trials [6,7], two notable factors that may explain the observed benefits in the “early invasive” strategy of TACTICS were the early use of an intravenous GPIIb/IIIa inhibitor with heparin and anti-ischemic therapy in all patients (so-called “*upstream therapy*”) and the use of intracoronary stents. Neither modality was tested in the TIMI-IIIB and VANQWISH Trials, because enrollment was completed before 1995. The benefit of GPIIb/IIIa inhibitors has been incontrovertibly tested over the last decade, both in unstable angina patients before intervention and during PCI. Similarly, stenting has emerged as the preferred PCI approach, with less repeat target vessel revascularization and angiographic restenosis, and with a synergistic im-

provement in clinical outcomes when combined with GPIIb/IIIa inhibition.

The potential benefit of this combined pharmacologic and interventional approach is most apparent in the extremely low (4.7%) absolute rate of death or MI at 30 days in the TACTICS “early invasive” group which, as the authors note, represents the lowest rate in any ACS trial reported to date. Moreover, compared with TIMI-IIIb, VANQWISH, and FRISC-II Trials (each of which showed an increased MI and death/MI rate within the first 7 days in the “early invasive” group), there was no early hazard observed with PCI in the TACTICS patients. One possible explanation for this difference is that tirofiban mitigated the consequences of incomplete platelet inhibition that led to excess in-hospital events observed in earlier studies.

Proposed classification of risk

High-risk patients

High-risk ACS patients who clearly warrant catheterization and early revascularization include those with rest angina with ST segment depression and/or elevated serum concentrations of cardiac markers of ischemic injury (CK-MB, troponin, myoglobin) (Fig. 1). Those who have rest angina with hemodynamic instability, heart failure, or an ejection fraction less than 40%, and those with rest

angina and prior revascularization (PCI or coronary artery bypass grafting) should be sent to the catheterization laboratory and undergo revascularization as indicated.

Intermediate-risk patients

Patients at an intermediate level of risk for future cardiac events appear to benefit from catheterization and early revascularization. This subset includes patients with Canadian Cardiovascular Society (CCS) class III or IV angina within the past 2 weeks, those with diabetes mellitus, and those who have deep T-wave inversions in more than five leads with chest discomfort or pain.

Low-risk patients

Patients with atypical or recurring symptoms that could be UA (CCS class I or II) are not likely to benefit from catheterization or early revascularization. These include patients with normal or nonspecific ECG changes, T-wave inversion without ST segment depression, and biochemical markers that are negative for CK-MB or troponin levels.

Conclusions

Risk stratification makes as much sense in 2001–2002 as it did 30 years ago because non-ST segment elevation ACS is heterogeneous, with a spectrum of risk ranging from low to high. The approach of watchful waiting with

Figure 1. Acute coronary syndromes

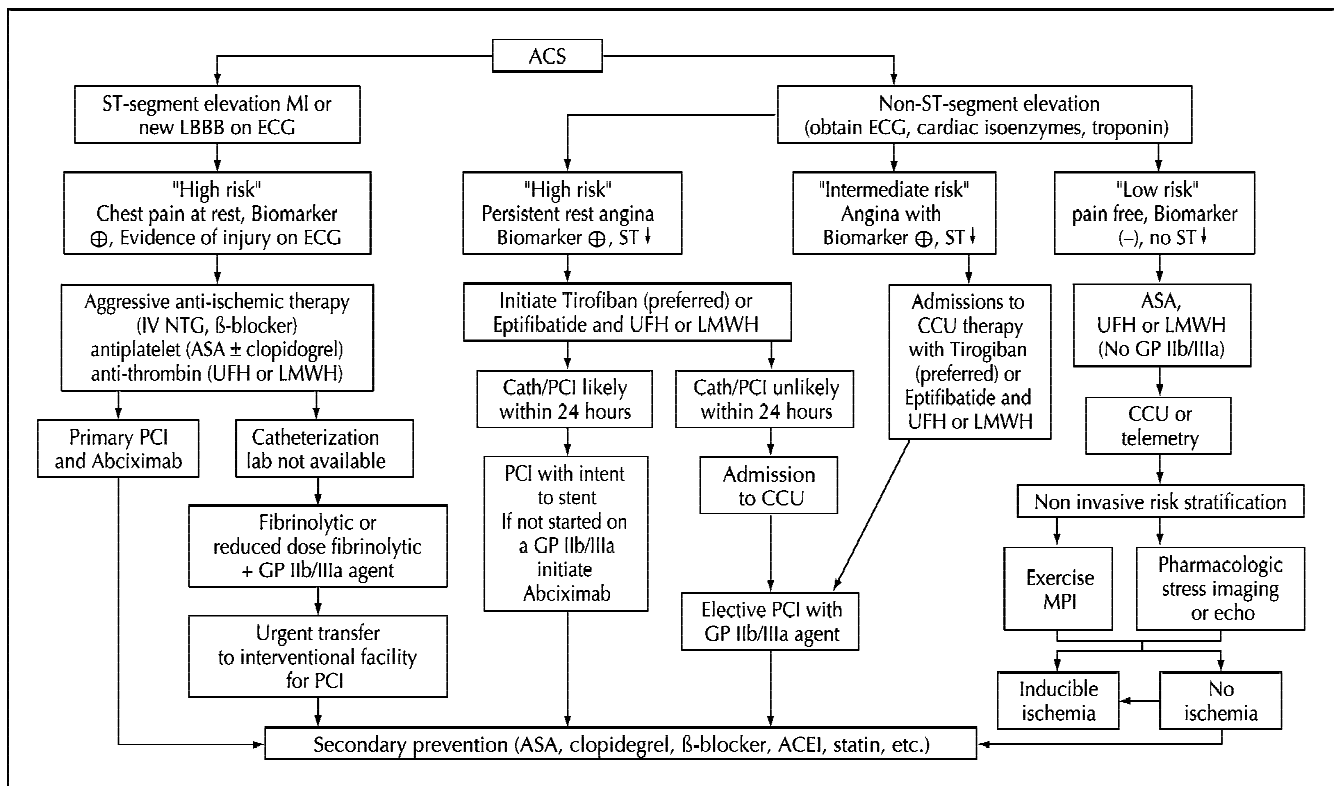


Diagram of acute coronary syndromes.

medical therapy and no PCI, though advocated in the United Kingdom and other parts of Europe, has little basis for support. Conversely, a routine invasive approach with acute revascularization for all patients may not be clinically effective or cost-effective, and may result in unnecessary complications in low-risk patients such as restenosis, need for revascularization, and risk of stroke (the VANQWISH trial demonstrated that 52% of non-Q wave MI patients randomized to the ischemia-guided strategy had a very low 30-day event rate of 1%). The balanced approach reserves catheterization and revascularization for high-risk patients; as defined in this article, this subgroup comprises 25% to 50% of all patients. Stress myocardial perfusion imaging, preferably using symptom-limited exercise at two to three days in the patients who are otherwise stable at the time of transfer to the coronary care unit will clearly delineate high- and intermediate-risk subgroups.

Aggressive pharmacologic therapy is indicated in all patients, with use of aspirin, with or without clopidogrel; glycoprotein IIb/IIIa receptor antagonists; low-molecular-weight heparin, especially enoxaparin; intravenous nitroglycerin; β -blockers; HMG Co-A reductase inhibitors (statins); and angiotensin-converting enzyme (ACE) inhibitors, as indicated.

Tailoring therapy to the level of risk is essential for optimizing efficacy and cost-effectiveness.

References

- 1 Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable angina and non-ST segment elevation myocardial infarction treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001, 344:1879–1887.
- 2 Montalescot G, Barragan P, Wittenberg O, et al. Clinical benefits of platelet glycoprotein IIb/IIIa blockade with coronary stenting in acute myocardial infarction. *N Engl J Med* 2001, 344:1895–1903.
- 3 Topol EJ, Moliterno DJ, Hermann HC, et al. Comparison of two platelet glycoprotein inhibitors, tirofiban and abciximab, for prevention of ischemic events with percutaneous coronary intervention. *N Engl J Med* 2001, 344:1888–1894.
- 4 Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol* 2000, 36:970–1062.
- 5 Braunwald E. Unstable angina: an etiologic approach to management. *Circulation* 1998, 98:2219–2222.
- 6 The TIMI IIIB Investigators. Effects 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. *Circulation* 1994, 89:1545–1556.
- 7 Boden WE, O'Rourke RA, Crawford MH, et al, for the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. *N Engl J Med* 1998, 338:1785–1792.
- 8 The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998, 338:1498–1505.
- 9 The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the Platelet Glycoprotein IIb/IIIa Receptor with Tirofiban in Unstable Angina and Non-Q-wave Myocardial Infarction. *N Engl J Med* 1998, 338:1488–1497.
- 10 The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatid in patients with acute coronary syndromes. *N Engl J Med* 1998, 339:436–443.
- 11 The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 1997, 96:1445–1453.
- 12 Cohen M, Demers C, Gurfinkel EP, et al, for the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events Study. *N Engl J Med* 1997, 337:447–452.
- 13 Antman EM, McCabe CH, Gurfinkel EP, et al, for the TIMI 11B Investigators. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) 11B Trial. *Circulation* 1999, 100:1593–1601.
- 14 Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999, 354:701–707.
- 15 The OASIS-2 Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. *Lancet* 1999, 353:429–438.
- 16 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996, 348:1329–1339.
- 17 Yusuf S. Clopidogrel in unstable angina to prevent recurrent ischemic events (CURE). Presented at the 50th Annual Scientific Session of the American College of Cardiology; March 19, 2001; Orlando, Florida.
- 18 Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease. FRISC II prospective randomised multicentre study. *Lancet* 1999, 354:708–715.
- 19 Lagerqvist B, Diderholm E, Lindahl B, et al. An early invasive treatment strategy reduces cardiac events regardless of troponin levels in unstable coronary artery (UCAD) with and without troponin-elevation: a FRISC II substudy. *Circulation* 1999 (Suppl I), 100:I-497 Abstract 2622.
- 20 Diderholm E, Andren B, Frostfeldt G, et al. ST depression in ECG at entry identifies patients who may benefit most from early revascularisation in unstable coronary artery disease: a FRISC II substudy. *Circulation* 1999 (Suppl I), 100:I-497 Abstract 2623.