Continuous ST-Segment Monitoring in Contemporary Acute Coronary Syndrome Patients
The Magic of MERLIN–TIMI 36*

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Acute coronary syndrome (ACS) is characterized by repeated transient ischemic episodes (TIE), which can be symptomatic or silent. The frequency of TIE reported in patients with ACS varies from 15% to 77% across studies, due to variations in inclusion/exclusion criteria, modalities of therapy, monitoring period and number of leads used for continuous electrocardiographic (cECG) monitoring (1,2). Klootwijk et al. (2) detected ischemic changes in 77% of 130 patients with unstable angina pectoris (UAP) using 12-lead cECG monitoring for 48 h. In the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events) study (3), monitoring 220 patients with non–ST-segment elevation (NSTE) ACS for 48 h with 3-lead Holter, Goodman et al. (3) recorded TIE in 25%. Akkerhuis et al. (4), who obtained data from the CAPTURE (C7E3 Fab Anti Platelet Therapy in Unstable Refractory Angina), the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy), and the FROST (French Randomized Optimal Stenting Trial) studies in patients with NSTE ACS found ischemic episodes in 27% of 995 patients who had 24-h cECG monitoring. Langer et al. (5) reported ischemic changes in 66% of 135 patients with UAP.

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Mechanism

Ischemia on cECG has been described in association with both severe and high risk morphology coronary anatomy in ACS patients. Bugiardini et al. (6) described prolonged (>60 min) duration of myocardial ischemia on Holter monitoring of patients with complex coronary disease, and Pozzatti et al. (7) reported both prolonged duration (85 vs. 33 min) and more frequent TIE (56% vs. 9%) in such patients compared to patients with smooth, less complex lesions. Like Scirica et al. (8) and the TIMI 36 (Thrombolysis In Myocardial Infarction 36) group, who in this issue of the Journal report an increased incidence of ischemia in patients with greater extent of coronary disease (12.3% of patients with single-vessel disease, 18.9% with double-vessel disease, and 28.0% with triple-vessel disease), Patel et al. (9) found that the dichotomous presence or absence of TIE was a very powerful predictor of complex coronary lesion or coronary thrombus (odds ratio: 7.1), whereas Langer et al. (5) reported more left main and severe multivessel disease in patients with TIE.

Patients with ACS have impaired endothelial function with increased tendency for coronary vasoconstriction (10,11). Scirica et al. (8) document ST-segment shifts in >10% of patients without flow-limiting coronary lesions, as well as in patients after complete revascularization with percutaneous coronary intervention. The combination of more complex and more advanced coronary pathology as well as increased coronary tone may provide further mechanistic insight into how strongly TIE relate to impaired prognosis even in the most modern setting of medical and percutaneous coronary intervention therapy.

Prognosis

Studies involving patients with NSTE ACS have consistently demonstrated that the presence of TIE is predictive of both short and long-term increase in mortality and infarction. Gottlieb et al. (12) were the first to demonstrate that TIE (mostly silent), which were present in 37 of 70 patients with UAP under best medical treatment, were the best predictors of early cardiac events among 15 tested variables. Similarly, in the 135 patients with UAP mentioned above, Langer et al. (5) found a higher frequency of cardiac events (48% vs. 20%) among patients with TIE than among patients without TIE. In the meta-analysis from the CAPTURE, PURSUIT, and FROST studies, Akkerhuis et al. (4) found death and myocardial infarct in 5.7% of patients without ischemic episodes, compared with 19.7% of patients who had ≥5 episodes. In the ESSENCE trial, Goodman et al. (3) reported death or myocardial infarction at 1 year in 18.4% of patients with TIE and in 8.3% of patients without TIE. Yan et al. (13) investigated the additional prognostic information of 48-h CECG monitoring in 681 NSTE ACS patients. Over 30 months, patients with ST-segment shifts had a higher risk of death (17.7% vs. 5.9%) or death and myocardial infarction (24.6% vs. 11.1%). In multivariate...
The use of cECG acutely for 24 to 72 h using 12-lead Holter monitoring, followed by exercise testing 5 to 7 days later, was not tested in the MERLIN–TIMI 36 trial as an alternative to a week of 2-lead Holter monitoring. That might yield more predictive information, as discussed below, with less logistical burden. It is widely appreciated that almost all patients who have TIE during ambulatory monitoring have abnormal exercise tests (14), and by 5 to 7 days, most ACS patients are ambulatory and can safely perform exercise tests.

### Technical Aspects of ST-Segment Monitoring for TIE

Signal fidelity, number of leads, lead location, and duration of monitoring are all key aspects of TIE quantification. Scirica et al. (8) used 2 bipolar leads at a 128-Hz sampling rate, whereas in other reports, continuous 3-lead vectorcardiographs or 12-lead cECG sampling at 500 to 1,000 Hz was used. This is an important difference because not only is ischemia episodic in time, but also it is focal over the precordial “space” as well (15). Too few precordial leads may miss TIE altogether or may underestimate duration or peak ST-segment deviation of TIE (2,16), a potential factor in why number of episodes, ischemia duration, and ST-segment deviation curve area were not predictive of clinical outcomes in the MERLIN–TIMI 36 report.

### Conclusions

This study by Scirica et al. (8) is the largest and most contemporary report of continuous Holter ST-segment monitoring of patients with coronary artery disease in the literature, and thus provides unique statistical power to examine key subgroups of interest. This study strongly confirms that TIE and/or ST-segment shift have prognostic significance for ACS patients, patients treated medically and/or undergoing percutaneous coronary intervention, patients with both complete and incomplete revascularization, and patients who are otherwise categorized as high or low risk using contemporary serologic markers and descriptor models.

Despite the very clear prognostic value of the information obtained from cECG monitoring and guidelines supporting this concept, at present it is not yet practical to perform continuous monitoring of all ACS patients for clinical purposes, as accurate and reliable online automated ischemia detection systems are not available. Even if and when such systems are developed, to go beyond research applications, it will be critical to show that cECG-guided therapy actually can lead to improved outcomes.

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REFERENCES


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