

# Accepted Manuscript

We Need to Do Better for Patients with Non-ST Elevation ACS who are Managed Without Revascularization

E. Magnus Ohman, MD, FACC Ralf E. Harskamp, MD



PII: S0735-1097(14)01655-6

DOI: [10.1016/j.jacc.2014.03.009](https://doi.org/10.1016/j.jacc.2014.03.009)

Reference: JAC 20011

To appear in: *Journal of the American College of Cardiology*

Received Date: 25 February 2014

Revised Date: 28 February 2014

Accepted Date: 4 March 2014

Please cite this article as: Ohman EM, Harskamp RE, We Need to Do Better for Patients with Non-ST Elevation ACS who are Managed Without Revascularization, *Journal of the American College of Cardiology* (2014), doi: 10.1016/j.jacc.2014.03.009.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

We Need to Do Better for Patients with Non-ST Elevation ACS who are Managed Without  
Revascularization

Running Title: NSTEMI Patients Managed Without Revascularization

E. Magnus Ohman, MD, FACC; Ralf E. Harskamp, MD

Duke University Medical Center and Duke Clinical Research Institute,  
Durham, North Carolina

**Contact information:**

E. Magnus Ohman, MD, FRCPI, FESC, FACC, FSCAI  
Professor of Medicine

The Kent and Siri Rawson Director, Duke Program for Advanced Coronary Disease

Associate Director, Duke Heart Center

Senior Investigator, Duke Clinical Research Institute

Duke University Medical Center

Box 3126 DUMC

Durham, NC 27710

Phone: 919-681-2069

Email: ohman001@mc.duke.edu

**Disclosures:**

Dr. Ohman served as the study chair of the TRILOGY ACS trial. He reports the following disclosures: Daiichi Sankyo, Eli Lilly & Company, Gilead Sciences (research grants); Abiomed, AstraZeneca, Daiichi Sankyo, Eli Lilly & Company, Gilead Sciences, Janssen Pharmaceuticals, Pozen, Inc., Sanofi Aventis, The Medicines Company, and WebMD (consultant).

Dr. Harskamp has no relevant disclosures.

**Key Words:** clopidogrel, outcomes, acute coronary syndrome

Patients with non-ST elevation myocardial infarction (NSTEMI) managed without revascularization represent a heterogeneous and understudied population. Several studies have highlighted the higher morbidity and mortality in such patients, with recent data showing a relative 50% increase in risk-adjusted mortality. (1,2) Strikingly similar higher rates of ischemic events worldwide have been reported, even after accounting for different preponderance for early revascularization in different regions of the world, suggesting that this is a high-risk population; and yet is under-treated with evidence-based therapies. (2,3)

The recommendation to use dual antiplatelet therapy (DAPT) with clopidogrel to prevent future ischemic events in these conservatively treated patients is based on the findings from a single study, the CURE trial, which was conducted over a decade ago. (4) In summary, the trial found a 2.1% absolute risk reduction for the composite of death, MI or stroke after DAPT versus aspirin alone, and its findings were consistent among medically managed (n=7,985) and revascularized patients (n=4,577). The management of patients with NSTEMI has evolved significantly since that trial. The U.S. contribution to the CURE trial was minimal, making it reasonable to explore the validity of these findings in current U.S. practice.

In this issue of *the journal*, Solomon and colleagues (5) performed a retrospective cohort study of conservatively managed NSTEMI patients within an integrated managed care consortium based in Northern California between 2003-2008. After applying exclusion criteria to mimic the CURE trial entry criteria, they evaluated longitudinal outcomes ( $\approx 2.5$  years) among 16,365 patients with NSTEMI in whom 5,961 (36%) patients were on clopidogrel treatment for  $\approx 6$  months on average. Outcomes were compared in a propensity-score matched cohort (n=8,562), and showed a significant reduction in the occurrence of death or MI (13.5% vs. 17.4%, hazard ratio of 0.74 [0.66-0.84]) after clopidogrel use, driven mainly by mortality reduction.

The findings of this “real world” study are compelling for a number of reasons. First, it illustrates once again that adherence to clopidogrel remains low, despite a class Ia indication for the use of clopidogrel. Secondly, it re-affirms that the benefit of clopidogrel persists over a longer duration after hospital discharge. (6) However, unlike the CURE trial, the majority of the benefit for clopidogrel was driven by a reduction in all-cause mortality (8.3% vs. 13.0%), whereas MI rates appeared similar (6.7% vs. 7.2%). While speculative, the lack of signal on MI probably relates to the low detection of MI in clinical practice compared with closely monitored clinical trials. Finally, the overall observed benefit for clopidogrel appeared to mainly result from patients with NSTEMI, but less so in those with unstable angina (HR: 0.67 vs. 1.25, with a  $p_{\text{int}} < 0.01$ ). Again these findings are in contrast with the CURE trial, where outcomes were similar between those with and without elevated cardiac markers. One possible explanation is the difference in diagnostic criteria used for MI (i.e., use of troponin instead of CK-MB). As such, a significant proportion of patients with unstable angina in the CURE trial would in the current era have been classified as NSTEMI. Another possible explanation could be that a proportion of patients in the unstable angina group were in fact patients with chest pain attributable to non-atherosclerotic causes, in whom no benefit from clopidogrel is to be expected.

One of the most intriguing findings of the present study was the benefit seen in the elderly, with significant interactions for patients  $>70$  years of age (HR: 0.70 vs. 0.88,  $p_{\text{int}} = 0.04$ ). This interaction was not observed in the CURE trial (4), nor in more recent trials with either prasugrel (7) or ticagrelor (8). However, the major benefit of ticagrelor over clopidogrel among the elderly was also mortality-related, which in conjunction with the present findings suggest that there may be substantial benefit of treating the elderly with DAPT.

There are a number of important limitations. First, due to its retrospective, non-randomized design, some of the treatment benefit of clopidogrel can be attributed to unmeasured and/or residual confounding. Second, although we presume to have compared DAPT versus aspirin, this is in fact speculative as the actual use of aspirin was unknown. Third, longitudinal follow-up on stroke or bleeding events were not collected, which affect the net risk/benefit ratio for the use of DAPT, particularly in the elderly. Fourth, a subgroup analysis among patients with continued clopidogrel for >12 months was not performed, while data on its benefit are sparse. Finally, including patient data over the years 2009-2012 would have made the results even more up-to-date with contemporary practice.

Novel, faster acting and more potent antiplatelet agents have been developed, of which prasugrel (a thienopyridine similar to clopidogrel) and ticagrelor (a reversible P2Y<sub>12</sub> receptor-blocker), have been tested in NSTEMI-ACS patients managed without revascularization. The TRILOGY-ACS trial compared prasugrel to clopidogrel on top of aspirin in medically managed NSTEMI-ACS patients either <75 years (n=7,243; prasugrel 10mg) or ≥75 years (n=2,083; prasugrel: 5mg) and found no difference in the composite of death from cardiovascular causes, nonfatal MI or stroke during a median follow-up of 17.1 months. (9) Although the main trial results were neutral, prasugrel was of benefit among patients who underwent catheterization (and thus known atherosclerosis) prior to randomization; and in the overall cohort a separation was seen beyond a year in clinical outcomes in favor of prasugrel.(10) The safety/efficacy of ticagrelor for medically managed ACS patients was explored in a secondary analysis from the PLATO trial, and showed a significant reduction in the composite endpoint of cardiovascular death, MI, and stroke after ticagrelor versus clopidogrel (12.0% vs. 14.3%, hazard ratio: 0.85, 95%-CI:0.73-1.00, p=0.04) as well as in overall mortality (6.1% vs. 8.2%, p=0.01). However, 40% of this

“non-invasively” treated group of patients were managed with revascularization during the study period. Thus, this is therefore not an entirely conservatively treated cohort. (11) The incidence of total bleeding events was not statistically different, although numerically higher (11.9% vs. 10.3%,  $p=0.08$ ). The final answer on the safety and efficacy of ticagrelor in preventing long-term cardiovascular events in patients with a history of MI (including those who were managed conservatively), may come from the PEGASUS trial (NCT:01225562) which targets to enroll 21,000 patients and randomizes patients to either ticagrelor (90 mg or 60 mg twice daily) or placebo. The primary goal of this study is to reduce the composite of cardiovascular death, MI, or non-fatal stroke up to 44 months. Thus, although findings are promising, the superiority of other novel antiplatelet agents over clopidogrel still remains to be proven in NSTEMI-ACS patients managed without revascularization. Clopidogrel therefore remains the mainstay for therapy in these patients.

In conclusion, the paper by Solomon and colleagues reaffirms that even with the existence of guidelines to help optimize care, implementation of these guidelines by treating physicians and institutions remain sub-optimal. The results of the study also suggest that in a “real world” setting the continued use of clopidogrel for several months after hospital discharge is of clear benefit to patients with NSTEMI-ACS, and particularly in those with NSTEMI and the elderly. We hope this “new body of evidence” will sway those who continue to withhold clopidogrel to consider further implementation of clopidogrel use into their practice to help improve outcomes in this high-risk patient population who are not revascularized in ACS.

## References

1. Chan MY, Becker RC, Harrington RA et al. Noninvasive, medical management for non-ST-elevation acute coronary syndromes. *American heart journal* 2008;155:397-407.
2. Roe MT, White JA, Kaul P et al. Regional patterns of use of a medical management strategy for patients with non-ST-segment elevation acute coronary syndromes: insights from the EARLY ACS Trial. *Circulation Cardiovascular quality and outcomes* 2012;5:205-13.
3. Amsterdam EA, Peterson ED, Ou FS et al. Comparative trends in guidelines adherence among patients with non-ST-segment elevation acute coronary syndromes treated with invasive versus conservative management strategies: Results from the CRUSADE quality improvement initiative. *American heart journal* 2009;158:748-754 e1.
4. Yusuf S, Zhao F, Mehta SR et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *The New England journal of medicine* 2001;345:494-502.
5. Solomon MD, Go AS, Shilane D et al. Comparative Effectiveness of Clopidogrel in Medically Managed Patients with Unstable Angina and non-ST Segment Elevation Myocardial Infarction. *Journal of the American College of Cardiology* 2014.
6. Yusuf S, Mehta SR, Zhao F et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation* 2003;107:966-72.
7. Roe MT, Goodman SG, Ohman EM et al. Elderly patients with acute coronary syndromes managed without revascularization: insights into the safety of long-term dual

- antiplatelet therapy with reduced-dose prasugrel versus standard-dose clopidogrel. *Circulation* 2013;128:823-33.
8. Husted S, James S, Becker RC et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: a substudy from the prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial. *Circulation Cardiovascular quality and outcomes* 2012;5:680-8.
  9. Roe MT, Armstrong PW, Fox KA et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *The New England journal of medicine* 2012;367:1297-309.
  10. Wiviott SD, White HD, Ohman EM et al. Prasugrel versus clopidogrel for patients with unstable angina or non-ST-segment elevation myocardial infarction with or without angiography: a secondary, prespecified analysis of the TRILOGY ACS trial. *The Lancet* 2013;382:605-13.
  11. James SK, Roe MT, Cannon CP et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. *Bmj* 2011;342:d3527.