

## Update: Acute Coronary Syndromes (II)

# Invasive Treatment of Non–ST-segment Elevation Acute Coronary Syndrome: Cardiac Catheterization/Revascularization for All?



Eva Swahn\* and Joakim Alfredsson

Faculty of Health Sciences, Linköping University Hospital, Linköping, Sweden

### Article history:

Available online 31 January 2014

### Keywords:

Non–ST-segment elevation acute coronary syndrome  
Invasive treatment  
Risk stratification

### ABSTRACT

Patients admitted to hospital with symptoms and signs of non–ST-segment elevation acute coronary syndromes have different risk profiles and are in need of an individualized approach that takes into consideration not only age and sex but also comorbidities such as diabetes, renal failure, hypertension, heart failure, peripheral artery disease, earlier revascularization, etc. According to evidence-based medicine and as documented in current guidelines, there is currently evidence for early catheterization and, if feasible, revascularization in high-risk patients, especially in men. Nevertheless, because of a lack of definitive evidence, there is uncertainty about treating women in the same way. Because women are usually older and have more comorbidities, they are frailer and revascularization should be indicated with greater caution. There is no evidence that catheterization as such is worse for women than for men; however, for both men and women with low risk, a less invasive approach, such as coronary computed tomography angiography, could be considered as a first diagnostic tool.

© 2013 Sociedad Española de Cardiología. Published by Elsevier España, S.L. All rights reserved.

## Tratamiento invasivo del síndrome coronario agudo sin elevación del segmento ST: ¿cateterismo cardiaco/revascularización en todos los casos?

### RESUMEN

Los pacientes hospitalizados con signos y síntomas de síndrome coronario agudo sin elevación del segmento ST presentan perfiles de riesgo diferentes y requieren un enfoque individualizado que tenga en cuenta no solamente la edad y el sexo, sino también las comorbilidades como diabetes mellitus, insuficiencia renal, hipertensión, insuficiencia cardiaca, enfermedad arterial periférica, revascularización más temprana, etc. Según la medicina basada en la evidencia y tal como se documenta en las guías, actualmente hay evidencia que respalda el uso temprano de cateterismo y, si es factible, la revascularización para los pacientes de alto riesgo, sobre todo varones. No obstante, dada la falta de evidencia clara, hay incertidumbre respecto a la conveniencia de tratar a las mujeres de la misma forma. Las mujeres suelen ser de más edad y con más comorbilidades, son más frágiles, por lo que la revascularización debe indicarse con más precaución. No hay evidencia de que el cateterismo como tal sea peor para las mujeres que para los varones; sin embargo, se podría considerar un abordaje menos invasivo, como la angiografía por tomografía computarizada, como primer método diagnóstico tanto para varones como para mujeres de riesgo bajo.

© 2013 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L. Todos los derechos reservados.

### Palabras clave:

Síndrome coronario agudo sin elevación del segmento ST  
Tratamiento invasivo  
Estratificación del riesgo

Section sponsored by AstraZeneca

## INTRODUCTION

The acute treatment of ST-segment elevation myocardial infarction is no longer under discussion as primary percutaneous coronary intervention has become the treatment of choice. In contrast, non–ST-segment elevation myocardial infarction and unstable angina pectoris, often referred to as non–ST-segment

elevation acute coronary syndrome (NSTEMACS), is still under debate regarding if, when, and how to invasively diagnose and treat the condition. Therefore, this review will deal only with this question.

The risk for new ischemic events varies immensely because of the heterogeneity of the NSTEMACS population. Thus, early risk stratification is mandatory in the management of these patients.

The clinical challenge today is to identify individual patients with the highest risk for ischemic events and to balance this risk against the early risk for complications with invasive treatment. Risk stratification aims to optimize the management of the patient before, during, and after the invasive intervention. This might include individualizing pharmacological treatment to minimize bleeding, renal, and other complications.<sup>1</sup>

\* Corresponding author: Department of Cardiology, University Hospital, SE58185 Linköping, Sweden.

E-mail address: [Eva.swahn@lio.se](mailto:Eva.swahn@lio.se) (E. Swahn).

## Abbreviations

CABG: coronary artery bypass surgery  
 MI: myocardial infarction  
 NSTEMACS: non-ST-segment elevation acute coronary syndrome

## RISK STRATIFICATION

Risk stratification is often based on electrocardiogram changes<sup>2–4</sup> and elevation of myocardial damage markers, in which troponins are currently the established choice for predicting death and myocardial infarction (MI) and benefit from an invasive strategy.<sup>5,6</sup>

Risk stratification is dependent not only on electrocardiogram and biomarkers but also on the patient's comorbidity and other risk factors for cardiovascular disease. A number of risk factor scores have been constructed, among them the GRACE (Global Registry of Acute Cardiac Events) score, the TIMI (Thrombolysis In Myocardial Infarction) score and the FRISC (Fast Revascularisation in Instability in Coronary Disease) score. In one rather small study, the TIMI-score was shown to correctly predict 30-day death, MI or revascularization in both men and women.<sup>7</sup> Whether the GRACE and FRISC-scores perform equally in men and women is not well known.

## REVASCULARIZATION

### Why and When?

Revascularization of NSTEMACS populations is done to relieve symptoms, increase quality of life, reduce the incidence of a new infarction, and possibly prolong life and is a class I-recommendation in European Society of Cardiology guidelines on NSTEMACS, at least for patients with medium- or high-risk features.<sup>1</sup>

For most patients with NSTEMACS, without need for urgent revascularization, there was an intense debate during the 1990s whether an invasive approach, with routine coronary angiography (followed by revascularization, if feasible) was superior to a more conservative approach, with pharmacological stabilization and coronary angiography only if the patient experienced symptoms or signs of ischemia (spontaneous or during a stress test). These 2 treatment strategies have been compared in a number of randomized trials. Most<sup>8–12</sup> but not all<sup>1,13,14</sup> of the studies have been in favor of a routine invasive strategy. A meta-analysis of 7 of the earlier trials showed a reduced rate of MI, severe angina, and rehospitalization at the end of a 17-month follow-up for routine invasive vs selective invasive treatment.<sup>15</sup> The long-term benefit came with an early hazard during initial hospitalization, with a significantly higher risk of death or MI in the routine invasive strategy arm. Many of the trials included in this meta-analysis do not reflect contemporary management strategies, and the use of stents and glycoprotein IIb/IIIa-inhibitors was low. The current paradigm was challenged by the ICTUS trial, which found no difference between a routine invasive vs a more selective invasive strategy in the composite of death, MI or rehospitalization for angina pectoris within 1 year.<sup>16</sup> A small difference in revascularization rate between the 2 groups and a regular use of thienopyridines and a much higher frequency of coronary catheterization in the selective arm in the ICTUS trial may at least partly explain the difference in results between the ICTUS trial and earlier trials.

Thus, in a subgroup of NSTEMACS patients with ongoing ischemic signs, there is consensus that early catheterization and, if feasible, revascularization is the preferred treatment strategy.

### In Whom?

There is no doubt whatsoever that a routine invasive strategy in men with NSTEMACS is indicated, as clearly shown in the FRISC II, RITA 3, and TACTICS-TIMI 18 trials.<sup>17–19</sup> A meta-analysis by O'Donoghue et al,<sup>20</sup> published in 2008 and including 8 trials (3075 women and 7057 men), showed no significant difference in outcome with a routine invasive vs a more selective invasive strategy in the endpoint of death/MI, either for men or women. The same results were shown in a meta-analysis presented together with data from the OASIS 5 women substudy that included women only but did not reach the required number of patients to draw proper conclusions.<sup>21</sup>

Thus, to date, there is no definitive evidence against treating women and men alike regarding an invasive approach in NSTEMACS even if there is a trend in women toward producing harm rather than benefit. This could of course entirely be caused by lack of power.

### Who Should Undergo Angiography Earlier?

In the 2010 guidelines on myocardial revascularization,<sup>22</sup> the timing of angiography and intervention is discussed and is summarized in table 11 of this guidelines. Ongoing or recurrent ischemia, dynamic spontaneous ST-changes, deep ST-depression in anterior leads indicating ongoing posterior transmural ischemia, hemodynamic instability, and major ventricular arrhythmia are all indicators for performing emergent coronary angiography. Furthermore, in high-risk patients with a GRACE risk score > 140, angiography should be performed within 24 h if possible.

### Type of Revascularization

In the early days of percutaneous coronary interventions, data from registries and randomized trials indicated differences in several aspects between the sexes. Women were older and were more likely to have hypertension, diabetes, and heart failure. Women were also more likely to be referred for catheterization in an acute situation.<sup>23,24</sup> Most of these early reports indicated increased risk for complications, including in-hospital death, for women after percutaneous coronary intervention. Whether this is true, with the contemporary pharmaceutical treatment of today, must be evaluated, especially in the setting of NSTEMACS.<sup>25,26</sup> However, despite higher age and comorbidity, women and men had similar long-term outcomes.<sup>27–29</sup>

In coronary artery bypass surgery (CABG), women had greater early mortality than men in earlier studies. However, after adjustment for differences in baseline risk factors, mortality rates for women have often,<sup>30,31</sup> but not always,<sup>32</sup> been similar to those of men. All 3 recent studies on sex differences in CABG surgery showed that female sex is associated with an increased risk for death after CABG even after multivariate and propensity score analyses.<sup>33–35</sup> As all these studies are based on observational data and on all consecutive CABG surgeries performed, it is not possible to draw conclusions on NSTEMACS only. In 1 of the studies,<sup>33</sup> 51% to 57% of men and women, respectively, had unstable angina whereas in another,<sup>34</sup> 62% and 68% of men and women, respectively, had either urgent or emergency CABG.

A report from the BARI trial, which randomized patients with multivessel disease to CABG or percutaneous coronary

intervention, revealed that women had a significantly lower risk of death, but not of death plus MI, than men.<sup>36</sup> This was a post hoc substudy analysis with 27% women, as was the gender analysis in the FRISC II study, in which women who had CABG surgery had 4 times higher in-hospital mortality than men with CABG surgery.<sup>37</sup>

In view of the above, the discussion about whether there are sex differences in outcomes associated with CABG surgery is still ongoing.

## CONCLUSION

The treatment of choice for NSTEMI is currently coronary angiography and, if feasible, revascularization, preferably percutaneous coronary intervention. The timing of angiography depends on the patient's risk. There is uncertainty about whether this is entirely true also for women, as data from underpowered subgroup analyses are divergent. However, for as long as there is insufficient evidence for doing otherwise, women and men should be treated equally. The clinical challenge is to identify individual patients, regardless of sex, with the highest risk for ischemic events and to balance this risk against the early risk for complications. Of utmost importance is to take into consideration renal failure (more common in women), bleeding risk (more common in women), diabetes, and frailty before deciding upon which pharmacological and interventional treatment is most suited to a specific patient. It is also important to improve prognosis after intervention by providing the patient with advice on lifestyle changes and properly tailored pharmacological treatment of known risk factors.

Lastly, in the future, we need fully powered new studies to answer the many questions we have regarding revascularization in women and older individuals of both sexes.

## CONFLICTS OF INTEREST

None declared.

## REFERENCES

- Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology, Bassand JP, Hamm CV, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007;28:1598–660.
- Cannon CP, McCabe CH, Stone PH, Rogers WJ, Schactman M, Thompson BW, et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. *Thrombolysis in Myocardial Ischemia. J Am Coll Cardiol*. 1997;30:133–40.
- Holmvang L, Clemmensen P, Lindahl B, Lagerqvist B, Venge P, Wagner G, et al. Quantitative analysis of the admission electrocardiogram identifies patients with unstable coronary artery disease who benefit the most from early invasive treatment. *J Am Coll Cardiol*. 2003;41:905–15.
- Savonitto S, Cohen MG, Politi A, Hudson MP, Kong DF, Huang Y, et al. Extent of ST-segment depression and cardiac events in non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2005;26:2106–13.
- Heidenreich PA, Alloggiamento T, Melsop K, McDonald KM, Go AS, Hlatky MA. The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: a meta-analysis. *J Am Coll Cardiol*. 2001;38:478–85.
- Morrow DA, Cannon CP, Rifai N, Frey MJ, Vicari R, Lakkis N, et al. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. *JAMA*. 2001;286:2405–12.
- Karounos M, Chang AM, Robey JL, Sease KL, Shofer FS, Follansbee C, et al. TIMI risk score: does it work equally well in both males and females? *Emerg Med J*. 2007;24:471–4.
- Clayton TC, Pocock SJ, Henderson RA, Poole-Wilson PA, Shaw TR, Knight R, et al. Do men benefit more than women from an interventional strategy in patients with unstable angina or non-ST-elevation myocardial infarction? The impact of gender in the RITA 3 trial. *Eur Heart J*. 2004;25:1641–50.

- Gehrie ER, Reynolds HR, Chen AY, Neelon BH, Roe MT, Gibler WB, et al. Characterization and outcomes of women and men with non-ST-segment elevation myocardial infarction and nonobstructive coronary artery disease: results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative. *Am Heart J*. 2009;158:688–94.
- Glaser R, Herrmann HC, Murphy SA, Demopoulos LA, DiBattiste PM, Cannon CP, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes. *JAMA*. 2002;288:3124–9.
- Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. *Circulation*. 1999;99:1165–72.
- Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–52.
- Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J*. 2008;29:932–40.
- Schnohr P, Jensen JS, Scharling H, Nordestgaard BG. Coronary heart disease risk factors ranked by importance for the individual and community. A 21 year follow-up of 12 000 men and women from The Copenhagen City Heart Study. *Eur Heart J*. 2002;23:620–6.
- Mehta SR, Cannon CP, Fox KA, Wallentin L, Boden WE, Spacek R, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA*. 2005;293:2908–17.
- De Winter RJ, Windhausen F, Cornel JH, Dunselmann PH, Janus CL, Bendermacher PE, et al.; Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) Investigators. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med*. 2005;353:1095–104.
- 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;354:708–15.
- Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al.; TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)—Thrombolysis in Myocardial Infarction 18 Investigators. 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;344:1879–87.
- Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, 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;360:743–51.
- O'Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, De Winter RJ, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA*. 2008;300:71–80.
- Swahn E, Alfredsson J, Afzal R, Budaj A, Chrolavicius S, Fox K, et al. Early invasive compared with a selective invasive strategy in women with non-ST-elevation acute coronary syndromes: a substudy of the OASIS 5 trial and a meta-analysis of previous randomized trials. *Eur Heart J*. 2012;33:51–60.
- Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Guidelines on myocardial revascularization. *Eur Heart J*. 2010;31:2501–55.
- Berg J, Björck L, Dudas K, Lappas G, Rosengren A. Symptoms of a first acute myocardial infarction in women and men. *Gen Med*. 2009;6:454–62.
- Cunningham MA, Lee TH, Cook EF, Brand DA, Rouan GW, Weisberg MC, et al. The effect of gender on the probability of myocardial infarction among emergency department patients with acute chest pain: a report from the Multicenter Chest Pain Study Group. *J Gen Intern Med*. 1989;4:392–8.
- Bell MR, Holmes Jr DR, Berger PB, Garratt KN, Bailey KR, Gersh BJ. The changing in-hospital mortality of women undergoing percutaneous transluminal coronary angioplasty. *JAMA*. 1993;269:2091–5.
- Weintraub WS, Wenger NK, Kosinski AS, Douglas Jr JS, Liberman HA, Morris DC, et al. Percutaneous transluminal coronary angioplasty in women compared with men. *J Am Coll Cardiol*. 1994;24:81–90.
- Mehilli J, Kastrati A, Dirschinger J, Bollwein H, Neumann FJ, Schomig A. Differences in prognostic factors and outcomes between women and men undergoing coronary artery stenting. *JAMA*. 2000;284:1799–805.
- Singh M, Rihal CS, Gersh BJ, Roger VL, Bell MR, Lennon RJ, et al. Mortality differences between men and women after percutaneous coronary interventions. A 25-year, single-center experience. *J Am Coll Cardiol*. 2008;51:2313–20.
- Srinivas VS, Garg S, Negassa A, Bang JY, Monrad ES. Persistent sex difference in hospital outcome following percutaneous coronary intervention: results from the New York State reporting system. *J Invasive Cardiol*. 2007;19:265–8.
- O'Connor GT, Morton JR, Diehl MJ, Olmstead EM, Coffin LH, et al. Differences between men and women in hospital mortality associated with coronary artery bypass graft surgery. The Northern New England Cardiovascular Disease Study Group. *Circulation*. 1993;88(5 Pt 1):2104–10.
- Vaccarino V, Abramson JL, Veledar E, Weintraub WS. Sex differences in hospital mortality after coronary artery bypass surgery: evidence for a higher mortality in younger women. *Circulation*. 2002;105:1176–81.
- Blankstein R, Ward RP, Arnsdorf M, Jones B, Lou YB, Pine M. Female gender is an independent predictor of operative mortality after coronary artery bypass graft

- surgery: contemporary analysis of 31 Midwestern hospitals. *Circulation*. 2005;112(9 Suppl):I323–7.
33. Alam M, Lee VV, Elayda MA, Shahzad SA, Yang EY, Nambi V, et al. Association of gender with morbidity and mortality after isolated coronary artery bypass grafting. A propensity score matched analysis. *Int J Cardiol*. 2013;167:180–4.
  34. Bukkapatnam RN, Yeo KK, Li Z, Amsterdam EA. Operative mortality in women and men undergoing coronary artery bypass grafting (from the California Coronary Artery Bypass Grafting Outcomes Reporting Program). *Am J Cardiol*. 2010;105:339–42.
  35. Takagi H, Manabe H, Umemoto T. A contemporary meta-analysis of gender differences in mortality after coronary artery bypass grafting. *Am J Cardiol*. 2010;106:1367.
  36. Jacobs AK, Kelsey SF, Brooks MM, Faxon DP, Chaitman BR, Bittner V, et al. Better outcome for women compared with men undergoing coronary revascularization: a report from the bypass angioplasty revascularization investigation (BARI). *Circulation*. 1998;98:1279–85.
  37. Lagerqvist B, Safstrom K, Stahle E, Wallentin L, Swahn E. Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? FRISC II Study Group Investigators. *J Am Coll Cardiol*. 2001;38:41–8.