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Coronary angiography in non-ST-elevation acute myocardial infarction – whom and when?

KRONIKK

KAARE HARALD BØNAA

E-mail: kaare.harald.bonaa@ntnu.no
Clinic for Heart Disease
St. Olavs Hospital - Trondheim University Hospital
and
Department of Public Health and Nursing
Norwegian University of Science and Technology
and
Department of Community Medicine
University of Tromsø – The Arctic University of Norway
Kaare Harald Bønaa (born 1952), specialist in cardiology and internal medicine, senior consultant in invasive cardiology, and professor of cardiovascular epidemiology. He is also director of the Norwegian Myocardial Infarction Register.
The author has completed the ICMJE form and reports no conflicts of interest.

TERJE STEIGEN

Department of Cardiology
University Hospital of North Norway
and
Department of Clinical Medicine
University of Tromsø – The Arctic University of Norway
Terje Steigen (born 1959), specialist in cardiology and internal medicine, senior consultant in invasive cardiology, and associate professor.
The author has completed the ICMJE form and reports no conflicts of interest.

Many patients with non-ST-elevation acute myocardial infarction (NSTEMI) ultimately undergo percutaneous coronary intervention or coronary artery bypass surgery. Both procedures require prior diagnostic coronary angiography. Should all patients with NSTEMI be referred for coronary angiography? And when in the disease course should patients be angiographed?

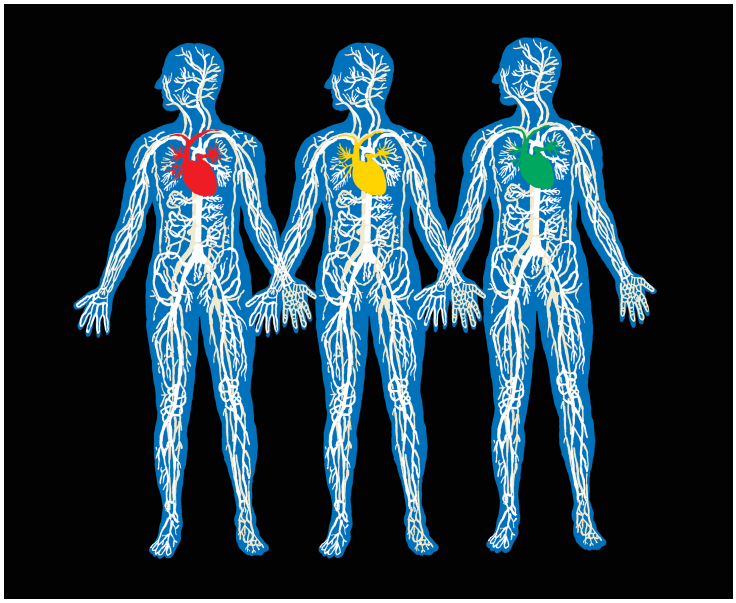

Illustration: Espen Friberg

Each year, approximately 9 500 patients are admitted to Norwegian hospitals with non-ST-elevation acute myocardial infarction (NSTEMI) (1). This represents 70 % of all patients with acute myocardial infarction. NSTEMI is usually caused by the rupture or fissure of an atherosclerotic plaque in a coronary artery, with ensuing thrombosis and myocardial ischaemia.

Pharmacological treatment comprises anti-thrombotic and anti-ischaemic drugs to stabilise the plaque and counteract ischaemia. The ultimate treatment is usually revascularisation by means of percutaneous coronary intervention and sealing of the ruptured plaque with a stent. Coronary artery bypass surgery, the other method of revascularisation, is currently performed in less than 10–20 % of patients (2). Both procedures require prior coronary angiography to map the extent of coronary artery disease.

About 5–10 % of patients with NSTEMI are clinically unstable with heart failure, cardiogenic shock, persistent chest pain or severe cardiac arrhythmias. It is well established that these patients should be angiographed immediately, and ideally within two hours (3–5).

Recommendations for clinically stable patients vary. The European Society of Cardiology recommends routine angiography within 24 hours of hospitalisation (3), whereas the European Acute Cardiovascular Care Association, a member organisation of the European Society of Cardiology, uses assessment within 72 hours as a clinical quality indicator (4). American guidelines recommend coronary angiography within 24 or 72 hours, dependent on risk profile (5). In 2015, an expert panel appointed by the Norwegian Society of Cardiology recommended routine angiography within 24 hours; the Board of the Society approved this recommendation, but noted that cases must be considered on an individual basis (6).

Healthcare regions in Norway differ in their recommendations and show major differences in treatment practice (1). In 2015, 21 % of patients under 80 years of age underwent coronary angiography within 24 hours of hospitalisation, and 58 % within 72 hours (1). Since 2015, the Norwegian Myocardial Infarction Register has used invasive assessment within 72 hours as a clinical quality indicator in NSTEMI (1).

Routine or selective angiography?

A number of randomised studies have compared the effectiveness of routine angiography during hospital stays with that of selective angiography performed only upon clinical signs of instability, such as refractory chest pain, dynamic ECG changes, heart failure, severe arrhythmias, or ischaemia during an exercise ECG. The results have been collated in several

meta-analyses (7–11).

Most of the studies have flaws. Neither the individual studies nor the meta-analyses had sufficient statistical power to examine effects on total mortality. The majority of the studies were conducted before modern stents and drugs became available. Several of the endpoints in the meta-analyses showed signs of heterogeneity, suggesting that it may not be entirely appropriate to analyse the studies together. Unstable patients with very high risk were excluded from most of the studies.

Several studies included recurrent ischaemia and revascularisation as efficacy outcomes. These are subjective endpoints, with a risk of bias in non-blinded studies. Routine angiography is also favoured in that revascularisations performed after routine angiography will not count as an endpoint, whereas all those performed after selective angiography will count. The main emphasis should be on hard clinical endpoints, such as mortality and reinfarction. Four out of five reviews found no statistically significant effect of routine angiography on total mortality; however, there was a significant reduction in non-fatal myocardial infarctions.

Long-term outcomes have been examined in an analysis based on three of the largest studies (10). After five years of follow-up, there was no significant effect of routine angiography on total mortality, but the risk of another myocardial infarction was reduced by 2.9 %. The primary endpoint, which comprised cardiovascular mortality plus non-fatal myocardial infarction, was reduced by 3.2 %. The effect was dependent on the patients' cardiovascular risk profile. In the low, intermediate and high risk groups, the primary endpoint was reduced by 2.0 %, 3.8 %, and 11.1 %, respectively. Even in the low risk group, which accounted for 54 % of randomised patients, the beneficial effect of routine angiography was of a similar magnitude to that of certain medications currently used in NSTEMI, such as ticagrelor.

We believe there is satisfactory evidence that routine angiography has clinical benefits in NSTEMI, even though no effect has been shown on mortality. The benefit is greatest in patients with increased risk of cardiovascular mortality and myocardial infarction.

Angiography within 24 hours?

The European guidelines include a class IA recommendation for angiography within 24 hours in NSTEMI (3). This implies that the authors of the guidelines believe the intervention has been shown to be beneficial, useful and effective. As supporting evidence, the authors cite two meta-analyses (12, 13) and the TIMACS study (14), the largest of a total of ten studies that have compared early versus late angiography.

The TIMACS study included 3 031 patients and is the only one of the studies that comes close to having reasonable statistical power. However, it was discontinued prematurely due to insufficient patient recruitment and the results should be interpreted with caution. The other two references are meta-analyses where the TIMACS study was combined with three and six smaller studies, respectively, and where it contributes 56 % and 75 % of the total number of patients. It thus weighs heavily in the evidence upon which the European guidelines are based.

In the TIMACS study, the median time to angiography was 14 hours in the group that underwent early angiography versus 50 hours in the group with delayed angiography. The primary endpoint was a composite of mortality, acute myocardial infarction or stroke at six months. There was no significant effect of early angiography on the primary endpoint. Both meta-analyses reached the same conclusion.

We must question whether the European Society of Cardiology has made the correct call when none of the three publications that form the basis for the class IA recommendation of early angiography showed an effect on the studies' primary endpoint. How might this have happened? The explanation is that the class IA recommendation is based on a subgroup

analysis in the TIMACS study, in which a beneficial effect of early angiography was found for the one-third of patients at highest risk, defined as a GRACE score of > 140 (Global Registry of Acute Coronary Events).

Several factors suggest that it may be inadvisable to place decisive weight on this subgroup analysis. As a general rule, one should be wary of placing too much weight on subgroup analyses, especially if the main analysis has not shown any effect. Moreover, the GRACE score was not developed to guide treatment, but to estimate the risk of mortality after an acute coronary syndrome (15). Age thus weighs heavily in this score.

Since the publication of the European guidelines in 2016, an additional meta-analysis has been published that includes three more recent studies (16). This analysis also found that angiography within 24 hours had no effect on hard clinical outcomes, but there was a significant reduction in the risk of further ischaemic episodes, and early angiography did lead to shorter hospital stays.

Summary

We believe that patients with NSTEMI who are clinically unstable due to heart failure, cardiogenic shock, persistent/recurrent chest pain, severe cardiac arrhythmias, or in whom echocardiography reveals a large ischaemic zone, should be referred for immediate coronary angiography. Stable patients should, as a rule, be referred for coronary angiography during their hospital stay. This applies in particular to patients with elevated cardiovascular risk who have no contraindications or marked comorbidities. Individual risk stratification is essential.

Routine early angiography of clinically stable patients within the first 24 hours of hospitalisation has not been shown to have an effect on hard clinical outcomes. For the majority of clinically stable patients with NSTEMI, a pragmatic approach should be used in deciding when to perform coronary angiography – with marginal medical benefits weighed against the practical and economic implications.

Early angiography may shorten hospital stays, but is associated with costs related to running angiographic laboratories and providing ambulance transport. Most of those who are acutely admitted with elevated troponin levels do not have myocardial infarction and do not require coronary angiography, but excluding a diagnosis of NSTEMI can often take time. Routine use of early angiography risks unnecessary referrals.

Professional guidelines from international expert panels are often assumed to represent the best of evidence-based medicine, but the quality of the evidence that underlies these recommendations varies. Our review has shown that the European Society of Cardiology guidelines lack a solid scientific basis with respect to early angiography in NSTEMI. We have previously demonstrated clear errors in the European guidelines for choice of stent type in percutaneous coronary intervention (PCI) (17, 18).

This is not the first time such observations have been made. Only 15 % of American cardiology guidelines were based on high quality studies (19). Judgement and subjective evaluations based on personal and/or organisational preferences are used when deciding which studies to include in the evidence base and how they should be weighted (20). There may also often be commercial interests linked to the drafting of professional guidelines (21).

It is therefore important that Norwegian medical professionals conduct independent evaluations of the evidence base for clinical practice, develop guidelines suited to national circumstances, and recognise that guidelines are recommendations, not rules.

REFERENCES:

1. Karlsaune H, Digre T, Sneeggen S et al. Norsk hjerteinfarktregister. Årsrapport 2015. https://stolav.no/norskhjerteinfarktregister (5.9.2017).

2. Hovland S, Seifert R, Rotevatn S. Norsk register for invasive kardiologi (NORIC). Årsrapport for 2015. https://www.kvalitetsregistre.no/registers/norsk-register-invasiv-kardiologi-noric (5.9.2017).

3. Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267 - 315. [PubMed][CrossRef]

4. Schiele F, Gale CP, Bonnefoy E et al. Quality indicators for acute myocardial infarction: A position paper of the Acute Cardiovascular Care Association. Eur Heart J Acute Cardiovasc Care 2017; 6: 34 - 59. [PubMed][CrossRef]

5. ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130: e344 - 426. [PubMed][CrossRef]

6. Anfinsen O-G, Nerdrum T, Bonarjee V. NCS – kvalitetsutvalget. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Hjerteforum 2016; 29: 15 - 8.

7. Mehta SR, Cannon CP, Fox KAA 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. [PubMed][CrossRef]

8. Bavry AA, Kumbhani DJ, Rassi AN et al. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. J Am Coll Cardiol 2006; 48: 1319 - 25. [PubMed][CrossRef]

9. O'Donoghue M, Boden WE, Braunwald E 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. [PubMed][CrossRef]

10. FIR Collaboration. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. J Am Coll Cardiol 2010; 55: 2435 - 45. [PubMed][CrossRef]

11. Elgendy IY, Kumbhani DJ, Mahmoud AN et al. Routine invasive versus selective invasive strategies for Non-ST-elevation acute coronary syndromes: An Updated meta-analysis of randomized trials. Catheter Cardiovasc Interv 2016; 88: 765 - 74. [PubMed][CrossRef]

12. Katritsis DG, Siontis GCM, Kastrati A et al. Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. Eur Heart J 2011; 32: 32 - 40. [PubMed][CrossRef]

13. Navarese EP, Gurbel PA, Andreotti F et al. Optimal timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes: a systematic review and meta-analysis. Ann Intern Med 2013; 158: 261 - 70. [PubMed][CrossRef]

14. TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009; 360: 2165 - 75. [PubMed][CrossRef]

15. Backus BE, Six AJ, Kelder JH et al. Risk scores for patients with chest pain: evaluation in the emergency department. Curr Cardiol Rev 2011; 7: 2 - 8. [PubMed][CrossRef]

16. Bonello L, Laine M, Puymirat E et al. Timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes and clinical outcomes: an updated meta-analysis. JACC Cardiovasc Interv 2016; 9: 2267 - 76. [PubMed][CrossRef]

17. NORSTENT Investigators. Drug-eluting or bare-metal stents for coronary artery disease. N Engl J Med 2016; 375: 1242 - 52. [PubMed][CrossRef]

18. Wiseth R, Bønaa KH. Potential implications of NORSTENT (Norwegian Coronary Stent Trial) in contemporary practice. Circulation 2017; 136: 701 - 3. [PubMed][CrossRef]

19. Han H, Chao H, Guerra A et al. Evolution of the American College of Cardiology/American Heart Association Clinical Guidelines. J Am Coll Cardiol 2015; 65: 2726 - 34. [PubMed][CrossRef]

20. Tunis SR. Reflections on science, judgement, and value in evidence-based decision making: a conversation with David Eddy. Health Aff (Millwood) 2007; 26: 500 - 15. [PubMed][CrossRef]

21. Jefferson AA, Pearson SD. Conflict of interest in seminal hepatitis C virus and cholesterol management guidelines. JAMA Intern Med 2017; 177: 352 - 7. [PubMed][CrossRef]

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