Baseline Risk, Timing of Invasive Strategy and Guideline Compliance in NSTEMI: Nationwide Analysis from MINAP

Short title: Guidelines recommended risk and receipt of invasive strategy

Muhammad Rashid[1,2], Nick Curzen[3], Tim Kinnaird[4], Claire A Lawson[5], Phyo K Myint[6], Evangelos Kontopantelis[7], Mohamed O Mohamed[1,2], Ahmad Shoaib[1,2], Chris P Gale[8], Adam Timmis[9], Mamas A. Mamas[1,2]

1. Keele Cardiovascular Research group, Centre of Prognosis Research, Institute of Primary Care Sciences, Keele University, Stoke on Trent, UK
2. Department of Cardiology, University Hospital of North Midlands, Stoke on Trent, UK
3. Coronary Research Group, University Hospital Southampton & Faculty of Medicine, University of Southampton, UK
4. Department of Cardiology, University Hospital of Wales, Cardiff, UK
5. Real World Evidence Unit, Diabetes Research Centre, University of Leicester, UK
6. Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, Scotland, UK
7. University of Manchester, Division of Population Health, Health Services Research and Primary Care, Manchester, UK
8. Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
9. Barts Heart Centre, Queen Mary University London, UK

Corresponding Author:

Dr Muhammad Rashid

Keele Cardiovascular Research Group,

Keele University, Stoke-on-Trent, UK

E-mail: doctorrashid7@gmail.com

Abstract:

Background: International guidelines recommend that for NSTEMI, the timing of invasive strategy (IS) is a function of patient's baseline risk. The extent to which this is delivered across and within healthcare systems is unknown.

Methods: Data were derived from 137,265 patients admitted with an NSTEMI diagnosis between 2010-2015 in England and Wales. Patients were stratified into low, intermediate and high-risk in keeping with international guidelines. Time to IS was categorised into early (24 hours), intermediate (25-72 hours) and late (>72 hours). Multivariable logistic regression models were used to identify independent predictors of guidelines recommended receipt of IS.

Results: There were 3,608 (2.6%) low, 5,037 (3.7%) intermediate and 128,621 (93.7%) high-risk patients. Guidelines recommended use of IS was significantly lower in high-risk (16.4%) compared to intermediate (64.7%) and low-risk (62.5%) groups. Both men and women in the low-risk category were almost twice as likely to receive early IS compared to high-risk men (28.9% vs 17%, p<0.001) and women (26.9% vs 15%, p<0.001). Women (OR 0.91 95%CI 0.88-0.94), troponin elevation (OR 0.39 95%CI 0.36-0.43) and acute heart failure on admission (OR 0.65 95%CI 0.61-0.70) were strong negative predictors of receiving IS within recommended time in the high-risk group.

Conclusion: Our study shows that IS for management of NSTEMI is not delivered according to international guidelines recommendations. Specifically, the disconnect between baseline risk and utility of IS increases with increasing risk and women achieve slower access than men to IS.

Keywords: Invasive strategy, non-ST elevation acute myocardial infarction, timing, risk stratification, guidelines indicated care.

Highlights:

- Invasive strategy in the management of patients admitted with NSTEMI is guided by their baseline risk.
- Based on risk criteria of two international guidelines, over 90% of patients admitted with diagnosis of NSTEMI are high-risk.
- Only one in ten of these high-risk patients received invasive strategy within the recommended time.
- Paradoxically, both men and women with low-risk are twice as likely to receive early invasive strategy compared to high-risk men and women.

1. Introduction:

An invasive strategy in the form of coronary angiography (CA) followed by revascularisation where appropriate, is associated with reduced ischemic complications and shorter in-hospital stays in patients presenting with non-ST elevation acute myocardial infarction (NSTEMI) (1-5). Current guidelines recommend that the timing of interventional management should be determined by baseline risk (6,7), with both the European Society of Cardiology (ESC) and American Heart Association / American College of Cardiology (AHA/ACC) guidelines advising early intervention (<24 hours) in patients meeting the high-risk criteria, whereas a period of medical management followed by invasive strategy within 25-72 hours is advised in patients with an intermediate-risk profile. Data from randomised control trials and condensed meta-analyses show improved survival in NSTEMI patients following an early invasive strategy compared to a later more conservative approach, particularly in high-risk patients such as those with GRACE risk-score >140 (8-10). However, the results from individual studies evaluating the optimal timing of invasive strategy in patients with different baseline risk

profiles are inconsistent(1,8,11,12). Although the debate around the optimal timing of invasive strategy in NSTEMI continues, current guidelines have adopted a time sensitive approach that is risk profile dependent.

Despite these guidelines, provision of invasive strategy in real world clinical practice is variable and often discrepant due to a variety of potential barriers (13-15). Given this variable practice and the perception that it is often discrepant with guidelines, we investigated the relationship between baseline risk and timing of access to invasive strategy in a large national population admitted with a diagnosis of NSTEMI in England and Wales. Specifically, we examined whether the timing of invasive strategy is related to this baseline risk as defined by the two major international guidelines and how this varies in different components of each risk criteria. Our second aim was to examine any inequalities in the utilization of guidelines based invasive strategy in women compared to men. Third, we studied independent predictors of receiving invasive strategy within the recommended time across all three risk groups.

2. Methods:

2.1 Study design

Data for this study were obtained from MINAP (Myocardial Infarction National Audit Project), a comprehensive, national clinical registry of patients hospitalised with a diagnosis of AMI in England and Wales. There are over 120 data fields in MINAP, encompassing baseline characteristics, comorbidities, timing of presentation and invasive intervention, peri-admission pharmacology, in-hospital outcome, diagnosis on discharge and receipt of secondary prevention treatment(16-18). Data collection is mandated by Department of Health across 235 acute hospitals in the National Health Service (NHS) and its management have previously been described(19).

2.2 Study Population

We included patients admitted with a diagnosis of NSTEMI in any of the 235 hospitals between 1st January 2010 to 31st December 2015. The discharge diagnosis of NSTEMI in the MINAP registry is determined by local clinicians according to presenting history, clinical examination, and the results of inpatient investigations in keeping with the consensus document of the Joint European Society of Cardiology and American College of Cardiology(20) Patients with missing information on age, gender, in-hospital mortality, timing of invasive strategy and those managed conservatively were excluded from the analysis (supplementary figure 1). This constituted a final cohort of 137,265 patients, which were then categorised into low, intermediate and high-risk groups as per ESC and AHA/ACC guidelines(6,7). MINAP variables which were mapped against each guideline risk stratification criterion are shown in supplementary table 1. In addition to the patient's risk factors, we also collected information on co-existing comorbidities, cardiac biomarkers, in-hospital and discharge medications, in-hospital outcomes including all-cause mortality, cardiac mortality, re-infarction, major bleeding, receipt of PCI and receipt of CABG. MINAP doesn't collect the calculated GRACE risk score as such, however, information available from variables within the dataset was used to calculate GRACE risk score which has been previously described and validated for use in this registry(21,22). Time to invasive strategy was calculated from time of admission to the hospital and time of coronary angiography or PCI, which was then categorised into early (within 24 hours), intermediate (within 25-72 hours) and late (>72 hours) groups. Current ESC and AHA/ACC guidelines advocate an immediate invasive strategy within 2 hours in patients presenting with haemodynamic instability, life-threatening arrhythmia, or recurrent or refractory angina, acute heart failure, mechanical complications of AMI or recurrent dynamic ECG changes. By contrast, invasive strategy within 24 h is recommended for patients presenting with elevated troponin or ischaemic ST-wave or T-wave changes or a Global Registry of Acute Coronary Events (GRACE) risk score of more than 140 points. As the timing

is not always captured in hours within the MINAP dataset, hence it was not possible to accurately ascertain the timing of invasive strategy up to two hours. Therefore, we merged the very high-risk into high-risk group as patients meeting any of these criteria would still be required to undergo an invasive strategy within 24 hours of admission.

2.3 Ethical approval

Secondary use of anonymised MINAP dataset for research purposes is authorised under NHS research governance arrangements and further supported under section 251 of NHS act 2006 (NIGB: ECC1-06(d)/2011), which allows researchers to use patient information collected within the dataset for medical research without patient consent. Therefore, a formal ethical approval was not sought for this study.

2.4 Statistical analysis

Stata college station version 14.1 was used to perform all the statistical analyses for this study. Baseline characteristics were reported using numbers and percentages for categorical variables, or median and interquartile ranges for continuous variables across the three groups. Chi square and Wilcoxon rank sum were used to make the comparisons across three groups, whereas proportion tests were used to test statistically differences in proportions. The missing information about each variable is provided in the supplementary table 2. We developed an imputation framework based on chained equations to account for missing data for each group characteristic variables. Age, gender, hospital catheter laboratory status, ethnicity, timing of invasive strategy and in-hospital all-cause and cardiac mortality were registered as regular variables in the imputations model whereas all other variables including body mass index (BMI), GRACE risk-score >140, troponin elevation, acute heart failure, cardiogenic shock, seen by cardiologists, left ventricular (LV) systolic function or congestive cardiac failure, ECG changes defined as ST depression or transient ST elevation, prior history of PCI, coronary

artery bypass graft (CABG), heart failure, hypercholesterolemia, angina, cerebrovascular disease, peripheral vascular disease, chronic renal failure, diabetes, hypertension, smoking status, asthma/COPD, family history of coronary disease, use of warfarin, loop diuretics, aspirin, P2Y12 inhibitors, statin, ACE inhibitor, beta-blocker were imputed. For the intermediate-risk group, we excluded high-risk group characteristics such as troponin elevation, acute heart failure, ECG changes, cardiogenic shock and GRACE risk score >140 from the imputation model. Similarly, intermediate-risk characteristics were excluded from low-risk imputation models. Using these models, 10 imputed datasets were generated for each of the risk group which were used to perform all the analyses. Multivariable logistic regression models were used to study the independent predictors of the receipt of invasive strategy within guidelines recommended timeframes. All aforementioned variables used in the multiple imputation models were used in the multivariable logistic regression models.

3. Results:

3.1 Baseline characteristics

From a total of 137,265 patients, 3608 (2.6%) were categorised as low-risk, whereas 5,037 (3.7%) and 128,621 (93.7%) were categorised as intermediate and high-risk respectively, according to both ESC and AHA/ACC guidelines. Typically, patients identified as low-risk were younger (61.4years vs 68years, p<0.001), more likely to be women (31.5% vs 29.8%, p<0.001) and less comorbid with lower prevalence of previous cerebrovascular disease (3.9% vs7.3%, p<0.001), peripheral vascular disease (2.6% vs 5.3%, p<0.001), hypertension (46.5% vs 55.9%, p<0.001), and asthma or COPD (12.5% vs 15.3%, p<0.001) compared to high-risk group (Table 1). Supplementary Table 3 compares the differences in the baseline characteristics, in-hospital and discharge pharmacology and outcomes amongst men and women across the three risk groups. In the low-risk group, there were 2,471 (68.5%) men and

1,137 (31.5%) women. Compared to low-risk men, low-risk women had a higher prevalence of hypertension (44.9% vs 38.1%, p<0.001), history of asthma or chronic obstructive airway disease (16.2% vs 10.2%, p<0.001). Within the intermediate-risk group, men had higher incidence of previous PCI (51.8% vs 41.7%, p<0.001) and CABG (18.6% vs 8.9%, p<0.001) respectively. Finally, high-risk women were significantly older (72year vs 66 year, p<0.001) and were likely to have more adverse features on presentation in the form of higher prevalence of acute heart failure (9.3% vs 6.2%, p<0.001), GRACE risk score > 140 (48.0% vs 42.6%, p<0.001), chronic renal failure (6.1% vs 5.7%, p<0.001) and history of diabetes (26.1% vs 24.5%, p<0.001) compared to high-risk men. Notably, higher risk women were also less likely to receive secondary prevention medications on discharge in the form of aspirin, statins, ACE inhibitors and beta-blockers.

3.2 Level of Compliance with guidelines

Overall, only one in six patients (16.4%) in the high-risk group received invasive strategy within the recommended target time (<24 hrs), whilst invasive strategy was provided within the recommended time targets in 35.3% of the intermediate and 37.5% of the low-risk cohorts category respectively (Figure 1). Both men and women respectively, in the low-risk category were almost twice as likely to receive early invasive strategy (within 24 hours) compared to high-risk men (28.9% vs 17%, p<0.001) and women (26.9% vs 15%, p<0.001) (Figure 2). Women were also consistently less likely to receive invasive strategy within the recommended time points across all groups; low-risk (35.6% vs 38.3%, p=0.02) intermediate-risk (33.0% vs 36.2%, p=0.03) and high-risk group (15.0% vs 17.0%, p<0.001) compared to men (Figure 2). Paradoxically, Women in the high-risk group also experienced greater delays: 51.2% of women were treated beyond 72 hours compared to 46.7% men.

Major differences were observed in the timing of invasive strategy amongst patients with high-risk features as defined by ESC or AHA/ACC guidelines. Early invasive strategy within recommended time were most commonly used in patients presenting with cardiac arrest (49.8%) or cardiogenic shock (22.1%) but lesser proportion of patients with a GRACE score >140 (14.0%) or presenting with acute heart failure (11.8%) received invasive strategy within recommended target time (figure 3). Furthermore, women in high-risk group (cardiogenic shock, cardiac arrest, acute heart failure, ST depression on the ECG, elevated troponin and GRACE risk score >140) were consistently less likely to receive an appropriately early invasive strategy compared to men (Figure 3). In addition, subgroup analysis demonstrated important differences in access to invasive strategy in intermediate-risk patients (supplementary Figure 2). For example, women with history of diabetes (29.3% vs 35.0%, p=0.007) and congestive cardiac failure (23.2% vs 29.4%, p<0.001) were less likely to receive invasive strategy within 25-72 hours compared to men, whereas receipt of invasive strategy within recommended time frames were similar in women with history of chronic renal disease (29.6% vs 26.4%, p=0.2) and intermediate GRACE risk-score (38.9% vs 38.6%, p=0.8) compared to men.

3.3 Independent predictors of guidelines compliance

Independent predictors of attainment of invasive strategy within the recommended timeframe for high, intermediate and low-risk are reported in supplementary Table 4. In the high-risk group, presence of cardiogenic shock (OR 2.78 95%CI 2.28-3.39), ST-segment changes (OR 1.67 95%CI 1.61-1.73) and cardiac arrest (OR 2.44 95%CI 2.24-2.64) were strong positive predictors of receiving invasive strategy with 24 hours. In contrast, troponin elevation (OR 0.39 95%CI 0.36-0.43), acute heart failure on presentation (OR 0.65 95%CI 0.61-0.70) were associated with reduced odds of receiving invasive strategy within 24 hours. High-risk females (OR 0.91 95%CI 0.88-0.94) and increasing age in high-risk group (OR 0.98 95%CI 0.986-0.988) were also least likely to receive invasive strategy within target time. High-risk patient

presenting to hospital with onsite PCI facilities were almost twice as likely to receive invasive strategy within target times (OR 2.49 95%CI 2.43-2.63), where patients managed at hospital with diagnostic cardiac catheter laboratory facilities were less likely to achieve these targets (OR 0.75 95%CI 0.68-0.83). Finally, an admission on the weekend was associated with significant delay (0.49 95%CI 0.46-0.51) in receipt of invasive strategy within guidelines recommended time point in high-risk group compared to those admitted during the week

3.4 Temporal Trends

Analysis of temporal trends showed an increase in uptake of invasive strategy in all groups, but with a greater proportional increase in low-risk women (22.9% to 41.9%, $p<0.001$), whereas high-risk women had the least increase from 11% to 19.3%, $p<0.001$ during the study period (supplementary Figure 3).

4. Discussion

In this analysis of nearly 140,000 NSTEMI patients from a national AMI registry, we report a significant disconnect between targets for timing of invasive strategy based upon baseline risk according to the guidelines. In our study population, over 90% of NSTEMI patients admitted within the United Kingdom are deemed to be high-risk according to ESC or AHA/ACC guidelines, and in this cohort the recommendation is for an early invasive strategy (within 24 hours). In reality, only one in ten such high-risk NSTEMI patients actually received invasive strategy within this target time. Paradoxically, patients in the lowest risk category were twice as likely to receive an early invasive strategy compared to high-risk patients. Finally, access to invasive strategy within guideline recommended time targets was significantly lower in women than men. Specifically, high-risk women were more likely to present with adverse baseline clinical characteristics, they were less likely to receive invasive strategy within the

recommended time points compared to men.. In fact, our findings show a wide variation in adherence to guidelines, particularly amongst high-risk women.

Current ESC guidelines around the management of NSTEMI recommend an early invasive strategy within 24 hours in patients with high-risk features on presentation such as rise or fall in cardiac troponin, dynamic ECG changes, and GRACE risk score >140, with an aim to offer invasive coronary angiography no later than 72hours in patients with intermediate-risk profile such as diabetes mellitus, renal disease, congestive cardiac failure, previous PCI or CABG and GRACE risk score >109 and <140 (6). The AHA/ACC risk stratification criteria and time points for offering invasive strategy are similar to the ESC guidelines(7). Almost 93% of the NSTEMI cohort in this study were deemed high-risk, in the majority of whom this was based upon them having at least one troponin level above the 99th percentile. Both ESC and AHA/ACC guidelines recommend that at least one elevated troponin level above the 99th percentile cut off is required to make diagnosis of NSTEMI. However, offering an early invasive strategy within 24 hours to patients meeting these criteria will have major resource implications for several reasons and is likely to require restructure of national ACS services. Firstly, condensed data from RCTs shows that only high-risk patients with GRACE risk score >140 benefit from an early invasive strategy and have better clinical outcomes whereas the optimal timing of invasive strategy in patients with other high-risk features such as troponin positive or ECG changes is less clear (8,12). Secondly, utilisation of increasingly highly sensitive troponin assays has resulted in increased detection of low-risk NSTEMI patients and concurrent fall in diagnosis of Unstable angina(23-25). Furthermore, the advent of highly sensitive troponin assays has facilitated the misinterpretation of apparently raised assay results to indicate Type 1 MI, when in fact the result may reflect Type 2 MI or myocardial injury(26). Although, rise or fall in cardiac troponin is important from a diagnostic point of view, optimal timing of intervention in this cohort requires further research. Therefore, mandating invasive

strategy within 24 hours to such large proportions of patients would require a major expansion in service structure and delivery in an already stretched healthcare system. Further data is required to elucidate an optimal time of intervention in patients with different high-risk features as currently prescribed by guidelines.

Our results show a clear disassociation between the recommendations for target times for invasive strategy access on one the hand and what is actually offered to patients on the other. We found a consistently lower real life use of invasive strategy in all risk groups. Remarkably, over 80% of patients in the high-risk group did not receive invasive strategy within a recommended time frame of 24 hours. More importantly, there was a significant risk-treatment paradox in that low and intermediate-risk patients were far more likely to get an early invasive strategy than those estimated to be at high-risk. This discrepancy may be explained by several factors such as treating physician bias, patient-related factors such as age, comorbidities and organisational factors such availability of onsite catheter lab facilities(27). In our analysis, we found that low-risk patients were almost three times more likely to receive invasive strategy when admitted to hospitals with onsite cardiac catheter laboratory facilities. Further efforts are required to develop a multifaceted approach in dissemination of guidelines, as well as to improve adherence and clinical care(15).

Our striking observation in this analysis was around inequalities in receipt of appropriate, guidelines based invasive strategy amongst women and men. We found that women presenting with high-risk features were not only less likely to receive invasive strategy within recommended time points, but experienced greater delays compared to men. Furthermore, there was also significant heterogeneity in the application of a guidelines based invasive approach in women with an intermediate-risk profile. Disparities in cardiovascular care and outcomes amongst men and women are widely reported in the literature (28-31).The lower survival in women presenting with AMI is not entirely explained by the differences in their presentation,

symptomology and comorbidities(32). Whilst previous studies have reported significant discrepancies in the use of coronary angiography amongst women(28,33), our study is the first one to highlight heterogeneity between use of invasive strategy and guideline prescribed risk criteria. Our findings indicate that women are only more likely to experience biases in receipt of guidelines-based invasive strategy compared to men but this gender gap appears to be greater with increasing baseline risk amongst women.

To best of our knowledge this is the first study to provide comprehensive illustration of real-world practice of guidelines recommended invasive strategy amongst men and women in a single national healthcare system. However, certain limitations should be considered whilst interpreting our observations. A majority of our patients were in a high-risk group due to significant number of patients having positive cardiac biomarkers. We didn't have information about dynamic changes in the cardiac troponin, instead we used the guideline recommended criteria of rise in cardiac troponin with at least one value above the 99th percentile. It is possible that some of these troponin rise may be related to type 2 MI for which the impetus for invasive strategy is less clear. We included patients with very high-risk features such as cardiogenic shock, cardiac arrest, acute heart failure and dynamic ECG changes into high-risk category. Current ESC and AHA/ACC guidelines actually recommend an immediate invasive strategy within 2 hours in these patients, but in this study we have had to include them in the group recommended to have invasive strategy within 24 hours.

5. Conclusion:

In this NSTEMI cohort, we found a significant disconnect between guidelines recommended risk and use of invasive strategy in clinical practice. Specifically, over two thirds of high-risk NSTEMI patient did not receive invasive strategy within guidelines recommended time points.

There also appear to be significant sex-based inequalities in that women were not only more likely to experience higher delays in receipt of invasive strategy, women presenting with high-risk characteristics were significantly less likely to be treated invasively in the recommended time points compared to men. Future efforts need to focus around development of quality improvement programmes and educational interventions to promote uniform delivery of guidelines-based care in this cohort.

Funding Source: None

Conflict of interest: None declared

Author Contributions: MAM and MR designed the project. MR performed the data analysis and wrote the first manuscript draft. All authors have revised and critically reviewed the manuscript for intellectual content. All authors have approved the final version of the manuscript.

References:

1. Milosevic A, Vasiljevic-Pokrajcic Z, Milasinovic D, Marinkovic J, Vukcevic V, Stefanovic B, Asanin M, Dikic M, Stankovic S, Stankovic G. Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients: The RIDDLE-NSTEMI Study. *JACC Cardiovasc Interv* 2016;**9**:541-549.

2. Montalescot G, Dabbous OH, Lim MJ, Flather MD, Mehta RH, Global Registry of Acute Coronary Events Investigators. Relation of timing of cardiac catheterization to outcomes in patients with non-ST-segment elevation myocardial infarction or unstable angina pectoris enrolled in the multinational global registry of acute coronary events. *Am J Cardiol* 2005;**95**:1397-1403.

3. de Winter RJ, Windhausen F, Cornel JH, Dunselman PH, Janus CL, Bendermacher PE, Michels HR, Sanders GT, Tijssen JG, Verheugt FW, 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**:1095-1104.

4. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol* 2006;**48**:1319-1325.

5. Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, Wheatley DJ, Pocock SJ, Randomized Intervention Trial of unstable Angina Investigators.

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**:743-751.

6. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol C, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J, 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.

7. Amsterdam EA, Wenger NK, Brindis RG, Casey DE,Jr, Ganiats TG, Holmes DR,Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ, American College of Cardiology, American Heart Association Task Force on Practice Guidelines, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Clinical Chemistry. 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. *J Am Coll Cardiol* 2014;**64**:e139-228.

8. Jobs A, Mehta SR, Montalescot G, Vicaut E, Van't Hof AWJ, Badings EA, Neumann FJ, Kastrati A, Sciahbasi A, Reuter PG, Lapostolle F, Milosevic A, Stankovic G, Milasinovic D, Vonthein R, Desch S, Thiele H. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. *Lancet* 2017;**390**:737-746.

9. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, Afzal R, Chrolavicius S, Jolly SS, Widimsky P, Avezum A, Rupprecht HJ, Zhu J, Col J, Natarajan MK, Horsman C, Fox KA, Yusuf S, TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009;**360**:2165-2175.

10. Katritsis DG, Siontis GC, Kastrati A, van't Hof AW, Neumann FJ, Siontis KC, Ioannidis JP. Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. *Eur Heart J* 2011;**32**:32-40.

11. Lindholm D, Alfredsson J, Angeras O, Bohm F, Calais F, Koul S, Lagerqvist B, Renlund H, Sarno G, Varenhorst C. Timing of percutaneous coronary intervention in patients with non-ST-elevation myocardial infarction: a SWEDEHEART study. *Eur Heart J Qual Care Clin Outcomes* 2017;**3**:53-60.

12. Bonello L, Laine M, Puymirat E, Lemesle G, Thuny F, Paganelli F, Michelet P, Roch A, Kerbaul F, Boyer L. 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**:2267-2276.

13. Bassand JP. Improving the quality and dissemination of guidelines: the quest for the Holy Grail. *Eur Heart J* 2000;**21**:1289-1290.

14. Schneider EC, Timbie JW, Fox DS, Van Busum KR, Caloyeras JP. Dissemination and Adoption of Comparative Effectiveness Research Findings When Findings Challenge Current Practices. *Rand Health Q* 2013;**2**:5.

15. Tilson EC. Dissemination and Adoption of Guidelines: The Experience of Community Care of North Carolina. *N C Med J* 2015;**76**:251-255.

16. Hall M, Dondo TB, Yan AT, Goodman SG, Bueno H, Chew DP, Brieger D, Timmis A, Batin PD, Deanfield JE, Hemingway H, Fox KA, Gale CP. Association of Clinical Factors and Therapeutic Strategies With Improvements in Survival Following Non-ST-Elevation Myocardial Infarction, 2003-2013. *JAMA* 2016;**316**:1073-1082.

17. Dondo TB, Hall M, Timmis AD, Gilthorpe MS, Alabas OA, Batin PD, Deanfield JE, Hemingway H, Gale CP. Excess mortality and guideline-indicated care following non-ST-elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2017;**6**:412-420.

18. Gale CP, Cattle BA, Woolston A, Baxter PD, West TH, Simms AD, Blaxill J, Greenwood DC, Fox KA, West RM. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003-2010. *Eur Heart J* 2012;**33**:630-639.

19. Herrett E, Smeeth L, Walker L, Weston C, MINAP Academic Group. The Myocardial Ischaemia National Audit Project (MINAP). *Heart* 2010;**96**:1264-1267.

20. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;**36**:959-969.

21. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA,Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;**333**:1091.

22. Simms AD, Reynolds S, Pieper K, Baxter PD, Cattle BA, Batin PD, Wilson JI, Deanfield JE, West RM, Fox KA, Hall AS, Gale CP. Evaluation of the NICE mini-GRACE risk scores for acute myocardial infarction using the Myocardial Ischaemia National Audit Project (MINAP) 2003-2009: National Institute for Cardiovascular Outcomes Research (NICOR). *Heart* 2013;**99**:35-40.

23. Chapman AR, Fujisawa T, Lee KK, Andrews JP, Anand A, Sandeman D, Ferry AV, Stewart S, Marshall L, Strachan FE, Gray A, Newby DE, Shah ASV, Mills NL. Novel high-sensitivity cardiac troponin I assay in patients with suspected acute coronary syndrome. *Heart* 2018;

24. Shah ASV, Sandoval Y, Noaman A, Sexter A, Vaswani A, Smith SW, Gibbins M, Griffiths M, Chapman AR, Strachan FE, Anand A, Denvir MA, Adamson PD, D'Souza MS,

Gray AJ, McAllister DA, Newby DE, Apple FS, Mills NL. Patient selection for high sensitivity cardiac troponin testing and diagnosis of myocardial infarction: prospective cohort study. *BMJ* 2017;**359**:j4788.

25. Welsh P, Preiss D, Shah ASV, McAllister D, Briggs A, Boachie C, McConnachie A, Hayward C, Padmanabhan S, Welsh C, Woodward M, Campbell A, Porteous D, Mills NL, Sattar N. Comparison between High-Sensitivity Cardiac Troponin T and Cardiac Troponin I in a Large General Population Cohort. *Clin Chem* 2018;**64**:1607-1616.

26. Mariathas M, Allan R, Ramamoorthy S, Olechowski B, Hinton J, Azor M, Nicholas Z, Calver A, Corbett S, Mahmoudi M, Rawlins J, Simpson I, Wilkinson J, Kwok CS, Cook P, Mamas MA, Curzen N. True 99th centile of high sensitivity cardiac troponin for hospital patients: prospective, observational cohort study. *BMJ* 2019;**364**:l729.

27. Engel J, Damen NL, van der Wulp I, de Bruijne MC, Wagner C. Adherence to Cardiac Practice Guidelines in the Management of Non-ST-Elevation Acute Coronary Syndromes: A Systematic Literature Review. *Curr Cardiol Rev* 2017;**13**:3-27.

28. Rashid M, Fischman DL, Gulati M, Tamman K, Potts J, Kwok CS, Ensor J, Shoaib A, Mansour H, Zaman A, Savage MP, Mamas MA. Temporal trends and inequalities in coronary angiography utilization in the management of non-ST-Elevation acute coronary syndromes in the U.S. *Sci Rep* 2019;**9**:240-018-36504-y.

29. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, Kiefe CI, Frederick PD, Sopko G, Zheng ZJ, NRMI Investigators. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA* 2012;**307**:813-822.

30. Bugiardini R, Ricci B, Cenko E, Vasiljevic Z, Kedev S, Davidovic G, Zdravkovic M, Milicic D, Dilic M, Manfrini O, Koller A, Badimon L. Delayed Care and Mortality Among Women and Men With Myocardial Infarction. *J Am Heart Assoc* 2017;**6**:10.1161/JAHA.117.005968.

31. Potts J, Sirker A, Martinez SC, Gulati M, Alasnag M, Rashid M, Kwok CS, Ensor J, Burke DL, Riley RD, Holmvang L, Mamas MA. Persistent sex disparities in clinical outcomes with percutaneous coronary intervention: Insights from 6.6 million PCI procedures in the United States. *PLoS One* 2018;**13**:e0203325.

32. Alabas OA, Gale CP, Hall M, Rutherford MJ, Szummer K, Lawesson SS, Alfredsson J, Lindahl B, Jernberg T. Sex Differences in Treatments, Relative Survival, and Excess Mortality Following Acute Myocardial Infarction: National Cohort Study Using the SWEDEHEART Registry. *J Am Heart Assoc* 2017;**6**:10.1161/JAHA.117.007123.

33. Rashid M, Fischman DL, Martinez SC, Capers Q,4th, Savage M, Zaman A, Curzen N, Ensor J, Potts J, Mohamed MO, Kwok CS, Kinnaird T, Bagur R, Mamas M. Temporal trends and predictors of time to coronary angiography following non-ST-elevation acute coronary syndrome in the USA. *Coron Artery Dis* 2019;

34. Alter DA, Naylor CD, Austin PC, Tu JV. Long-term MI outcomes at hospitals with or without on-site revascularization. *JAMA* 2001;**285**:2101-2108.

35. Curran HJ, Hubacek J, Southern D, Galbraith D, Knudtson ML, Ghali WA, Graham MM, APPROACH Investigators. The effect of a regional care model on cardiac catheterization rates in patients with Acute Coronary Syndromes. *BMC Health Serv Res* 2014;**14**:550-014-0550-0.

36. Dehmer GJ, Weaver D, Roe MT, Milford-Beland S, Fitzgerald S, Hermann A, Messenger J, Moussa I, Garratt K, Rumsfeld J, Brindis RG. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the United States: a report from the CathPCI Registry of the National Cardiovascular Data Registry, 2010 through June 2011. *J Am Coll Cardiol* 2012;**60**:2017-2031.

37. Barnhart J, Lewis V, Houghton JL, Charney P. Physician knowledge levels and barriers to coronary risk prevention in women: survey results from the Women and Heart Disease Physician Education Initiative. *Womens Health Issues* 2007;**17**:93-100.

38. Mochari-Greenberger H, Mills T, Simpson SL, Mosca L. Knowledge, preventive action, and barriers to cardiovascular disease prevention by race and ethnicity in women: an American Heart Association national survey. *J Womens Health (Larchmt)* 2010;**19**:1243-1249.

39. National Clinical Guideline Centre (UK). Unstable Angina and NSTEMI: The Early Management of Unstable Angina and Non-ST-Segment-Elevation Myocardial Infarction. London: Royal College of Physicians (UK); 2010. (NICE Clinical Guidelines, No. 94.) Appendix B, The analysis of MINAP data for the cost–effectiveness analysis.
.
https://www.ncbi.nlm.nih.gov/books/NBK62740/ (19th May, 2017)

Table 1: Baseline Characteristics of patient stratified into low, intermediate and high-risk groups according to ESC and AHA/ACC guidelines

Variables	Low risk N=3608	Intermediate risk N= 5037	High Risk N=128,621	P value
Age (Years)	61.4[52.4-70]	66[57-74]	68[58-77]	<0.001
Women (%)	1,137 (31.5%)	1,383 (27.5%)	38,291 (29.8%)	<0.001
Caucasians (%)	2,805 (77.7%)	3,592 (71.3%)	103,644 (80.6%)	<0.001
BMI median [IQR]	27.7 [24.9-31.0]	28.4 [25.4-3.6]	27.5 [24.5-31.1]	<0.001
high risk Characteristics				
Cardiogenic shock	-	-	463 (0.4%)	
ECG ST changes	-	-	34,288 (26.9%)	
Cardiac arrest	-	-	3,092 (2.5%)	
Acute heart failure	-	-	9,203 (7.2%)	
High risk GRACE score >140	-	-	35,298 (44.2%)	
Troponin positive	-	-	125,070 (98.0%)	
Intermediate risk characteristics				
Intermediate risk GRACE score 109-140	-	1,423 (49.3%)	25,388 (31.9%)	<0.001
Chronic renal failure	-	215 (4.4%)	7,148 (5.8%)	0.01
Percutaneous coronary intervention	-	2,426 (49.0%)	20,713 (16.8%)	<0.001
Coronary artery bypass graft	-	789 (16.0%)	11,015 (8.9%)	<0.001
Diabetes	-	2,106 (42.2%)	31,729 (25.0%)	0.001
LVEF<40% or CCF	-	837 (34.5%)	24,548 (35.7%)	<0.001
Other clinical characteristics				
Hypercholesterolemia	1,306 (43.5%)	2,904 (59.6%)	50,757 (41.7%)	0.10
Angina	764 (26.5%)	2,609 (54.0%)	34,840 (28.4%)	<0.001
Cerebrovascular disease	119 (3.9%)	351 (7.2%)	9,019 (7.3%)	<0.01
Peripheral vascular disease	77 (2.6%)	219 (4.6%)	6,501 (5.3%)	<0.001
Hypertension	1,423 (46.5%)	3,224 (65.2%)	69,088 (55.9%)	<0.001
Smoking status				
Previous smoker	1,026 (33.0%)	2,064 (42.4%)	46,156 (37.1%)	<0.001
Current smoker	842 (27.1%)	846 (17.4%)	32,305 (26.0%)	<0.001
Asthma / COPD	378 (12.5%)	779 (15.9%)	18,776 (15.3%)	<0.001
Seen by cardiologist	3,367 (98.56%)	4,912 (98.8%)	126,664 (99.1%)	0.03
Heart rate, bpm, median (IQR)	70 [61-80]	70 [60-80]	75 [65-88]	<0.001
Systolic blood pressure, median (IQR)	140 [125-155]	138 [122-155]	140 [124-159]	<0.001
Family history of CHD	1,191 (44.8%)	1,686 (39.2%)	38,970 (35.6%)	0.001
Hospital catheter lab status				
No onsite laboratory	292 (8.1%)	319 (6.3%)	8,999 (7.0%)	0.01
Onsite diagnostic laboratory	354 (9.8%)	457 (9.1%)	16,262 (12.6%)	
Onsite PCI laboratory	2,962 (82.1%)	4,261 (84.6%)	103,360 (80.4%)	
In-hospital Pharmacology				
Low molecular weight heparin	1,208 (41.5%)	2,129 (46.8%)	57,214 (50.8%)	<0.001
Warfarin	61 (2.2%)	245 (4.1%)	5,713 (5.2%)	0.001
Loop Diuretic	196 (7.0%)	708 (15.9%)	22,529 (20.7%)	<0.001
Glycoprotein use	117 (4.1%)	188 (4.1%)	6,869 (6.2%)	<0.001
Discharge Medications				
Aspirin	2,920 (96.9%)	4,440 (96.9%)	110,412 (97.0%)	0.79

P2Y12 inhibitors	3,098(94..1%)	4,673 (95.4%)	122,474 (96.9%)	0.001
Statins	2,869 (96.5%)	4,396 (96.0%)	108,940 (96.6%)	0.04
ACE inhibitors	1,619 (85.3%)	2,805 (89.3%)	69,293 (89.5%)	<0.001
Beta-Blockers	2,395 (83.7%)	3,785 (85.3%)	97,628 (87.2%)	<0.001
Crude outcomes				
Death	3 (0.1%)	6 (0.1%)	1,354 (1.0%)	0.001
Cardiac mortality	1 (0.1%)	3 (0.1%)	1,125 (0.9%)	0.001
Reinfarction	12 (0.4%)	33 (0.7%)	1,028 (0.8%)	0.01
Major bleeding	48 (1.4%)	97 (2.0%)	2,032 (1.6%)	0.06

GRACE= Global Registry of Acute Coronary Events, CRF= chronic renal failure, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, CCF= congestive cardiac failure, LVEF= left ventricular ejection fraction, COPD= chronic obstructive airway disease.

Figure legends:

Figure 1: Overall proportion of patients receiving invasive strategy within guidelines recommended time frame according to their risk

Figure 2: Proportion of Men and Women receiving invasive strategy within guidelines recommended time frame according to their risk

Figure 3: Men, women and overall proportions in the high-risk group receiving invasive strategy within guidelines recommended time points