European Heart Journal Supplements (2021) **23** (Supplement C), C196–C203
The Heart of the Matter
doi:10.1093/eurheartj/suab068

ESC European Society of Cardiology

ANMCO POSITION PAPER: Timing of coronary angiography in non-ST-segment elevation acute coronary syndromes

Adriano Murrone[1]*, Fortunato Scotto di Uccio[2], Vincenzo Amodeo[3], Nadia Aspromonte[4], Pasquale Caldarola[5], Gianni Casella[6], Manlio Cipriani[7], Leonardo De Luca[8], Andrea Di Lenarda[9], Stefano Domenicucci[10], Giuseppina Maura Francese[11], Massimo Imazio[12], Loris Roncon[13], Stefano Urbinati[14], Serafina Valente[15], Giuseppe Di Pasquale[16], Michele Massimo Gulizia[11,17], Furio Colivicchi[18], and Domenico Gabrielli[8]

[1]*Cardiology-ICU Department, Ospedali di Città di Castello e di Gubbio-Gualdo Tadino, AUSL Umbria 1, Via Guerriero Guerra, Perugia 06127, Italy*
[2]*Cardiology-ICU Department, Cath Lab, Ospedale del Mare, Napoli, Italy*
[3]*Cardiology-ICU Department, Ospedale Santa Maria degli Ungheresi, Polistena, RC, Italy*
[4]*Heart Failure Unit, Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy*
[5]*Cardiology-ICU Department, Ospedale San Paolo, Bari, Italy*
[6]*Cardiology Department, Ospedale Maggiore, Azienda USL di Bologna, Bologna, Italy*
[7]*Cardiology 2-Cardiac Failure and Trasplantation Unit, Cardiotoracovascular Department "A. De Gasperis", ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy*
[8]*Cardiology Unit, Cardiotoracovascular Department, Azienda Ospedaliera San Camillo Forlanini, Roma, Italy*
[9]*Cardiovascular and non Cardiovascolular, Cardiovascolular and Sports Medicine Department, Azienda Sanitaria Universitaria Giuliano Isontina-ASUGI, Trieste, Italy*
[10]*Regional Health Agency, Liguria, Italy*
[11]*Cardiology Department, Azienda di Rilievo Nazionale e Alta Specializzazione "Garibaldi", Catania, Italy*
[12]*Cardiology Department, P.O.U. Santa Maria della Misericordia, Udine, Italy*
[13]*Cardiology Department, Ospedale Santa Maria della Misericordia, Rovigo, Italy*
[14]*Cardiology Department, Ospedale Bellaria, Azienda USL di Bologna, Bologna, Italy*
[15]*Clinical-Surgical Cardiology and ICU Department, A.O.U. Senese, Ospedale Santa Maria alle Scotte, Siena, Italy*
[16]*Medical Center, Azienda USL di Bologna, Bologna, Italy*
[17]*Fondazione per il Tuo cuore—Heart Care Foundation, Firenze, Italy*
[18]*Clinical and Rehabilitation Cardiology Department, Presidio Ospedaliero San Filippo Neri, ASL Roma 1, Roma, Italy*

KEYWORDS
Non-ST-segment elevation acute coronary syndromes;
Risk stratification;
Revascularization timing

The European Society of Cardiology guidelines on non-ST-elevation acute coronary syndromes suggest different temporal strategies for the angiographic study depending on the risk profile. The scientific evidence underlying the guideline recommendations and the critical issues currently existing in Italy, that often do not allow either an extended strategy of revascularization within 24 h or the application of the principle of the same day transfer from a spoke to a hub centre, are analysed. The position paper focuses, in particular, on the subgroup of patients with a defined diagnosis

*Corresponding author. Tel: +393933364578, Email: adriano.murrone@gmail.com

of non-ST-elevation myocardial infarction by proposing a timing of coronary angiography/revascularization that takes into account the available scientific evidence and the organizational possibilities of a considerable part of national cardiology services.

Introduction

The recent guidelines of the European Society of Cardiology (ESC) on Non-ST-elevation acute coronary syndromes (NSTE-ACS),[1] confirming the content of the 2015 guidelines, indicate different timing strategies based on the risk profile for the transfer of patients to facilities equipped with Cath Labs.

The prognostic stratification, in accordance with the guidelines, identifies three risk categories:

(1) very high (an immediate invasive strategy is indicated, <2 h): cardiogenic shock, recurrent angor, or chest pain refractory to medical treatment, life-threatening arrhythmias, mechanical complications, acute heart failure associated with NSTE-ACS, ST-segment depression >1 mm in 6 or more leads plus ST-segment elevation aVR and/or V1;
(2) high (an early invasive strategy is recommended, <24 h): established diagnosis of Non-ST-segment elevation myocardial infarction (NSTEMI), new or presumed new dynamic ST-T segment/wave changes (symptomatic or silent), resuscitated cardiac arrest in the absence of ST-elevation myocardial infarction (STEMI) or cardiogenic shock, GRACE (Global Registry of Acute Coronary Events) risk score >140; and
(3) low (opt for an elective invasive strategy): absence of high or very high-risk factors.

This document intends to focus its attention on high-risk NSTE-ACS patients, and in particular, on the subgroup with defined diagnosis of NSTEMI identified, on the basis of the fourth universal definition of myocardial infarction,[2] by the typical curve of the high-sensitivity troponin associated with angor or electrocardiographic/echocardiographic alterations. The ESC Guidelines recommend an early invasive strategy with a coronary angiography performed within 24 h of hospitalization for this subgroup of patients, the most numerous in clinical practice, with the additional specification of same day transfer from a spoke centre to a centre with a Cath Lab. These recommendations, necessarily need to be adapted to each country and local territory, taking into consideration the different organization, the different geographic features and the available resources.

Scientific evidence

Invasive strategy <24 h

Various studies have analysed the effects of an early (within 24 h) or delayed revascularization strategy in NSTE-ACS patients.[3]

The ISAR-COOL Study (Intracoronary Stenting with Antithrombotic Regimen Cooling-Off) randomized 410 patients to early (median value 2.4 h) or delayed revascularization (median value 86 h). The primary endpoint, consisting of death or non-fatal infarction at 30 days, was recorded in 5.9% of the early invasive strategy group compared to the 11.6% of the delayed group strategy ($P = 0.04$).[4] Later, the ELISA Study (Early or Late Intervention in Unstable Angina),[5] enrolled 220 patients, comparing an early invasive strategy (median value 6 h) with a delayed strategy after 24–48 h of pre-treatment with tirofiban (median value 50 h). No difference in the two groups was noted with regard to deaths or infarction at 30 days (9.2% vs. 9%, $P = 0.97$). The ELISA-3 Study randomized 542 high-risk NSTE-ACS patients to an early invasive strategy (median value 2.6 h) vs a delayed strategy (median 54.9 h). The primary endpoint (death, re-infarction, and revascularization at 30 days) resulted reduced, although not significantly, by the early invasive strategy.[6] Zhang *et al.*[7] compared an early invasive (<24 h) with a delayed strategy (≥36 h) demonstrating a risk reduction of infarction in patients revascularized within 24 h. In the ICTUS Study (Invasive vs. Conservative treatment in Unstable coronary Syndromes), 1200 patients were randomized to an early invasive strategy with revascularization within 24–48 h or a selective strategy. After receiving optimal medical treatment, only the patients with refractory or clinical relevant ischaemia, detected by ergometric test performed prior to the hospital discharge, were revascularized. The primary endpoint, a composite of death, re-infarction and re-hospitalization for angina, was not different in the two groups at 1 or 10 years of follow-up.[8] The two largest trials that verified the efficacy of an early invasive strategy vs a delayed strategy, also reported by the ESC Guidelines, are VERDICT (Very Early vs. Deferred Invasive evaluation using Computerized Tomography)[9] and TIMACS (Timing of Intervention in Patients with Acute Coronary Syndrome).[10] The execution time of the coronary angiography as per protocol and the real execution timing in the two trials are indicated in *Table 1*.

The results of the two studies, which enrolled over 5000 patients, show that among non-selected NSTE-ACS patients, an early invasive strategy, compared to a delayed strategy, is not 'superior' regard to the composite primary endpoint (death, myocardial infarction or stroke, at 6 months in the TIMACS Study, death from all causes, non-fatal myocardial infarction, hospital admission due to refractory myocardial ischaemia or heart failure in the VERDICT Study). From a further analysis of the VERDICT Study, the secondary endpoint (non-fatal infarction, refractory ischaemia, heart failure, death, and new revascularization) resulted significantly reduced in the early strategy only in regard to non-fatal infarction [hazard ratio

Table 1 Execution timing as for protocol and real execution timing of coronary angiography—the VERDICT and TIMACS studies[9,10]

	VERDICT study		TIMACS study	
	Protocol	Execution timing	Protocol	Execution timing
'Early Strategy' arm	ICA within 12 h from randomization	Median ICA timing 4.7 h from randomization	ICA within 24 h from randomization	Median ICA timing 14 h from randomization
'Delayed Strategy' arm	ICA within 48–72 h from randomization	Median ICA timing 61.6 h from randomization	ICA at ≥36 h from randomization	Median ICA timing 50 h from randomization

ICA, invasive coronary angiography; TIMACS, timing of intervention in patients with acute coronary syndromes; VERDICT, Very EaRly Deferred Invasive evaluation using Computerized Tomography.

(HR) 0.73, 95% confidence interval (CI) 0.56–0.96, $P = 0.025$]. Also, in the TIMACS study, the secondary endpoint (death, myocardial infarction, or refractory ischaemia at 6 months) was significantly inferior in the early invasive arm (95% vs. 12.9%; HR 0.72, 95% CI 0.58–0.89, $P = 0.003$), but this result was mainly determined by the reduction of refractory ischaemia (1.0% vs. 3.3%, $P < 0.001$).

Both the TIMACS and VERDICT studies present a number of limitations that must be taken into consideration. In the TIMACS, the examined sample population, even if numerically considerable (over 3000 patients) is relatively 'underpowered' if we consider the number of events. In the VERDICT study, instead, coronary angiography was not performed in some of the patients assigned to the delayed strategy group, mitigating therefore a potential clinical advantage. Even the ESC guidelines, with regard to the two studies, underline how an important limitation is represented by the fact that 'coronary angiography timing' was calculated from the randomization and not from the symptom onset or hospital admission. Furthermore, while in the early strategy groups coronary angiography was performed in the majority of the cases within 24 h from randomization, in the delayed strategy group, the timing of coronary angiography resulted extremely heterogenous (up to 90 h), so that it was impossible to identify a time range in which, potentially, the results would have been different. From the pre-specified subgroups analysis of the TIMACS and VERDICT studies, results that only patients with a GRACE score >140 (about one-third of the population of TIMACS) benefited from an early invasive strategy in terms of reduction of the primary endpoint (TIMACS: HR 0.65, 95% CI 0.48–0.89 vs. HR 1.12, 95% CI 0.81–1.56, P by interaction = 0.01; VERDICT: HR 0.81, 95% CI 0.67–1.01 vs. HR 1.21, 95% CI 0.92–1.60; P by interaction = 0.02). It is notable that both trials used the original GRACE score for in-hospital death while, in consideration of the different weight of the variables, the use of other GRACE score would have led, in the same patient, to a different risk, and to a consequential different decisional strategy. The subgroups analysis of the TIMACS and VERDICT patients with a GRACE score >140 does not allow, however, to draw any definitive conclusions, due to the insufficient numeric sample of the population.

Invasive strategy <2 h

Numerous are also the studies concerning a very early (within 2 h) or delayed revascularization strategies in NSTE-ACS patients.[3] The OPTIMA Study (Optimal Timing of PCI in Unstable Angina) randomized 142 patients to a very early (within 2 h) vs a delayed revascularization strategy (median value 25 h). The primary endpoint, a composite of death, non-fatal infarction, and urgent revascularization, was observed more frequently in patients who underwent immediate revascularization ($P = 0.004$); the same result was observed in regard to acute myocardial infarction ($P = 0.005$).[11] The LIPSIA-NSTEMI Trial (Leipzig Immediate vs early and late PercutaneouS coronary Intervention trial in NSTEMI), a three-arm trial, randomized 602 patients to immediate (<2 h), early (10–48 h) and deferred revascularization after, or in case of failure of medical therapy. The median access time to coronary angiography was 1.1 h for the immediate revascularization group, 18.6 h for the early invasive group, and of 67.2 h in the selective strategy group. The primary endpoint was constituted by the creatine phosphokinase-MB peak during hospitalization, as surrogate of the extension of myocardial damage. The study did not observe any differences in the incidence of the primary endpoint nor in the secondary clinical endpoints at 6 months.[12] The RIDDLE-NSTEMI Study (immediate vs. delayed invasive intervention for non-STEMI patients) randomized 323 NSTE-ACS patients who underwent invasive strategy within 2 h or 72 h (median time 62 h). The early invasive therapy arm was superior in the reduction of primary composite endpoint of death and re-infarction at 30 days ($P = 0.008$) and at 1 year, especially for the minor incidence of in-hospital ischaemic recurrence.[13] The ABOARD Study (Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndrome) randomized 352 NSTE-ACS patients to immediate coronary angiography (median value 1 h) or delayed invasive strategy (median value 20 h). The primary endpoint, represented by the median value of troponin peak during hospitalization, was not different in the two groups. After 30 days, the clinical secondary endpoints did not differ in the two groups.[14] The recent EARLY Study (Early or Delayed Revascularization for Intermediate and High-Risk Non-ST-elevation Acute Coronary Syndromes) randomized 741 medium-high risk NSTE-ACS patients to an immediate coronary angiography (within 2 h) vs a delayed strategy (12–72 h) without pre-treatment with dual

antiplatelet therapy. The study showed that an early strategy reduces the primary endpoint (composite of cardiovascular death, ischaemic recurrences in need of urgent revascularization) at 30 days compared to the delayed arm. The result was mainly determined by the reduction of ischaemic recurrences. The absence of dual antiplatelet therapy before coronary angiography could, however, have caused a disadvantage to the delayed arm.[15]

Meta-analysis and ongoing studies

Many meta-analyses, which evaluated the pooled data of randomized controlled trials on NSTE-ACS in unselected patients, and relative to the benefit based on the execution time of coronary angiography, have not shown evidence of superiority of the early strategy with regard to death, non-fatal myocardial infarction or stroke. Some of the meta-analysis have only demonstrated, in the early strategy, a risk reduction of recurrent/refractory ischaemia and a shorter hospital stay.[16-20] Only one meta-analysis observed a benefit in terms of survival in high-risk patients but with an inconclusive interaction test.

The data from the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to recommended Therapies) Registry (1995–2014) pointed out that the implementation of the ESC guidelines has led, in addition to an increase of the number of patients with optimized therapy, also to a significant increase in revascularization procedures and a reduction of mortality and ischaemic events at 1 year, regardless of the execution time of the coronary angiography.[21] The RapidNSTEMI Trial (Very Early vs. Delayed Angiography +/− Intervention on Outcomes in Patients With NSTEMI) (ClinicalTrials.gov Identifier: NCT 03707314), which is currently in the recruitment phase, will provide more reliable data on the efficacy of an early invasive strategy in a contemporary context.

The situation and the issues in Italy

According to the data provided by the 2015 Census of the Italian cardiological facilities conducted by the Italian Association of Hospital Cardiologists (ANMCO) and the Italian Society of Cardiology (SIC), the ratio of the hospitals equipped with Intensive Cardiac Care Units (ICCU) present on national territory is 6.58 to 1 million inhabitants ($n = 395$), while the ratio of the hospitals with Cath Labs that perform coronary angioplasty (PCI) is 4.37 to 1 million inhabitants ($n = 263$), in line with the 2019 data reported by the Italian Society of Interventional Cardiology (SICI_GISE) ($n = 269$).[22] It is therefore quite clear that a relevant number of cardiological facilities with ICCU must necessarily send NSTE-ACS patients to hub centres equipped with Cath Labs. Data from the 2020 National Outcomes Program (NOP) of the Age.na.s (National Agency for Regional Health Services), referred to the year 2019, indicate that in Italy the percentage of myocardial infarctions treated with PCI within 2 days is 49.96%. These data overestimate the percentage of NSTE-ACS patients who underwent PCI within the 48 h, as it also includes STEMI which, in most of the national territory, can benefit from a more structured and efficient network. The NOP also quantifies in over 60 000 the volume of hospital admissions for NSTEMI, presenting a clear indication of the entity of the problem.[23-25]

A recent study, carried out in Emilia Romagna on a 'service strategy' for early access to the Cath Lab of NSTE-ACS patients admitted to spoke hospitals, executed in a region with a well-structured and organized network, reports a medium time, between hospital admission and access to the Cath Lab for coronary angiography/PCI, of 46.6 h (range 27.5–71.2 h).[26] Noteworthy are the data provided by the EYESHOT Study (EmploYed antithrombotic therapies in patients with acute coronary Syndromes Hospitalized in iTalian cardiac care units), a large, multi-centre, observational, prospective registry which enrolled 2585 consecutive patients with acute coronary syndrome in 203 Italian cardiological facilities with ICCU. In this study, the median timing between hospital admission and coronary angiography for the 388 patients with NSTE-ACS was 40.5 h [interquartile range (IQR) 19.8–73.5] in hospitals with Cath Labs and 67.2 h (IQR 42.5–126.7) in those without ($P < 0.0001$).[27] Therefore, it is important to note that in Italy the admission-coronary angiography time-frame varies considerably among centres that have or do not have on-site Cath Labs, and that the proportion of ICCU cardiological facilities with or without Cath Labs is inverted compared to the centres that participated in the EYESHOT Study (66% of Cardiology Services with Cath Labs in the EYESHOT Study and 60% of cardiology centres without Cath Labs according to the Census of Cardiology Services in Italy).[28]

Therefore, the situation in Italy indicates that a significant proportion of Cardiology Services are obliged to send NSTE-ACS patients to the referred hub, that the number of NSTEMI patients is extremely high, that the timings to coronary angiography are far from those recommended by the guidelines, probably due to organizational issues (secondary transport, relations with emergency services, availability of professional health staff and ambulances, possibility of immediate receptivity of hub centres).

Table 2 and *Figures 1 and 2* summarize some of the national data and the main issues caused by the application of the ESC guidelines on early revascularization strategy and same day transfer of NSTE-ACS patients.[22-28]

Non-ST-segment elevation acute coronary syndromes and revascularization timing: the ANMCO proposal

From the overall assessment of the presented data it follows that:

- the scientific evidences, in regard to the superiority of an early invasive strategy versus a delayed strategy in NSTE-ACS patients, do not indicate a clear superiority in terms of the primary endpoint of the largest trials conducted on these patients; the benefit of an early invasive strategy is essentially limited to the need of further revascularizations or to an infarction recurrence. The main trials show limitation in terms

Table 2 Non-ST-segment elevation acute coronary syndrome patients: same-day transfer and coronary angiography within 24 h

Italian data	Problems/issues
Spoke centres (Cardiology Units with ICCU): $n = 395$	An important part of Cardiology Units are obliged to send NSTE-ACS patients to the referred Hub centres
Hub centres (Cardiology Units with Cath Labs): *n*: 263[28]	
N NSTEMI—2019 hospital admission volume: 65 964[24] (*Figure 1*)	Elevated number of hospital admissions for NSTEMI.
PCI in NSTEMI—2019 hospital admission volume: 34 176[23] (*Figure 2*)	Low percentage of AMI treated with PCI within 2 days (including STEMI); difficult to imagine a doubling of such a percentage, in terms of NSTEMI revascularization without contraindications, in half the time (24 h).
AMI treated with PCI within 2 days: 49.96%[25]	
PCI/100 000 inhabitants: 2624 (national average) 31 (regional average from 1623 to 3607)[22]	Considerable unhomogenous data at both local and regional level, to testimony of different organizational levels. Therefore, it is conceivable that an univocal behaviour at regional level for NSTE-ACS is impractical.
pPCI/100 000 inhabitants: 614 (national average) (regional average from 473 to 780)[22]	
Time between hospital admission and coronary angiography/PCI in NSTE-ACS in Italy:	Recent data show that in Italy the time between hospital admission for NSTE-ACS and coronary angiography is about 2 days[26,27] and nearly 3 days in hospitals without Cath Lab.[27]
Average value 46.6 h[26]	
Average value 40.5 h in hospitals with Cath Lab[27]	
Average value 67.2 h in hospitals without Cath Lab[27]	
Current national cardiology units organization structured in Hub and Spoke centres	If the recommendations of the European guidelines were applied to the letter, the role of spoke centres would be reduced in favour of a 'centralization' of patients, with inevitable organizational and logistics repercussions.
	Spoke centres: need for '*ad hoc*' medical and nursing staff shift work for transfers (dubious cost/efficacy), ready availability for daytime/working days not allowed by the NCLA, secondary transport resources not viable for in-service medical staff, already engaged in the ward/surgery.
	Hub centres: need for a structuring of a network with similar characteristics to the STEMI network, at the moment not feasible due to the non-programmable 'emergency' procedures, the availability of hospital beds and the overload of non-programmable procedures. Pre-holiday and holiday activities not at the same level as working days.
Organization of 'back transfer' applied in many local realities to the Spoke centres for ACS-NSTE cases.	Organization of 'back transfer' not feasible in case of extended early invasive strategy and same-day transfers (difficult application of a 'STEMI-like' network for immediate revascularization and re-transfer to the spoke centres). Only few NSTE-ACS patients could undergo coronary angiography/revascularization at arrival at the hub centre, to allow an early re-transfer to the spoke centre after the procedure.

The Italian issues and data.

AMI, acute myocardial infarction; ICCU, intensive cardiac care unit; NCLA, national collective labour agreement; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, primary coronary angioplasty; pPCI, primary coronary angioplasty; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction.

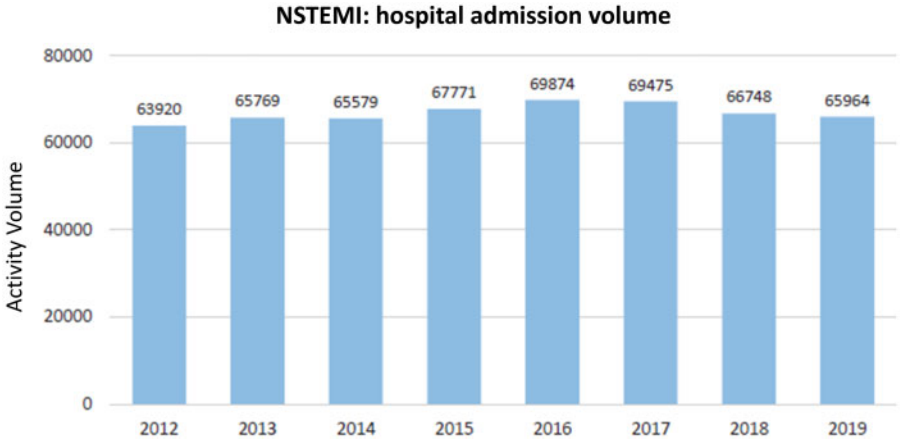

Figure 1 Non-ST-segment elevation myocardial infarction: hospital admission time curve in Italy.

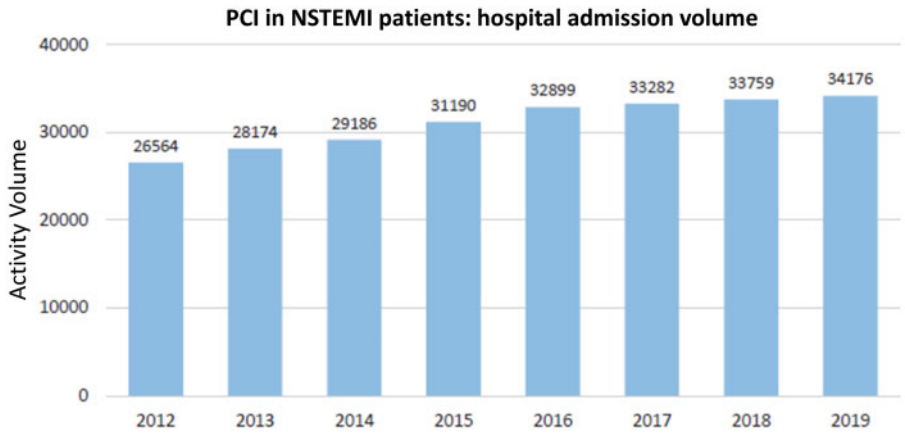

Figure 2 Coronary angioplasty (primary coronary angioplasty) in patients with non-ST-segment elevation myocardial infarction: hospital admission time curve in Italy.[23]

Table 3 Non-ST-segment elevation acute coronary syndrome patients: ANMCO proposal for risk stratification and coronary angiography/revascularization timing

Risk stratification	Category	Invasive strategy timing
Very high risk	Hemodynamic instability, cardiogentic shock, recurrent chest pain or refractory to medical treatment, life-threatening arrhythmias, mechanical complications, acute heart failure clearly related to NSTE-ACS, ST-Segment depression >1 mm in ≥6 leads plus elevation in aVR and/or V1	Immediate (<2 h)
High risk	GRACE risk score >140 Resuscitated cardiac arrest in absence of STEMI or cardiogenic shock	Within 72 h
Medium risk	Defined diagnosis of NSTEMI New or presumed new dynamic ST/T variations (silent or with symptoms at admission but responsive to treatment).	Preferably within 72 h, however always during index hospitalization
Low risk	Absence of medium, high or very high-risk characteristics	Selective invasive strategy; if indicated to be performed during index hospitalization

NSTEMI, Non-ST-Segment Elevation Myocardial Infarction; NSTE-ACS, Non-ST-Segment Elevation Acute Coronary Syndromes; STEMI, ST-Segment Elevation Myocardial Infarction.

of 'underpowerment' with respect to the number of events;
- the results of smaller studies, as well as the results of meta-analysis on the topic, are contrasting;
- the optimal timing of coronary angiography in NSTE-ACS patients therefore still constitutes a 'gap in evidence' that needs to be filled through adequate sized randomized clinical trials, as also pointed out by the authors of the guidelines[29];
- the Italian reality shows that a large number of the Cardiology Services with ICCUs must refer to centres with Cath Labs;
- the issue regarding secondary transport, being unable to provide a same-day transfer of NSTE-ACS patients, is particularly relevant in many regional realities;
- the hub centres could not be able to deal with the impact of an immediate transfer of NSTE-ACS patients from the spoke centres;
- an analysis of subgroups of the largest trials shows that the benefit of an early revascularization strategy, in terms of 'hard' endpoint, is obtained in patients with a GRACE score >140 (quantified in about one-third of the total NSTE-ACS patients). However, such data derive from the analysis of subgroups with insufficient statistical power to draw definitive conclusions;
- the data of the 2020 NOP, which refer to the year 2019,[23,24] relative to the number of revascularization procedures in NSTEMI patients (over 34 000), indicate that in the national reality the early revascularization strategy in all NSTE-ACS patients is not feasible, at the moment;
- the local and regional realities show heterogeneous data in terms of early revascularization rate, also for primary PCI,[22] demonstrating significant differences in resources/organization.

On the basis of such a premise, it seems reasonable to propose a timing for revascularization in NSTE-ACS patients that necessarily takes into account the scientific evidence and the regional issues that render impractical both an extended strategy of revascularization within 24 h and the application of the principle of "same day transfer" (*Table 3*). It is important to take into consideration that the timing proposal interests 'quantitatively' especially the NSTEMI subgroups that, with the use of high sensitivity troponin, represent the majority of NSTE-ACS.

The proposal does not take into account the presence of any comorbidities, such as anaemia and renal impairment, that inevitably need minimal aetiological investigations or treatment that could lead to a reasonable delay in the execution of the coronary angiography. On this issue, we note that the data deriving from the VALIDATE-SWEDEHEART (Bivalirudin vs. Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy In the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Registry)[30] indicate that about 15% of the patients with acute coronary syndrome present anaemia (defined by a $<$13 g/dL haemoglobin value in males and $<$12 g/dL in females) and confirm a high prevalence of renal insufficiency (defined by an estimated glomerular filtration rate $<$60 mL/min/1.73 m^2), present in 31% of the anaemic patients and in 13% of the non-anaemic patients.

Conclusions

The scientific evidences relative to 'hard' endpoint are not univocal in presenting a significative advantage of an early revascularization strategy in a population of unselected NSTE-ACS patients. In addition, the epidemiological and organizational data in Italy do not allow a literal application of the ESC guidelines on NSTE-ACS, with regard to the recommendations to perform coronary angiography within 24 h from admission with a same-day transfer to a hub centre. The ANMCO proposal is a necessary and reasonable compromise in consideration of all the available scientific evidences and the organizational possibilities of a considerable part of national cardiology services.

Conflict of interest: none declared.

Disclaimers

This Position Paper was originally published in the Italian language in 'Position paper ANMCO: Timing di esecuzione della coronarografia in pazienti con sindrome coronarica acuta senza sopraslivellamento del tratto ST', official journal of Italian Federation of Cardiology (IFC), published by Il Pensiero Scientifico Editore. Translated by a representative of the Italian Association of Hospital Cardiologists (ANMCO) and reprinted by permission of IFC and Il Pensiero Scientifico Editore.

References

1. Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;**42**:1289–1367.
2. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Mickley H, Crea F, Van de Werf F, Bucciarelli-Ducci C, Katus HA, Pinto FJ, Antman EM, Hamm CW, De Caterina R, Januzzi JL, Apple FS, Alonso Garcia MA, Underwood SR, Canty JM, Lyon AR, Devereaux PJ, Zamorano JL, Lindahl B, Weintraub WS, Newby LK, Virmani R, Vranckx P, Cutlip D, Gibbons RJ, Smith SC, Atar D, Luepker RV, Robertson RM, Bonow RO, Steg PG, O'Gara PT, Fox KAA, Hasdai D, Aboyans V, Achenbach S, Agewall S, Alexander T, Avezum A, Barbato E, Bassand J-P, Bates E, Bittl JA, Breithardt G, Bueno H, Bugiardini R, Cohen MG, Dangas G, de Lemos JA, Delgado V, Filippatos G, Fry E, Granger CB, Halvorsen S, Hlatky MA, Ibanez B, James S, Kastrati A, Leclercq C, Mahaffey KW, Mehta L, Müller C, Patrono C, Piepoli MF, Piñeiro D, Roffi M, Rubboli A, Sharma S, Simpson IA, Tendera M, Valgimigli M, van der Wal AC, Windecker S, Chettibi M, Hayrapetyan H, Roithinger FX, Aliyev F, Sujayeva V, Claeys MJ, Smajić E, Kala P, Iversen KK, El Hefny E, Marandi T, Porela P, Antov S, Gilard M, Blankenberg S, Davlouros P, Gudnason T, Alcalai R, Colivicchi F, Elezi S, Baitova G, Zakke I, Gustiene O, Beissel J, Dingli P, Grosu A, Damman P, Juliebø V, Legutko J, Morais J, Tatu-Chitoiu G, Yakovlev A, Zavatta M, Nedeljkovic M, Radsel P, Sionis A, Jemberg T, Müller C, Abid L, Abaci A, Parkhomenko A, Corbett S; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;**40**:237–269.
3. Zagnoni S, Bernucci D, Verardi FM, Cardelli LS, Massafra RF, Verardi R, Filippini E, D'Angelo C, Galvani M, Di Pasquale G, Casella G... Strategia invasiva precoce ($<$24 h) nelle sindromi coronariche acute senza sopraslivellamento del tratto ST ad alto rischio, ovvero quando le raccomandazioni delle linee guida dovrebbero essere contestualizzate. *G Ital Cardiol* 2020;**21**:835–846.
4. Neumann F-J, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn H-P, Schmitt C, Seyfarth M, Dirschinger J, Schömig A. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA* 2003;**290**:1593–1599.
5. van't Hof AWJ, de Vries ST, Dambrink J-HE, Miedema K, Suryapranata H, Hoorntje JCA, Gosselink ATM, Zijlstra F, de Boer M-J, .. A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: results of the Early or Late Intervention in unstable Angina (ELISA) pilot study 2b/3a upstream therapy and acute coronary syndromes. *Eur Heart J* 2003;**24**:1401–1405.
6. Badings EA, The SHK, Dambrink J-HE, van Wijngaarden J, Tjeerdsma G, Rasoul S, Timmer JR, van der Wielen MLJ, Lok DJA, van 't Hof AWJ. Early or late intervention in high-risk non-ST-elevation acute coronary syndromes: results of the ELISA-3 trial. *EuroIntervention* 2013;**9**:54–61.
7. Zhang MB, Guo C, Li M, Lv YH, Fan YD, Wang ZL. Comparison of early and delayed invasive strategies in short-medium term among patients with non-ST segment elevation acute coronary syndrome: a systematic review and meta-analysis. *PLoS One* 2019;**14**:e0220847.
8. de Winter RJ, Windhausen F, Cornel JH, Dunselman PHJM, Janus CL, Bendermacher PEF, Michels HR, Sanders GT, Tijssen JGP, Verheugt FWA; 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.
9. Kofoed KF, Kelbæk H, Hansen PR, Torp-Pedersen C, Høfsten D, Kløvgaard L, Holmvang L, Helqvist S, Jørgensen E, Galatius S, Pedersen F, Bang L, Saunamaki K, Clemmensen P, Linde JJ, Heitmann M, Wendelboe Nielsen O, Raymond IE, Kristiansen OP, Svendsen IH, Bech J, Dominguez Vall-Lamora MH, Kragelund C, Hansen TF, Dahlgaard Hove J, Jørgensen T, Fornitz GG, Steffensen R, Jurlander B, Abdulla J, Lyngbæk S, Elming H, Therkelsen SK, Abildgaard U, Jensen JS, Gislason G, Køber LV, Engstrøm T. Early versus standard

care invasive examination and treatment of patients with non-ST-segment elevation acute coronary syndrome. *Circulation* 2018;**138**: 2741–2750.
10. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand J-P, Faxon DP, Afzal R, Chrolavicius S, Jolly SS, Widimsky P, Avezum A, Rupprecht H-J, Zhu J, Col J, Natarajan MK, Horsman C, Fox KAA, Yusuf S; TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009;**360**:2165–2175.
11. Riezebos RK, Ronner E, Ter Bals E, Slagboom T, Smits PC, ten Berg JM, Kiemeneij F, Amoroso G, Patterson MS, Suttorp MJ, Tijssen JGP, Laarman GJ; OPTIMA Trial. Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. *Heart* 2009;**95**:807–812.
12. Thiele H, Rach J, Klein N, Pfeiffer D, Hartmann A, Hambrecht R, Sick P, Eitel I, Desch S, Schuler G; LIPSIA-NSTEMI Trial Group. Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI trial). *Eur Heart J* 2012;**33**:2035–2043.
13. 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.
14. Montalescot G, Cayla G, Collet J-P, Elhadad S, Beygui F, Le Breton H, Choussat R, Leclercq F, Silvain J, Duclos F, Aout M, Dubois-Randé J-L, Barthélémy O, Ducrocq G, Bellemain-Appaix A, Payot L, Steg P-G, Henry P, Spaulding C, Vicaut E; ABOARD Investigators. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. *JAMA* 2009;**302**:947–954.
15. Lemesle G, Laine M, Pankert M, Boueri Z, Motreff P, Paganelli F, Baumstarck K, Roch A, Kerbaul F, Puymirat E, Bonello L. Optimal timing of intervention in NSTEACS without pre-treatment: the EARLY randomized trial. *JACC Cardiovasc Interv* 2020;**13**:907–917.
16. Navarese EP, Gurbel PA, Andreotti F, Tantry U, Jeong Y-H, Kozinski M, Engstrøm T, Di Pasquale G, Kochman W, Ardissino D, Kedhi E, Stone GW, Kubica J. 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**:261–270.
17. Milasinovic D, Milosevic A, Marinkovic J, Vukcevic V, Ristic A, Asanin M, Stankovic G. Timing of invasive strategy in NSTE-ACS patients and effect on clinical outcomes: a systematic review and meta-analysis of randomized controlled trials. *Atherosclerosis* 2015;**241**:48–54.
18. Jobs A, Mehta SR, Montalescot G, Vicaut E, Van't Hof AWJ, Badings EA, Neumann F-J, Kastrati A, Sciahbasi A, Reuter P-G, 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.
19. Katritsis DG, Siontis GCM, Kastrati A, van't Hof AWJ, Neumann F-J, Siontis KCM, Ioannidis JPA. Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. *Eur Heart J* 2011;**32**:32–40.
20. 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.
21. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, James S, Kellerth T, Lindahl B, Ravn-Fischer A, Rydberg E, Yndigegn T, Jernberg T. Relations between implementation of new treatments and improved outcomes in patients with non-ST-elevation myocardial infarction during the last 20 years: experiences from SWEDEHEART registry 1995 to 2014. *Eur Heart J* 2018;**39**:3766–3776.
22. SICI-GISE (Società Italiana di Cardiologia Invasiva) - Dati di attività dei Laboratori di Emodinamica 2019. *G Ital Cardiol* 2020;**17**:6–42.
23. Programma Nazionale Esiti – Agenzia Nazionale per i Servizi Sanitari Regionali, edizione 2020. PTCA in pazienti NSTEMI: volume di ricoveri. https://pne.agenas.it/risultati/tipo5/intr_struasl5_HC.php?ind=152&tipo=5&area=1 (12 April 2021).
24. Programma Nazionale Esiti – Agenzia Nazionale per i Servizi Sanitari Regionali, edizione 2020. N-STEMI: volume di ricoveri. https://pne.agenas.it/risultati/tipo5/intr_struasl5_HC.php?ind=99&tipo=5&area=1 (12 April 2021).
25. Programma Nazionale Esiti – Agenzia Nazionale per i Servizi Sanitari Regionali, edizione 2020. Infarto miocardico acuto: proporzione di trattati con PTCA entro 2 giorni. https://pne.agenas.it/risultati/tipo1/intr_struasl1_HC.php?ind=6&tipo=2&area=1 (12 April 2021).
26. Mantovani F, Guiducci V, Colaiori I, *Pignatelli G, Manca F, Guerri E, Calzolari M, Catellani E, Reverzani A, Navazio A...* Strategia "service" per l'accesso precoce all'Emodinamica dei pazienti con sindrome coronarica acuta senza sopraslivellamento del tratto ST ricoverati presso gli ospedali spoke: risultati a 5 anni dei percorsi assistenziali della rete cardiologica provinciale di Reggio Emilia. *G Ital Cardiol* 2020;**21**:807–815.
27. De Luca L, Leonardi S, Smecca IM, Formigli D, Lucci D, Gonzini L, Tuccillo B, Olivari Z, Gulizia MM, Bovenzi FM, De Servi S; EYESHOT Investigators. Contemporary antithrombotic strategies in patients with acute coronary syndromes managed without revascularization: insights from the EYESHOT study. *Eur Heart J Cardiovasc Pharmacother* 2015;**1**:168–178.
28. Gulizia MM, Gregorio G, Lucci D, Romeo F. Struttura ed organizzazione della Cardiologia italiana. 7° Censimento delle Strutture Cardiologiche in Italia. Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) - Società Italiana di Cardiologia (SIC) Anno 2015. *G Ital Cardiol* 2017;**18**:337–459.
29. Di Pasquale G, Casella G, Navazio A, Galvani M. Il timing della coronarografia nelle linee guida ESC 2020 sulle sindromi coronariche acute senza sopraslivellamento del tratto ST: quando le linee guida non aiutano. *G Ital Cardiol* 2021;**22**:336.
30. Wester A, Attar R, Mohammad MA, *Andell P, Hofmann R, Jensen J, Szummer K, Erlinge D, Koul S...* Impact of baseline anemia in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a prespecified analysis from the VALIDATE-SWEDEHEART trial. *J Am Heart Assoc* 2019;**8**:e012741.