Three-year outcomes between early and delayed invasive strategies in older adults with non-ST-segment elevation myocardial infarction receiving new- generation drug-eluting stents

Yong Hoon Kim (yhkim02@kangwon.ac.kr)
Kangwon National University School of Medicine
Ae-Young Her
Kangwon National University School of Medicine
Seung-Woon Rha
Korea University Guro Hospital
Cheol Ung Choi
Korea University Guro Hospital
Byoung Geol choi
Korea University Guro Hospital
Ji Bak Kim
Korea University Guro Hospital
Soohyung Park
Korea University Guro Hospital
Dong Oh Kang
Korea University Guro Hospital
Ji Young Park
Eulji University
Sang-Ho Park
Soonchunhyang University Cheonan Hospital
Myung Ho Jeong
Chonnam National University Hospital

Article

Keywords: drug-eluting stent, elderly, non-ST-segment elevation myocardial infarction, percutaneous coronary intervention

Posted Date: April 21st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1540475/v1

Abstract

We evaluated the 3-year clinical outcomes following early invasive (EI) and delayed invasive (DI) strategies in older adults with non-ST-segment elevation myocardial infarction (NSTEMI) undergoing successful new-generation drug-eluting stents (DESs) implantation to reflect current real-world practice. Overall, 4513 patients with NSTEMI were recruited from Korea Acute Myocardial Infarction Registry-National Institute of Health. They were divided into two groups according to their ages: group A (age ≥65 years, n = 2,253) and group B (age <65 years, n = 2,260). These two groups of patients were further divided into two subgroups: group EI (A1 or B1) and DI (A2 or B2). The primary clinical outcome was the occurrence of major adverse cardiac and cerebrovascular events (MACCEs), defined by all-cause death, recurrent MI (re-MI), and any repeat coronary revascularization. The secondary clinical outcome was stent thrombosis (ST). In both, group A and B, after multivariable-adjusted and propensity score-adjusted analyses, the primary and secondary clinical outcomes were not significantly different between the EI and DI groups. Even after the analysis was confined to those having complex lesions, these major clinical outcomes were similar between these two groups. The EI and DI strategies in older adults with NSTEMI receiving new-generation DES showed comparable results.

Clinical Trial Registration: URL: http://cris.nih.go.kr/cris/en/; Unique identifier: KCT0000863.

Introduction

In patients with non-ST-segment elevation (STE) acute coronary syndrome (NSTE-ACS), an early invasive (EI) strategy is defined as coronary angiography (CAG) and percutaneous coronary intervention (PCI) performed within 24 hours of hospital admission (1, 2). The European guideline recommends an EI strategy in patients with a high-risk (≥ 1) criterion, including an established non-STE myocardial infarction (MI) (NSTEMI) diagnosis, dynamic new or presumably new continuous ST/T-segment changes, resuscitated cardiac arrest without STE or cardiogenic shock or a high Global Registry of Acute Coronary Events (GRACE) risk score (> 140) (class 1 and level of evidence A) (1). The American College of Cardiology/American Heart Association guideline recommends an EI strategy for initially stabilized high-risk patients with NSTE-ACS and a delayed invasive (DI) strategy defined as CAG and PCI performed after 24 hours of hospital admission as reasonable for high/intermediate risk patients (class IIa and level of evidence B) (1, 2). The preference for EI strategy in patients with NSTEMI in the European and American guidelines are based on the result of the Timing of Intervention in Acute Coronary Syndrome (TIMACS) trial (3). This trial showed that individuals who underwent invasive CAG within 24 hours of admission had a reduced rate of recurrent ischemia at 6 months when compared with CAG ≥ 36 hours after admission (hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.58–0.89; $p = 0.003$) (3). The data from a recent registry (4) showed that in high-risk (GRACE score ≥ 140) NSTE-ACS patients, early CAG was associated with significantly reduced mortality rate (HR, 0.79; 95% CI, 0.62–0.98). In the Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography study comprising a mean follow-up of 4.3 years, a very early strategy (median time from diagnosis to revascularization = 4.7 hours) improved the primary outcomes compared with the standard invasive treatment (HR, 0.81; 95% CI, 0.67–1.01) in the high-risk subgroup but did not improve overall long-term clinical outcomes compared with an invasive strategy conducted within 2 to 3 days in patients with NSTE-ACS (5). In another study, the EI strategy did not significantly reduce the risk of death or MI except for recurrent ischemia and the duration of in-hospital stay (6). Hence, the optimal timing of PCI in NSTEMI has not been conclusively defined. For NSTE-ACS, age was an important determinant of outcomes in those patients (7, 8). However, the published data concerning the results of an EI strategy in the context of the older patients with NSTEMI are limited and are the subject of this study (1). Tegn et al. reported that invasive strategy was superior to a conservative strategy for the reduction of MI, urgent revascularization, stroke, and death in patients aged ≥ 80 years with NSTE-ACS (9). Unfortunately, the majority of the previous studies did not confine the study population to patients who received successful PCI or those who received new-generation drug-eluting stents (DESs) (3–8). Currently, the new-generation DESs have nearly replaced bare-metal stents and first-generation DES for routine PCI; the new-generation DES is more effective than first-generation DES in reducing major clinical outcomes in patients with acute MI (AMI) (10). Although we believe that these previous studies (3–8) are valuable for estimating comparative clinical outcomes among different treatment strategies (EI, DI, or conservative treatment) in patients with NSTE-ACS, their findings have some limitations with respect to the current real-world practices. Hence, in this study, we evaluated the 3-year major clinical outcomes between the EI and DI strategies in older adults with NSTEMI undergoing successful new-generation DES implantation.

Results

Baseline characteristics. Table 1 and Supplementary Table S1 show the baseline, laboratory, angiographic, and procedural characteristics of the study population. In both group A and B, the mean values of peak creatine kinase myocardial band (CK-MB), and Troponin-I, and the number of patients with pre-PCI thrombolysis in myocardial infarction (TIMI) flow grade 0/1 were higher in the EI group (group A1 or B1) than in DI (group A2 or B2). In contrast, the patients who had Killip class ≥ 3, had reduced renal function (estimated glomerular filtration rate [eGFR], < 60 mL/min/1.73 m^2), and received clopidogrel as discharge medication; mean value of serum creatinine; the use of intravascular ultrasound/optical coherent tomography/fractional flow rate were higher in the DI group than in EI. In group A (group A1 and A2), the mean value of left ventricular ejection fraction (LVEF), the number of current smokers, and the prescription rates of ticagrelor, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as discharge medications were higher in the EI group (group A1) than those in DI (group A2). However, the mean age of enrolled patients; mean values of BMI, SBP, and DBP; number of patients with dyslipidemia and multivessel disease; and mean number of deployed stents were higher in the DI group (group A2) than in EI (group A1). In group B (group B1 and B2), the prescription rates of prasugrel, beta-blockers, and statin; the use of glycoprotein IIb/IIIa inhibitor; and transradial approach were higher in the EI group (group B1) than in DI (group B2). In contrast, the number of patients with previous MI and PCI, and higher GRACE risk score (> 140) were higher in the DI group (group B2) than in EI (group B1) (Table 1).

Clinical Outcomes. The 3-year major clinical outcomes are summarized in Table 2 and Fig. 1. After multivariable-adjusted analysis, in group A, the major adverse cardiac and cerebrovascular events (MACCE, adjusted HR [aHR], 1.198; 95% CI, 0.944–1.521; $p = 0.137$), all-cause death (aHR, 1.150; $p = 0.434$), cardiac death (CD, aHR, 1.100; $p = 0.692$), non-CD (aHR, 1.207; $p = 0.485$), recurrent MI (re-MI, aHR, 1.061; $p = 0.809$), any repeat revascularization (aHR, 1.247; $p = 0.186$), stroke (aHR, 1.255; $p = 0.394$), and stent thrombosis (ST [definite or probable], aHR, 2.969; 95% CI, 0.978–9.017; $p = 0.055$) rates were not significantly different between group A1 and A2. In group B, the MACCE (aHR, 1.236; 95% CI, 0.913–1.673; $p = 0.171$), all-cause death (aHR, 1.065; $p = 0.869$), CD (aHR, 1.359; $p = 0.527$), non-CD (aHR, 1.447; $p = 0.570$), re-MI (aHR, 1.259; $p = 0.478$), any repeat revascularization (aHR, 1.289; $p = 0.145$), stroke (aHR, 1.523; $p = 0.299$), and ST (definite or probable, aHR, 4.152; 95% CI, 0.501–32.82; $p = 0.101$) rates were not significantly different between group B1 and B2. In the total study population, MACCE (aHR, 1.199; 95% CI, 0.995–1.445; $p = 0.056$), all-cause death (aHR, 1.078; $p = 0.636$), CD (aHR, 1.060; $p = 0.780$), non-CD (aHR, 1.281; $p = 0.313$), re-MI (aHR, 1.034; $p = 0.864$), any repeat revascularization (aHR, 1.258; $p = 0.056$), stroke (aHR, 1.351; $p = 0.175$), and ST (definite or probable, aHR, 1.091; 95% CI, 0.449–2.651; $p = 0.847$) rates were not significantly different between the EI group (group A1 + B1) and DI group (group A2 + B2) (Table 2). These results were confirmed after PS-adjusted analysis. After PS-adjusted analysis in both group A and B, the primary and secondary clinical outcomes were not significantly different between groups A1 and A2 or groups B1 and B2 (Table 2). For further assessment of major clinical outcomes between the EI and DI groups of group A and B, we compared these major clinical outcomes by limiting the study population to patients with complex lesions (Table 3). The number of patients with complex lesions in each group was more than 40% (group A1, 49.6%; group A2, 55.5%; group B1, 40.9%; group B2, 46.5%) (Fig. 2). The MACCE rates were similar between the EI and DI group (group A1 vs. group A2; aHR, 1.149; 95% CI, 0.843–1.564; $p = 0.379$; group B1 vs. group B2; aHR, 1.136; 95% CI, 0.754–1.713; $p = 0.542$) (Table 3). The ST (definite or probable) rates were also similar between the EI and DI group (group A1 vs. group A2; aHR, 3.777; 95% CI, 0.673–116.94; $p = 0.139$; group B1 vs. group B2; aHR, 1.140; 95% CI, 0.030–43.82; $p = 0.944$, Table 3). Additionally, the all-cause death, CD, non-CD, re-MI, any repeat revascularization, and stroke rates were not significantly different between the EI group and DI groups after adjustment (Table 3). Figure 3 shows the subgroup analysis for MACCE in groups A and B. The results of subgroup analysis using Cox logistic regression model revealed that in the all subgroups except for those showing significant *p*-for-interaction demonstrated comparable MACCE rates in this study.

Discussion

The main findings of this prospective, observational study were: (1) in both groups A and B, after multivariable-adjusted and PS-adjusted analyses, MACCE, all-cause death, CD, non-CD, re-MI, any repeat revascularization, stroke, and ST (definite or probable) rates were similar between the EI and DI groups; (2) even after limiting the study population to patients who had complex lesions

in both group A and B, the primary and secondary clinical outcomes were not significantly different between the EI and DI groups.

Theoretically, through the EI strategy, the operator could find significant lesions earlier in patients with NSTEMI and could have the opportunity for early revascularization, salvage of ischemic myocardium, and facilitation of earlier discharge from a facility (2, 11). In contrast, DI strategy may provide adequate time for optimal medical treatment in order to decrease thrombus burden and improve plaque stability (11). In the recent European guideline, the recommended diagnostic and interventional strategies for older patients and younger patients are the same (class I and level of evidence B) (1). However, the optimal timing of PCI in NSTEMI remains a subject of debate. The clinical presentation of NSTE-ACS in older person is atypical (12, 13) and the electrocardiographic changes are less frequent in older than in younger patients (8, 13). Despite the significant decrease in mortality and morbidities of ACS because of evidence based therapy (14), these improvements in ACS treatment strategy have not equally improved outcomes for older adults (2). Regarding these characteristics (2, 8, 12, 13) in older people, the information dealing with the preferred treatment option between the EI and DI strategies could be important for the interventional cardiologist. In the old reports, EI strategy showed significantly improved clinical outcomes compared with conservative treatment in elderly patients with NSTE-ACS (31, 32). However, these studies were not performed in the era of new-generation DES and that did not compare clinical outcomes between the EI and DI strategies (15, 16). Furthermore, since the available data on this subject is limited (9), the comparative results between the EI and DI strategies in older patients with NSTEMI are limited. Hence, in this study, we investigated the long-term clinical outcomes between the EI and DI strategies in older adults with NSTEMI undergoing successful new-generation DES implantation. In our study, the major clinical outcomes were not significantly different between the EI and DI groups after adjustments (multivariable or PS-adjusted) during a 3-year follow-up period. The current guidelines suggested that older patients with NSTE-ACS should be considered for invasive management with CAG and PCI (1, 2). An EI strategy is useful but increases the risks of stroke and bleeding, which are the main complications of this strategy (15, 16). The key study of the current guidelines (1, 2) was the TIMACS trial (3). Since the study was performed between April 2003 and June 2008; nearly half of the cases used bare-metal stents, and the first-generation DES might be used at that time. Moreover, less than 60% of the patients underwent PCI. At 6 months, the primary outcome (a composite of death, MI, or stroke) were similar between the EI and DI groups (HR, 0.85; 95% CI, 0.68–1.06; $p = 0.15$) (3). Although this study showed valuable results for understanding the beneficial effect of EI CAG in patients with ACS (3), accounting for the limitations mentioned, the results of our study could be more impactful. In the most recently published registry data, the EI strategy was associated with lower all-cause death (HR, 0.61; 95% CI, 0.51–0.71), CD (HR, 0.52; 95% CI, 0.43–0.63), and MACE (HR, 0.62; 95% CI, 0.54–0.71) than those in the DI strategy (17). However, similarly with TIMACS trial (3), this study was conducted between the years 2003 and 2017. Therefore, the type of DES did not belong to the new-generation DES.

In our study, the proportion of men decreased with age in group A (≥ 65 years) compared with B (< 65 years). Additionally, comorbidities including hypertension, diabetes mellitus, previous MI, previous HF, previous stroke, renal insufficiency (eGFR < 60 mL/min/1.73 m^2) were more prevalent in group A than in B (Table 1). Therefore, the patient characteristics in our study are consistent with the previously published data (9, 17). This increasing prevalence of cardiovascular disease with aging has been attributed to several age-related changes including vascular wall elasticity, coagulation and hemostatic system, and endothelial dysfunction (18–20). Therefore, age related decline in organ function increases cardiovascular diseases (20).

To clearly estimate the long-term clinical outcomes, we performed additional analysis as shown in Table 3. Even after considering the patients with complex lesions, the 3-year major clinical outcomes were not significantly different (Table 3). Subgroup analyses for MACCE in group A and B (Fig. 3) showed that all subgroups except for those showing significant p-for-interaction had comparable MACCE rates.

We agree with the current guideline recommendations that suggest that the management of older patients should be based on ischemic and bleeding risks, estimated life expectancy, comorbidities, the need for non-cardiac surgery, quality of life, frailty, cognitive, functional impairment, patient values and preferences, and the estimated risks and benefits of revascularization (1). Our results showed that in the era of new-generation DES, the major clinical outcomes were not significantly different between the EI and DI strategies in older adults with NSTEMI after successful stent implantation during a 3-year follow-up period. Hence, we suggested that the current guideline (1, 2) about the management of older patients with NATE-ACS with CAG and PCI needs

to be reevaluated under the era of new-generation DES. In this study, although the population may have been insufficient to provide meaningful results, 20 tertiary high-volume University hospitals participated in the registry. Therefore, we believe that our results could provide helpful information to interventional cardiologists in terms of long-term effects of EI and DI strategies in older adults with NSTEMI undergoing successful implantation of new-generation DES.

This study had other limitations. First, even though this study is a prospective, observational registry, it is not a randomized controlled study; there may have been some selection bias. Moreover, the variables that were not included in the data registry might have affected the study outcome despite the multivariable and PS-adjusted analyses. Second, because we set the cut-off value of older adults at age ≥ 65 years in our study, our results could change according to different cut-off ages. Third, as mentioned, although bleeding is an important complication that occurs after PCI in older adults (15, 16), anti-platelet therapy after 1 year index PCI was different among the physicians; we could not include bleeding complication as an outcome parameter in our study during a 3-year follow-up period. This is a major shortcoming of our study. Fourth, the 3-year follow-up duration was insufficient to evaluate long-term adverse events.

In conclusion, in the era of new-generation DES, the major clinical outcomes were not significantly different between the EI and DI strategies in older adults with NSTEMI after successful stent implantation during a 3-year follow-up period. However, further randomized, large-scale, and long-term follow-up studies are needed to clarify the differences of the clinical outcomes between these two different reperfusion strategies in those patients.

Methods

Study population. A total of 13,104 patients with AMI between November 2011 and December 2015 were recruited from Korea AMI Registry-National Institute of Health (KAMIR-NIH) (21). KAMIR-NIH is a nation-wide prospective multicenter registry integrated from 20 high-volume centers in the Republic of Korea. Detailed information on this registry can be found on the website (http://www.kamir.or.kr). All patients aged ≥ 18 years at the time of hospital admission were included. Patients who did not receive PCI (n = 1,369, 10.4%) or who received unsuccessful PCI (failed PCI [n = 61, 0.5%] and suboptimal PCI [n = 94, 0.7%]), received plain old balloon angioplasty (n = 739, 5.6%), were treated with bare-metal stent or first-generation DES (n = 563, 4.3%), underwent coronary artery bypass graft (n = 38, 0.3%), had STE MI (STEMI) (n = 5342, 40.8%), had cardiogenic shock or in-hospital death (n = 228, 1.7%), and were unavailable for follow-up (n = 157, 1.2%) were excluded. Overall, 4,513 patients with NSTEMI who underwent successful new-generation DES implantation were included (Fig. 4). The types of new-generation DES used are listed in Table 1. The definition of older adults is controversial. In general, a person is considered old if their civil age is ≥ 60 or 65 years (22). The average age at which individuals experience a first heart attack is 65.8 years for men and 70.4 years for women (13). Additionally, based on the Consensus Development Conference on Diabetes and Older Adults (age ≥ 65 years) convened by the American Diabetes Association in Feb 2012 (23) and other report (24) showed that multimorbidity and polypharmacy are highly prevalent among adults aged ≥ 65 years, we set the cut-off value at ≥ 65 years for older adults in our study. These patients were divided into two groups according to their ages: group A (age ≥ 65 years, n = 2253, 49.9%) or group B (age < 65 years, n = 2260, 50.1%). Subsequently, these two groups of patients were further divided into two subgroups: group EI (group A1 [n = 1612, 71.5%] or B1 [n = 1688, 74.7%]) and DI (group A2 [n = 641, 28.5] or B2 [n = 572, 25.3%]) (Fig. 4). Trained research coordinators at each center collected patient data using a web-based report form on the Internet-based Clinical Research and Trial management system, supported by a grant from the Korean Centers for Disease Control and Prevention since November 2011 (URL: http://cris.nih.go.kr/cris/en/; Unique identifier: KCT0000863; First registration: 01/11/2011). The study was conducted in accordance with the ethical guidelines of the 2004 Declaration of Helsinki. The study was approved by the ethics committee of each participating center and the Chonnam National University Hospital Institutional Review Board ethics committee (CNUH-2011-172). All patients included in the study provided written informed consent prior to enrollment. They were followed-up via face-to-face interviews, phone calls, or chart reviews and they completed a 3-year follow-up schedule. All clinical events were evaluated by an independent event adjudication committee. The event adjudication process has previously been described by the KAMIR investigators (21).

PCI procedure and medical treatment. CAG and PCI were performed via a transfemoral or transradial approach in accordance with the general guidelines (25). Aspirin (200–300 mg) and clopidogrel (300–600 mg), ticagrelor (180 mg), or prasugrel (60 mg)

were prescribed to the patients as loading doses before PCI. After PCI, all patients were recommended to take aspirin (100 mg/day) along with clopidogrel (75 mg/day), ticagrelor (90 mg twice a day), or prasugrel (5–10 mg/day) for at least 1 year. The access site, revascularization strategy, and selection of DES were left to the discretion of the individual operators.

Study definitions and clinical outcomes. NSTEMI was defined as the absence of persistent STE with increased levels of cardiac biomarkers and appropriate clinical context (1, 2). A successful PCI was defined as residual stenosis of < 30% and thrombolysis in MI (TIMI) flow grade 3 in the infarct-related artery. Glomerular function for estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Eq. (26). The GRACE risk score (27) was calculated for all the patients. Complex lesions were defined as PCI for unprotected left main (LM) coronary disease, multivessel PCI, multiple stents implantation (≥ 3 stents per patient), and those with the total length of deployed stent being over 38 mm. (28, 29). The primary clinical outcome was the occurrence of major adverse cardiac and cerebrovascular events (MACCE), which was defined by all-cause death, recurrent MI (re-MI), any repeat coronary revascularization, including target lesion revascularization, target vessel revascularization (TVR), non-TVR, and stroke. According the American Heart Association/American Stroke Association guideline (30), an acute cerebrovascular event resulting in death or neurological deficit for > 24 hours or the presence of acute infarction demonstrated by imaging studies was defined as a stroke. An all-cause death was considered a cardiac death (CD) unless an undisputed non-cardiac cause was present (31). The secondary clinical outcome was definite or probable stent thrombosis (ST) during a 3-year follow-up period. Stent thrombosis was defined according to the definition provided by the Academic Research Consortium (32). The definitions of re-MI, TLR, TVR, and non-TVR have been published previously (33).

Statistical analysis. For continuous variables, the differences between the groups were evaluated using unpaired t-tests. Data are expressed as the mean ± standard deviation, or median (interquartile range). For discrete variables, the differences between the groups were expressed as counts and percentages and were analyzed using the chi-squared or Fisher's exact test. Univariate analysis was performed for all variables of EI and DI groups with the *p*-value set at < 0.05. Subsequently, we performed a multicollinearity test (34) between the included variables to confirm non-collinearity between them (Supplementary Table S2). Variance inflation factor (VIF) values were calculated to measure the degree of multicollinearity among the variables. A VIF of > 5 indicated a high correlation (35). When the tolerance value was < 0.1 (36) or the condition index was > 10 (35), the presence of multicollinearity was considered. The variables included in the multivariable Cox regression analysis were: male sex, left ventricular ejection fraction (LVEF), body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), symptom-to-door time, Killip class ≥ 3, hypertension, diabetes mellitus, dyslipidemia, previous PCI, previous heart failure (HF), previous stroke, current smoker, peak creatine kinase myocardial band (CK-MB), peak troponin-I, serum creatinine, eGFR < 60 mL/min/1.73 m^2), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, GRACE risk score > 140, clopidogrel, ticagrelor, prasugrel, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and statin. Moreover, to adjust for potential confounders, propensity score (PS)-adjusted analysis was performed using a logistic regression model. We tested all potentially relevant variables such as baseline clinical, angiographic, and procedural factors (Table 1). The c-statistic for the PS-matched (PSM) analysis in this study was 0.684. Patients in the EI group were matched to those in the DI group (1:1) using the nearest available pair-matching method according to PSs. The subjects were matched with a caliper width of 0.01. This procedure yielded 2318 well-matched pairs (Supplementary Table S3). Various clinical outcomes were estimated using a Kaplan–Meier curve analysis, and group differences were compared using the log-rank test. Statistical significance was defined as a 2-tailed p-value of < 0.05. All statistical analyses were performed using SPSS software v. 20 (IBM; Armonk, NY, USA).

Declarations

Competing interests

The authors declare no competing interests.

Data availability statement

Data is contained with the article or supplementary material.

FINANCIAL SUPPORT

This research was supported by a fund (2016-ER6304-02) by Research of Korea Centers for Disease Control and Prevention.

AUTHOR CONTRIBITIONS

Y.H.K. and A.-Y.H. researched data and wrote the manuscript. Y.H.K., A.-Y.H., S.-W.R., C.U.C., B.G.C., J.B.K., J.Y.P., and S.-H.P. contributed to study design. S.-W.R., C.U.C., B.G.C., J.B.K., S.P., D.O.K., and M.H.J. contributed to the collection research data. Y.H.K., A.-Y.H., S.-W.R., C.U.C., B.G.C., J.B.K., J.Y.P., S.-H.P., and M.H.J contributed to provide intellectual inputs for the discussion. Y.H.K., A.-Y.H., B.G.C., S.P., D.O.K., J.Y.P., and S.-H.P. contributed to data analysis and edited the manuscript. Y.H.K., S.-W.R., and M.H.J contributed to provide supervisor role during the full processes of manuscript submitting and editing. All authors have read and approved the manuscript, and all authors take full responsibility for this work.

ACKNOWLEDGEMENTS

Investigators of KAMIR-NIH (Korea Acute Myocardial Infarction Registry-National Institutes of Health)

Myung Ho Jeong, Chonnam National University Hospital, Gwangju, Korea, Young Jo Kim, Yeungnam University Medical Center, Daegu, Korea, Chong Jin Kim, Kyunghee University Hospital at Gangdong, Seoul, Korea, Myeong Chan Cho, Chungbuk National University Hospital, Cheongju, Korea, Hyo-Soo Kim, Seoul National University Hospital, Seoul, Korea, Hyeon-Cheol Gwon, Samsung Medical Center, Seoul, Korea, Ki Bae Seung, Seoul St. Mary's Hospital, Seoul, Korea, Dong Joo Oh, Korea University Guro Hospital, Seoul, Korea, Shung Chull Chae, Kyungpook National University Hospital, Daegu, Korea, Kwang Soo Cha, Pusan National University Hospital, Busan, Korea, Junghan Yoon, Wonju Severance Christian Hospital, Wonju, Korea, Jei-Keon Chae, Chonbuk National University Hospital, Jeonju, Korea, Seung Jae Joo, Jeju National University Hospital, Jeju, Korea, Dong-Ju Choi, Seoul National University Bundang Hospital, Bundang, Korea, Seung-Ho Hur, Keimyung University Dongsan Medical Center, Daegu, Korea, In Whan Seong, Chungnam National University Hospital, Daejeon, Korea, Doo Il Kim, Inje University Haeundae Paik Hospital, Busan, Korea, Seok Kyu Oh, Wonkwang University Hospital, Iksan, Korea, Tae Hoon Ahn, Gachon University Gil Medical Center, Incheon, Korea, Jin-Yong Hwang, Gyeongsang National University Hospital, Jinju, Korea.

References

1. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 42, 1289–1367 (2021)
2. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., et al. 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. 64, e139-e228 (2014)
3. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, et al. Early versus delayed invasive intervention in acute coronary syndromes. New Engl J Med. 360, 2165–2175 (2009)
4. Álvarez Álvarez B, Abou Jokh Casas C, Cordero A, Martínez Gómez Á, Cid Álvarez AB, Agra Bermejo R, et al. Early revascularization and long-term mortality in high-risk patients with non-ST-elevation myocardial infarction. The CARDIOCHUS-HUSJ registry. Rev Esp Cardiol (Engl Ed). 73, 35–42 (2020)
5. Kofoed KF, Kelbæk H, Hansen PR, Torp-Pedersen C, Høfsten D, Kløvgaard L, et al. Early Versus Standard Care Invasive Examination and Treatment of Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. Circulation. 138, 2741–2750 (2018)
6. Bonello L, Laine M, Puymirat E, Lemesle G, Thuny F, Paganelli F, 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. 9, 2267–2276 (2016)
7. Fox KA, Eagle KA, Gore JM, Steg PG, Anderson FA. The Global Registry of Acute Coronary Events, 1999 to 2009–GRACE. Heart. 96, 1095–1101 (2010)

8. Rosengren A, Wallentin L, Simoons M, Gitt AK, Behar S, Battler A, et al. Age, clinical presentation, and outcome of acute coronary syndromes in the Euroheart acute coronary syndrome survey. Eur Hear J. 27, 789–795 (2006)
9. Tegn N, Abdelnoor M, Aaberge L, Endresen K, Smith P, Aakhus S, et al. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet. 387, 1057–1065 (2016)
10. Kim YH, Her AY, Jeong MH, Kim BK, Hong SJ, Kim JS, et al. Impact of stent generation on 2-year clinical outcomes in ST-segment elevation myocardial infarction patients with multivessel disease who underwent culprit-only or multivessel percutaneous coronary intervention. Catheter Cardiovasc Interv. 95, E40-E55 (2020)
11. Mahendiran T, Nanchen D, Meier D, Gencer B, Klingenberg R, Räber L, et al. Optimal Timing of Invasive Coronary Angiography following NSTEMI. *J Interv Cardiol*. 2020, 8513257 (2020)
12. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation. 115, 2549–2569 (2007)
13. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, et al. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. Chest. 126, 461–469 (2004)
14. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA, Jr., Granger CB, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999–2006. JAMA. 297, 1892–1900 (2007)
15. Bauer T, Koeth O, Jünger C, Heer T, Wienbergen H, Gitt A, et al. Effect of an invasive strategy on in-hospital outcome in elderly patients with non-ST-elevation myocardial infarction. Eur Heart J. 28, 2873–2878 (2007)
16. Bach RG, Cannon CP, Weintraub WS, DiBattiste PM, Demopoulos LA, Anderson HV, et al. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. Ann Intern Med. 141, 186–195 (2004)
17. González Ferrero T, Álvarez Álvarez B, Cordero A, Martinón Martínez J, Cacho Antonio C, Sestayo-Fernández M, et al. Early angiography in elderly patients with non-ST-segment elevation acute coronary syndrome: The cardio CHUS-HUSJ registry. Int J Cardiol. 351, 8–14 (2022)
18. Abbate R, Prisco D, Rostagno C, Boddi M, Gensini GF. Age-related changes in the hemostatic system. Int J Clin Lab Res. 23, 1–3 (1993)
19. Brandes RP, Fleming I, Busse R. Endothelial aging. Cardiovasc Res. 66, 286–294 (2005)
20. Usta C, Bedel A. Update on pharmacological treatment of acute coronary syndrome without persistent ST segment elevation myocardial infarction in the elderly. J Geriatr Cardiol. 14, 457–464 (2017)
21. Kim JH, Chae SC, Oh DJ, Kim HS, Kim YJ, Ahn Y, et al. Multicenter Cohort Study of Acute Myocardial Infarction in Koreaã-Interim Analysis of the Korea Acute Myocardial Infarction Registry-National Institutes of Health Registry. Cir J. 80, 1427–1436 (2016)
22. Kim YH, Her AY, Jeong MH, Kim BK, Hong SJ, Park SH, et al. Outcomes between prediabetes and type 2 diabetes mellitus in older adults with acute myocardial infarction in the era of newer-generation drug-eluting stents: a retrospective observational study. BMC geriatrics. 21, 653 (2021)
23. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al. Diabetes in older adults. Diabetes care. 35, 2650–2664 (2012)
24. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 380, 37–43 (2012)
25. Grech ED. ABC of interventional cardiology: percutaneous coronary intervention. II: the procedure. BMJ. 326, 1137–1140 (2003)
26. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 150, 604–612 (2009)

27. Pieper KS, Gore JM, FitzGerald G, Granger CB, Goldberg RJ, Steg G, et al. Validity of a risk-prediction tool for hospital mortality: the Global Registry of Acute Coronary Events. Am Heart J. 157, 1097–1105 (2009)
28. Choi KH, Song YB, Lee JM, Lee SY, Park TK, Yang JH, et al. Impact of Intravascular Ultrasound-Guided Percutaneous Coronary Intervention on Long-Term Clinical Outcomes in Patients Undergoing Complex Procedures. JACC Cardiovasc Interv. 12, 607–620 (2019)
29. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 39, 213–260 (2018)
30. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 44, 2064–2089 (2013)
31. Lee JM, Rhee TM, Hahn JY, Kim HK, Park J, Hwang D, et al. Multivessel Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction With Cardiogenic Shock. J Am Coll Cardiol. 71, 844–856 (2018)
32. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 115, 2344–2351 (2007)
33. Kim YH, Her AY, Jeong MH, Kim BK, Lee SY, Hong SJ, et al. Impact of renin-angiotensin system inhibitors on long-term clinical outcomes in patients with acute myocardial infarction treated with successful percutaneous coronary intervention with drug-eluting stents: Comparison between STEMI and NSTEMI. Atherosclerosis. 280, 166–173 (2019)
34. Vatcheva KP, Lee M, McCormick JB, Rahbar MH. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. Epidemiology (Sunnyvale) 6, 227 (2016)
35. Kim JH. Multicollinearity and misleading statistical results. Korean J Anesthesiol. 72, 558–569 (2019)
36. Kalantari S, Khalili D, Asgari S, Fahimfar N, Hadaegh F, Tohidi M, et al. Predictors of early adulthood hypertension during adolescence: a population-based cohort study. BMC public health. 17, 915 (2017)

Tables

Table 1. Baseline clinical, laboratory, angiographic and procedural characteristics. Values are means ± standard deviation or median (interquartile range) or numbers and percentages. The *p* values for continuous data were obtained from the unpaired t-test. The *p* values for categorical data from chi-square or Fisher's exact test.

Variables	Group A (Age, ≥65 years, n = 2,253)			Group B (Age, <65 years, n = 2,260)		
	Group A1 Early invasive (n = 1,612)	Group A2 Delayed invasive (n = 641)	*p* value	Group B1 Early invasive (n = 1,688)	Group B2 Delayed invasive (n = 572)	*p* value
Male, n (%)	927 (57.5)	371 (57.9)	0.872	1476 (87.4)	513 (89.7)	0.153
Age, years	74.3 ± 5.8	75.0 ± 5.9	0.007	54.4 ± 7.3	54.5 ± 7.2	0.760
LVEF, %	53.2 ± 10.6	51.6 ± 12.3	0.005	55.9 ± 9.4	55.1 ± 10.9	0.149
BMI, kg/m^2	23.2 ± 3.1	23.5 ± 3.3	0.048	25.0 ± 3.2	24.8 ± 3.1	0.120
SBP, mmHg	133.5 ± 26.4	135.4 ± 25.8	<0.001	137.0 ± 25.8	139.2 ± 25.8	0.087
DBP, mmHg	80.4 ± 15.7	81.3 ± 14.8	0.038	83.9 ± 15.8	83.8 ± 15.1	0.874
Symptom-to-door time, h	8.0 (3.0-28.6)	8.8 (2.7-45.3)	0.054	5.8 (2.0-19.3)	4.5 (1.6-23.9)	0.181
Door-to-balloon time, h	6.0 (2.9-16.1)	46.4 (31.1-71.6)	<0.001	6.9 (3.0-16.1)	43.2 (29.8-58.6)	<0.001
Killip class ≥ 3	181 (11.2)	98 (15.3)	0.011	65 (3.9)	34 (5.9)	0.044
Hypertension, n (%)	1,050 (65.1)	427 (66.6)	0.505	662 (39.2)	243 (42.5)	0.183
Diabetes mellitus, n (%)	567 (35.2)	227 (35.4)	0.914	408 (24.2)	154 (26.9)	0.198
Dyslipidemia, n (%)	154 (9.6)	83 (12.9)	0.022	225 (13.3)	92 (16.1)	0.109
Previous MI, n (%)	136 (8.4)	48 (7.5)	0.496	73 (4.3)	388 (6.6)	0.033
Previous PCI, n (%)	112 (6.9)	33 (5.1)	0.128	66 (3.9)	34 (5.9)	0.046
Previous CABG, n (%)	6 (0.4)	3 (0.5)	0.720	2 (0.1)	1 (0.2)	0.749
Previous HF, n (%)	27 (1.7)	15 (2.3)	0.302	9 (0.5)	6 (1.0)	0.230
Previous stroke, n (%)	124 (7.7)	57 (8.9)	0.346	60 (3.6)	23 (4.0)	0.608
Current smokers, n (%)	324 (20.1)	102 (15.9)	0.023	921 (54.6)	309 (54.0)	0.846
Peak CK-MB, mg/dL	20.9 (6.4-78.6)	13.9 (5.0-42.6)	<0.001	29.0 (7.2-99.0)	15.6 (4.6-56.7)	<0.001
Peak Troponin-I, ng/mL	10.6 (2.1-22.1)	4.7 (1.1-18.9)	<0.001	14.3 (2.8-23.1)	5.4 (1.0-21.1)	<0.001
Blood glucose, mg/dL	158.6 ± 72.7	162.1 ± 80.2	0.338	153.6 ± 73.4	158.9 ± 79.6	0.157
Hs-CRP (mg/dL)	1.53 ± 3.24	1.78 ± 7.72	0.440	1.07 ± 2.50	1.11 ± 2.10	0.687
Serum creatinine (mg/L)	1.12 ± 1.15	1.26 ± 1.34	0.023	1.04 ± 1.27	1.21 ± 1.73	0.034
eGFR <60mL/min/1.73m^2, n (%)	570 (35.4)	269 (42.0)	0.003	193 (11.4)	86 (15.0)	0.027
Total cholesterol, mg/dL	171.9 ± 43.3	171.7 ± 44.1	0.900	188.5 ± 43.1	185.3 ± 41.9	0.117
Triglyceride, mg/L	111.7 ± 71.8	112.8 ± 82.7	0.771	152.7 ± 96.3	156.2 ± 94.3	0.523
HDL cholesterol, mg/L	43.1 ± 11.4	44.5 ± 82.7	0.013	42.1 ± 10.8	42.2 ± 10.6	0.913
LDL cholesterol, mg/L	108.7 ± 34.7	106.0 ± 35.3	0.101	120.2 ± 36.8	116.9 ± 35.3	0.053

GRACE risk score	151.2 ± 34.5	154.4 ± 36.7	0.058	105.8 ± 28.4	106.5 ± 32.3	0.676
> 140, n (%)	979 (60.7)	390 (60.8)	0.961	171 (10.1)	81 (14.2)	0.011
Atrial fibrillation, n (%)	93 (5.8)	44 (6.9)	0.329	26 (1.5)	13 (2.3)	0.265
ST-depression, n (%)	392 (24.3)	157 (24.5)	0.930	334 (19.8)	103 (18.0)	0.352
T-wave inversion, n (%)	370 (23.0)	155 (24.2)	0.534	291 (17.2)	119 (20.8)	0.060
Discharge medications, n (%)						
Aspirin, n (%)	1,600 (99.3)	635 (99.1)	0.645	1,678 (99.4)	568 (99.3)	0.778
Clopidogrel, n (%)	1,251 (77.6)	540 (84.2)	<0.001	1,065 (63.1)	406 (71.0)	0.001
Ticagrelor, n (%)	283 (17.6)	77 (12.0)	0.001	361 (21.4)	109 (19.1)	0.257
Prasugrel, n (%)	78 (4.8)	24 (3.7)	0.106	262 (15.5)	57 (10.0)	0.001
BBs, n (%)	1,354 (84.0)	542 (84.6)	0.742	1,491 (88.3)	485 (84.8)	0.029
ACEIs or ARBs, n (%)	1,361 (84.4)	506 (78.9)	0.002	1,423 (84.3)	462 (80.8)	0.051
Statin, n (%)	1,534 (95.2)	601 (93.8)	0.178	1,631 (96.6)	541 (94.6)	0.033
Anticoagulant, n (%)	50 (3.1)	25 (3.9)	0.362	11 (0.7)	10 (1.7)	0.024
Infarct-related artery						
Left main, n (%)	50 (3.1)	25 (3.9)	0.362	33 (2.0)	23 (4.0)	0.008
LAD, n (%)	684 (42.4)	286 (44.6)	0.346	723 (42.8)	238 (41.6)	0.625
LCx, n (%)	400 (24.8)	141 (22.0)	0.172	459 (27.2)	150 (26.2)	0.663
RCA, n (%)	478 (29.7)	189 (29.5)	0.959	473 (28.0)	161 (28.1)	0.957
Multivessel disease, n (%)	971 (60.2)	423 (66.0)	0.011	811 (48.0)	300 (52.4)	0.073
ACC/AHA type B2/C lesions	1373 (85.2)	544 (84.9)	0.854	1413 (83.7)	467 (81.6)	0.271
Pre-PCI TIMI flow grade 0/1	633 (39.3)	199 (31.0)	<0.001	760 (45.0)	177 (30.9)	<0.001
GP IIb/IIIa inhibitor	133 (8.3)	43 (6.7)	0.258	174 (10.3)	41 (7.2)	0.026
Transradial approach	781 (48.4)	309 (48.2)	0.926	959 (56.8)	292 (51.0)	0.017
IVUS/OCT, n (%)	346 (21.5)	174 (27.1)	0.004	421 (24.9)	202 (35.3)	<0.001
FFR, n (%)	27 (1.7)	23 (3.6)	0.010	33 (2.0)	24 (4.2)	0.005
Drug-eluting stents						
ZES, n (%)	374 (23.2)	155 (24.2)	0.621	419 (24.8)	142 (24.8)	0.999
EES, n (%)	860 (53.3)	332 (51.8)	0.504	878 (52.0)	294 (51.4)	0.809
BES, n (%)	326 (20.2)	144 (22.5)	0.237	340 (20.1)	125 (21.9)	0.402
Others, n (%)	52 (3.2)	10 (1.6)	0.032	51 (3.0)	11 (1.9)	0.184
Stent diameter (mm)	3.04 ± 0.40	3.03± 0.41	0.531	3.12 ± 0.43	3.10± 0.44	0.196
Stent length (mm)	30.2 ± 14.4	31.1 ± 14.9	0.205	28.6 ± 13.2	29.8 ± 14.5	0.074
Number of stents	1.22 ± 0.46	1.26 ± 0.50	0.044	1.17 ± 0.42	1.22 ± 0.47	0.030

LVEF left ventricular ejection fraction, *BMI* body mass index, *SBP* systolic blood pressure, *DBP,* diastolic blood pressure, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *HF* heart failure, *CK-MB*

creatine kinase myocardial band, *Hs-CRP* high sensitivity C-reactive protein, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *GRACE* Global Registry of Acute Coronary Events, *BBs* ß-blockers, *ACEIs* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, LAD left anterior descending artery, *LCx* left circumflex artery, *RCA* right coronary artery, *ACC/AHA* American College of Cardiology/American Heart Association, *TIMI* thrombolysis in myocardial infarction, *GP* glycoprotein, *IVUS* intravascular ultrasound, *OCT* optical coherence tomography, *FFR* fractional flow reserve, *ZES* zotarolimus-eluting stent, *EES* everolimus-eluting stent, *BES* biolimus-eluting stent.

Table 2. Comparison of clinical outcomes at 2 years.

	Group A (Age, ≥65 years, n = 2,253)								
Outcomes	Group A1 Early invasive (n = 1,612)	Group A2 Delayed invasive (n = 641)	Log-rank	Unadjusted		Multivariable-Adjusted[a]		Propensity score-Adjusted	
				HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
MACCE	265 (16.4)	97 (15.1)	0.434	1.097 (0.869-1.384)	0.435	1.198 (0.944-1.521)	0.137	1.176 (0.889-1.500)	0.255
All-cause death	118 (7.5)	47 (7.5)	0.997	0.999 (0.713-1.401)	0.997	1.150 (0.810-1.633)	0.434	1.269 (0.850-1.894)	0.244
Cardiac death	63 (4.0)	27 (4.3)	0.749	0.929 (0.592-1.458)	0.749	1.100 (0.687-1.761)	0.692	1.127 (0.694-1.913)	0.659
Non-cardiac death	55 (3.5)	20 (3.2)	0.729	1.095 (0.656-1.826)	0.729	1.207 (0.712-2.043)	0.485	1.487 (0.803-2.753)	0.207
Recurrent MI	60 (3.9)	24 (3.9)	0.980	0.994 (0.619-1.595)	0.980	1.061 (0.654-1.722)	0.809	1.035 (0.584-1.653)	0.907
Any repeat revascularization	146 (9.4)	50 (8.1)	0.325	1.175 (0.852-1.620)	0.326	1.247 (0.899-1.730)	0.186	1.236 (0.843-1.710)	0.277
Stroke	44 (2.8)	22 (3.6)	0.380	0.796 (0.477-1.327)	0.381	1.255 (0.745-2.114)	0.394	1.067 (0.570-2.000)	0.839
ST (definite or probable)	8 (0.5)	6 (1.0)	0.231	0.529 (0.184-1.525)	0.239	2.969 (0.978-9.017)	0.055	1.490 (0.421-5.281)	0.537
	Group B (Age, <65 years, n = 2,260)								
Outcomes	Group B1 Early invasive (n = 1,688)	Group B2 Delayed invasive (n = 572)	Log-rank	Unadjusted		Multivariable-Adjusted[a]		Propensity score-Adjusted	
				HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
MACCE	185 (11.0)	56 (9.8)	0.457	1.120 (0.831-1.510)	0.458	1.236 (0.913-1.673)	0.171	1.317 (0.918-1.890)	0.135
All-cause death	24 (1.5)	14 (2.5)	0.098	0.577 (0.299-1.116)	0.102	1.065 (0.506-2.239)	0.869	1.583 (0.614-4.085)	0.342
Cardiac death	13 (0.8)	10 (1.8)	0.044	0.438 (0.192-0.999)	0.050	1.359 (0.525-3.517)	0.527	1.024 (0.212-2.984)	0.925
Non-cardiac death	11 (0.7)	4 (0.7)	0.892	0.924 (0.294-2.901)	0.892	1.447 (0.405-5.172)	0.570	1.505 (0.517-6.102)	0.342
Recurrent MI	42 (2.4)	13 (2.3)	0.784	1.091 (0.586-	0.784	1.259 (0.666-2.382)	0.478	1.147 (0.746-	0.717

				2.032)				2.411)	
Any repeat revascularization	155 (9.2)	43 (7.6)	0.246	1.221 (0.871-1.711)	0.247	1.289 (0.917-1.813)	0.145	1.347 (0.921-2.018)	0.149
Stroke	17 (1.0)	10 (1.8)	0.151	0.569 (0.260-1.242)	0.157	1.523 (0.688-3.369)	0.299	1.446 (0.551-3.109)	0.454
ST (definite or probable)	10 (0.6)	1 (0.2)	0.218	3.376 (0.432-26.37)	0.246	4.152 (0.501-32.82)	0.101	2.984 (0.310-23.68)	0.344
	Group A1+B1	Group A2+B2							
Outcomes	Early invasive (n = 3,300)	Delayed invasive (n = 1,213)	Log-rank	Unadjusted		Multivariable-Adjusted[a]		Propensity score-Adjusted	
				HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
MACCE	450 (13.6)	153 (12.6)	0.380	1.086 (0.904-1.304)	0.380	1.199 (0.995-1.445)	0.056	1.225 (0.998-1.528)	0.071
All-cause death	142 (4.3)	61 (5.1)	0.295	0.852 (0.631-1.150)	0.295	1.078 (0.790-1.470)	0.636	1.130 (0.798-1.630)	0.512
Cardiac death	76 (2.3)	37 (3.1)	0.154	0.752 (0.508-1.144)	0.155	1.060 (0.704-1.595)	0.780	1.058 (0.655-1.521)	0.807
Non-cardiac death	66 (2.0)	24 (2.0)	0.980	1.006 (0.631-1.605)	0.980	1.281 (0.792-2.074)	0.313	1.451 (0.821-2.566)	0.200
Recurrent MI	102 (3.2)	37 (3.1)	0.960	1.010 (0.693-1.471)	0.960	1.034 (0.706-1.516)	0.864	1.029 (0.654-1.498)	0.902
Any repeat revascularization	301 (9.3)	93 (7.9)	0.132	1.195 (0.947-1.508)	0.133	1.258 (0.994-1.591)	0.056	1.235 (0.975-1.575)	0.075
Stroke	61 (1.9)	32 (2.7)	0.095	0.696 (0.454-1.067)	0.097	1.351 (0.875-2.087)	0.175	1.037 (0.635-1.812)	0.792
ST (definite or probable)	18 (0.6)	7 (0.6)	0.893	0.942 (0.393-2.255)	0.893	1.091 (0.449-2.651)	0.847	1.001 (0.351-2.553)	0.999

MACCE major adverse cardiac and cerebrovascular events, *ST* stent thrombosis, *HR* hazard ratio, *CI* confidence interval, *LVEF* left ventricular ejection fraction, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *PCI* percutaneous coronary intervention, *HF* heart failure, *CK-MB* creatine kinase myocardial band, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *GRACE* Global Registry of Acute Coronary Events, *ACEIs* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers. [a]Adjusted by male sex, LVEF, BMI, SBP, DBP, symptom-to-door time, Killip class ≥3, hypertension, DM, dyslipidemia, previous PCI, previous HF, previous stroke, current smoker, peak CK-MB, peak troponin-I, serum creatinine, eGFR <60mL/min/1.73m^2, HDL-cholesterol, LDL-cholesterol, GRACE risk score >140, clopidogrel, ticagrelor, prasugrel, ACEI or ARB, statin

Table 3. Comparison of clinical outcomes in patient with complex coronary lesions

	Group A (Age, ≥65 years, n = 2,253)						
Outcomes	Group A1 Early invasive (n = 799)	Group A2 Delayed invasive (n = 356)	Log-rank	Unadjusted		Multivariable-Adjusted[a]	
				HR (95% CI)	*p*	HR (95% CI)	*p*
MACCE	141 (17.6)	61 (17.1)	0.829	1.034 (0.765-1.396)	0.829	1.149 (0.843-1.564)	0.379
All-cause death	64 (8.2)	27 (7.7)	0.814	1.056 (0.673-1.655)	0.814	1.254 (0.784-2.006)	0.345
Cardiac death	31 (4.0)	16 (4.5)	0.632	0.863 (0.472-1.578)	0.632	1.021 (0.539-1.934)	0.949
Non-cardiac death	33 (4.2)	11 (3.2)	0.404	1.336 (0.675-2.643)	0.406	1.616 (0.794-3.286)	0.185
Recurrent MI	31 (4.0)	14 (4.1)	0.966	0.986 (0.525-1.854)	0.966	1.097 (0.574-2.097)	0.780
Any repeat revascularization	76 (9.9)	35 (10.3)	0.893	0.973 (0.652-1.452)	0.893	1.041 (0.691-1.568)	0.849
Stroke	25 (3.2)	14 (4.1)	0.490	0.795 (0.413-1.529)	0.491	1.338 (0.688-2.601)	0.391
ST (definite or probable)	4 (0.5)	3 (0.9)	0.488	0.592 (0.133-2.646)	0.493	3.777 (0.673-16.94)	0.139
	Group B (Age, <65 years, n = 977)						
Outcomes	Group B1 Early invasive (n = 691)	Group B2 Delayed invasive (n = 286)	Log-rank	Unadjusted		Multivariable-Adjusted[a]	
				HR (95% CI)	*p*	HR (95% CI)	*p*
MACCE	89 (12.9)	33 (12.4)	0.892	1.028 (0.689-1.533)	0.892	1.136 (0.754-1.713)	0.542
All-cause death	12 (1.7)	10 (3.8)	0.062	0.458 (0.198-1.061)	0.068	1.005 (0.384-2.629)	0.991
Cardiac death	7 (1.0)	6 (2.3)	0.136	0.446 (0.150-1.327)	0.147	0.968 (0.285-3.288)	0.958
Non-cardiac death	5 (0.7)	4 (1.5)	0.258	0.476 (0.128-1.774)	0.269	1.026 (0.174-6.046)	0.978
Recurrent MI	14 (2.0)	5 (1.9)	0.892	1.073 (0.687-2.980)	0.892	1.347 (0.471-3.856)	0.579
Any repeat revascularization	74 (10.8)	25 (9.6)	0.614	1.124 (0.714-1.768)	0.614	1.136 (0.716-1.802)	0.589
Stroke	6 (0.9)	8 (3.1)	0.013	0.293 (0.098-0.815)	0.019	2.923 (0.949-9.002)	0.062
ST (definite or probable)	1 (0.1)	1 (0.4)	0.480	3.383 (0.024-6.117)	0.497	1.140 (0.030-43.82)	0.944

MACCE major adverse cardiac and cerebrovascular events, *ST* stent thrombosis, *HR* hazard ratio, *CI* confidence interval, *LVEF* left ventricular ejection fraction, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *PCI* percutaneous coronary intervention, *HF* heart failure, *CK-MB* creatine kinase myocardial band, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *GRACE* Global Registry of Acute Coronary Events, *ACEIs* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers. [a]Adjusted by male sex, LVEF, BMI, SBP, DBP, symptom-to-door time, Killip class ≥3, hypertension, DM, dyslipidemia, previous PCI, previous HF, previous stroke, current smoker, peak CK-MB, peak troponin-I, serum creatinine, eGFR <60mL/min/1.73m^2, HDL-cholesterol, LDL-cholesterol, GRACE risk score >140, clopidogrel, ticagrelor, prasugrel, ACEI or ARB, statin

Figures

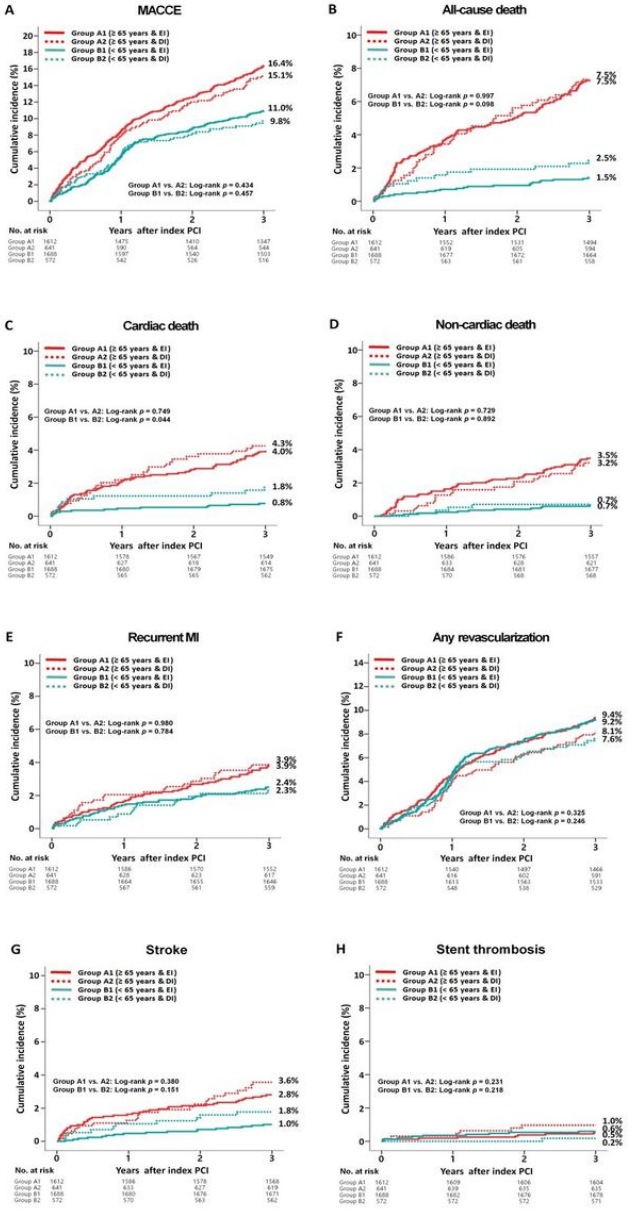

Figure 1

Kaplan-Meier curved analysis for MACCE (A), all-cause death (B), cardiac death (C), non-cardiac death (D), recurrent MI (E), any repeat revascularization (F), stroke (G), and stent thrombosis (H). MACCE major adverse cardiac and cerebrovascular events, MI

myocardial infarction, PCI percutaneous coronary intervention, EI early invasive, DI delayed invasive

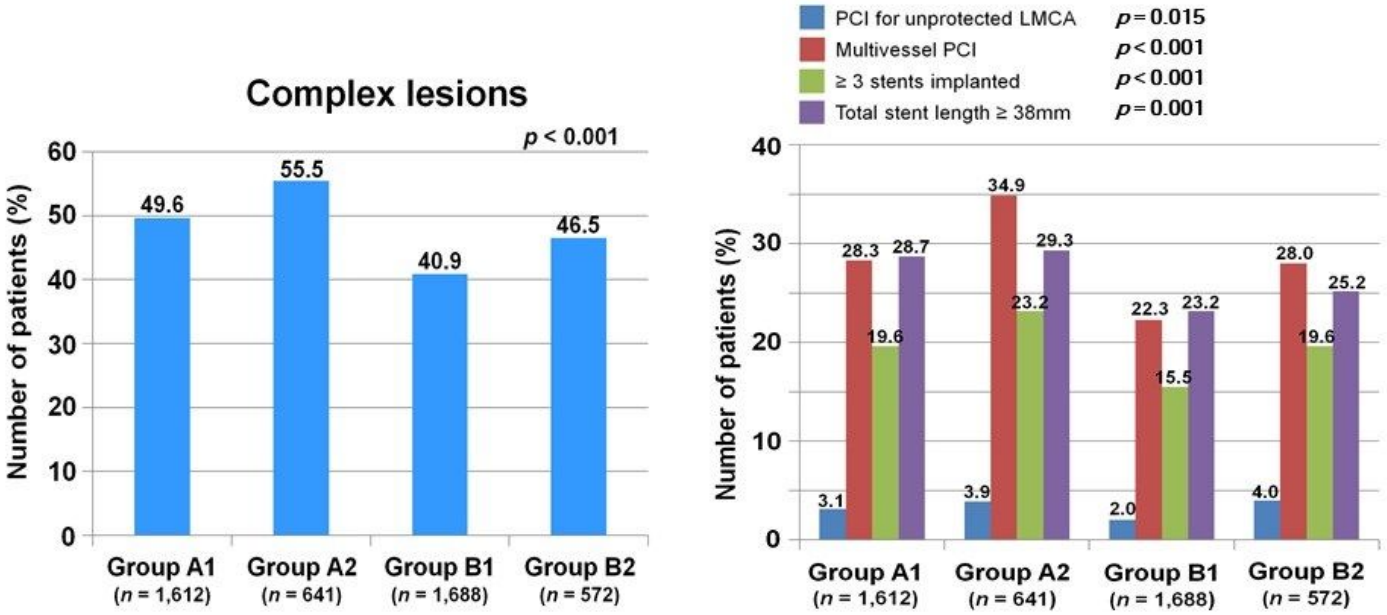

Figure 2

Distribution of complex lesions in the 4 groups. Group A1 ≥ 65 years and early invasive, Group A2 ≥ 65 years and delayed invasive, Group B1 < 65years and early invasive, Group B2 < 65 years and delayed invasive, PCI percutaneous coronary intervention, LMCA left main coronary artery

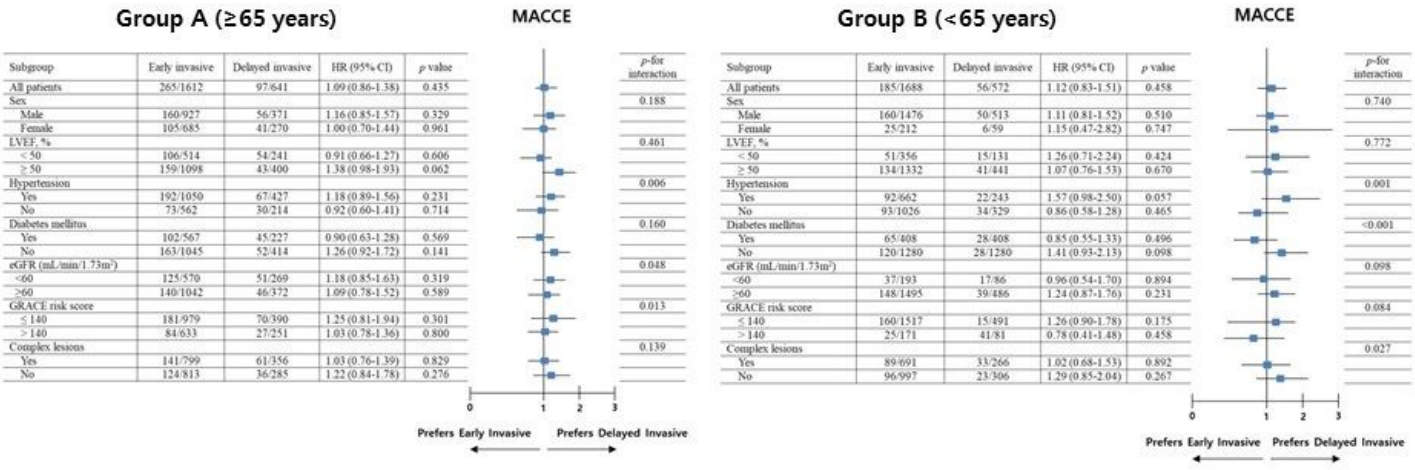

Figure 3

Subgroup analysis for MACCE in group A and B. MACCE major adverse cardiac and cerebrovascular events, HR hazard ratio, CI confidence interval, LVEF left ventricular ejection fraction, eGFR estimated glomerular filtration rate, GRACE Global Registry of Acute Coronary Events

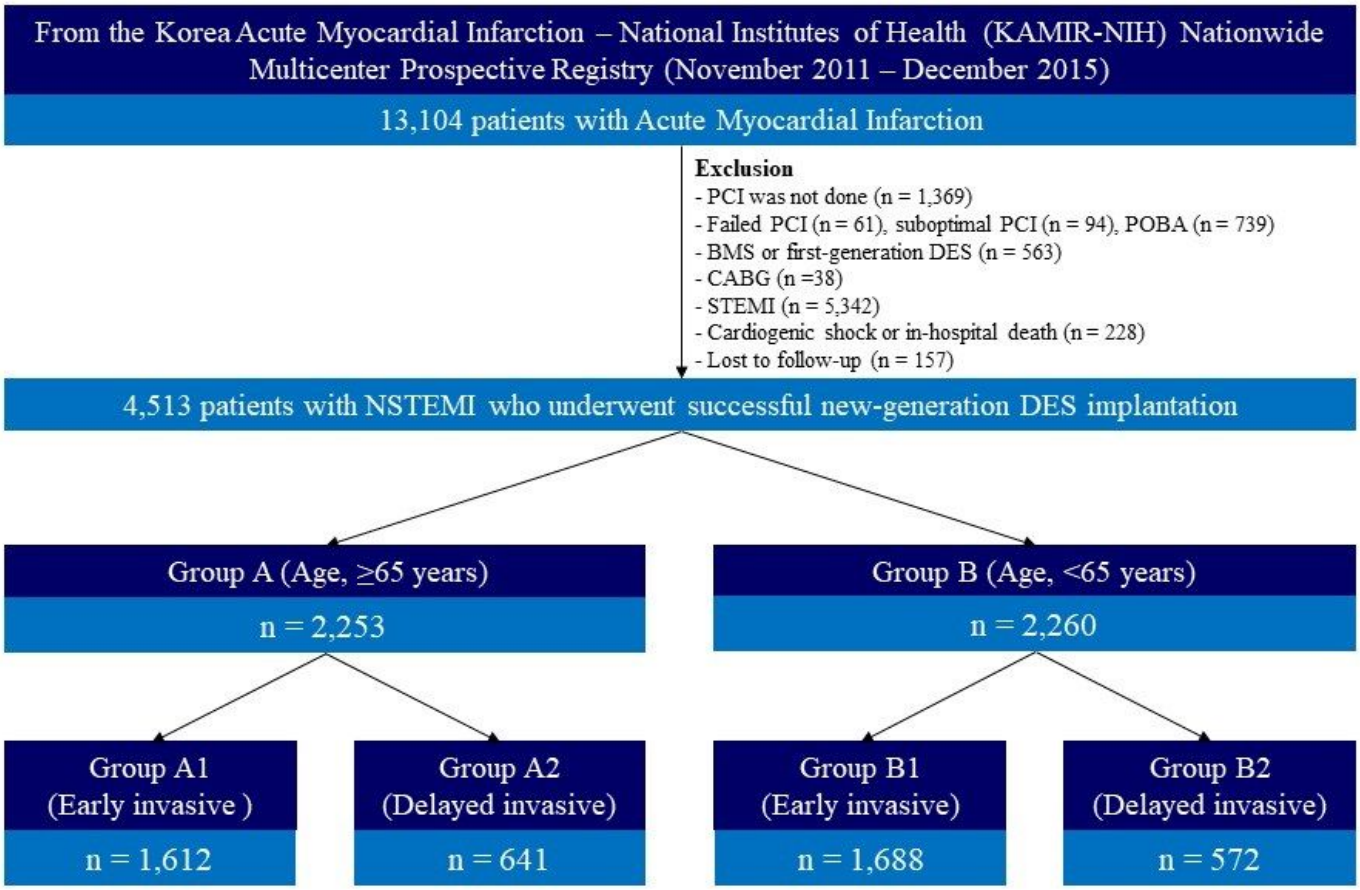

Figure 4

Flowchart. PCI percutaneous coronary intervention, POBA plain old balloon angioplasty, BMS bare-metal stent, DES drug-eluting stent, CABG coronary artery bypass graft, STEMI ST-segment elevation myocardial infarction, NSTEMI non-STEMI

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ScientificReportsSupplementaryAppendix.docx