Prevalence and Prognosis of High-risk Myocardial Infarction Patient Candidates to Extended Antiplatelet Therapy

Marrugat J, Elosua R, Grau M, Sayols-Baixeras S, Dégano IR*

ABSTRACT

Introduction and objectives: Secondary prevention in myocardial infarction patients is paramount to prevent recurrences. Dual antiplatelet therapy has shown to reduce the risk of subsequent events up to one year, and beyond, in the PEGASUS-TIMI 54 trial. This study aimed to estimate the annual number of myocardial infarction patients with PEGASUS characteristics in Spain; and to analyze short- and long-term outcomes in these patients.

Methods: The number of myocardial infarction patients was estimated assuming a Poisson distribution. Myocardial infarction incidence and mortality rates obtained from population registries (IBERICA and REGICOR) were properly adjusted. The proportion of myocardial infarction patients with PEGASUS characteristics was estimated with a REGICOR cohort of consecutive patients from 2003-2009 (n=1391). This cohort follow-up was used to compare occurrence of re-infarction and death at 1-year and at the end of the follow-up (4.7 years) in patients with and without PEGASUS characteristics by cox regression.

Results: The estimated annual number of stable myocardial infarction patients ≥ 50 years old, without bleeding events, was 41 311. Of those, 22 493 had at least one PEGASUS characteristic (diabetes, previous myocardial infarction or chronic kidney disease). At 4.7 years of follow-up, having any PEGASUS characteristic or age ≥ 65 years was associated with a higher risk of cardiovascular and all-cause death in adjusted analyses (hazard ratio= 3.44 and 2.21, 95% confidence interval, 1.22-9.74 and 1.11-4.42, respectively).

Conclusions: In Spain, more than 50% of the stable myocardial infarction patients ≥ 50 years old are estimated to have at least one PEGASUS characteristic, which increases substantially long-term risk of cardiovascular and all-cause death.

Keywords: Myocardial infarction. Prognosis. Epidemiology. Follow-up studies. Diabetes mellitus.
Coronary disease. Survival.

Abbreviations

ACE inhibitor: angiotensin-converting enzyme inhibitor

ARB: angiotensin receptor blocker

AMI: acute myocardial infarction

CHD: coronary heart disease

CKD: chronic kidney disease

CV: cardiovascular

DAPT: dual antiplatelet therapy

INTRODUCTION

Coronary heart disease (CHD) is the single most common cause of death in Europe, and acute myocardial infarction (AMI) is its major contributor. In Spain, nearly 100 000 individuals have an AMI each year, and 33% die before reaching a medical facility.¹ For hospitalized AMI patients, 28-day case-fatality is 13%,¹ and for those surviving the first 28-days, 2-year coronary event incidence is 12.6%.²

Aspirin effectively prevents recurrences in patients with a prior coronary event. Dual antiplatelet therapy (DAPT), with aspirin and P2Y₁₂-inhibitors (e.g. clopidogrel, prasugrel, ticagrelor), further reduces the risk of subsequent coronary events in high-risk patients up to one year.³⁻⁶ Recently, the PEGASUS-TIMI 54 trial (“Prevention of cardiovascular events in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin-thrombolysis in myocardial infarction 54”) showed that aspirin+ticagrelor beyond 1 year reduced the primary combined end point of cardiovascular death, AMI or stroke in AMI patients but increased the risk of major bleeding.⁷

Patients included in the PEGASUS were stable AMI patients aged 50 years and older, with at least one of the following risk factors: diabetes, a second previous AMI, multivessel CHD, chronic kidney disease (CKD) or age ≥ 65 years.⁸ Due to the scarcity of data on stable AMI patients and the effectiveness of aspirin + ticagrelor in high-risk AMI patients, it would be useful to know how many AMI patients could benefit from this therapy beyond the first year after the event, and which is the long-term risk of these patients.

In the present study, we aimed first to estimate the annual number of stable AMI patients with PEGASUS characteristics in Spain. And second to compare, in stable AMI patients with and without PEGASUS characteristics, the risk of AMI and death during the second year after the index AMI, and at the end of the follow-up (4.7 years).

METHODS

Study Design

To estimate the annual number of stable AMI patients with PEGASUS characteristics, we used data from two population-based AMI registries: IBERICA,⁹ conducted in 1997-1998 in seven Spanish regions, and REGICOR,¹⁰ conducted in 1990-2009 in Girona province.

Patients with AMI were classified as having PEGASUS characteristics if they were ≥ 50 years old and had previous AMI, diabetes or CKD, or were at least 65 years old. Multivessel CHD was not taken into account because the information was missing for 60% of the patients. Previous AMI was based on clinical history and information reported in standardized questionnaires. Diabetes was based on clinical history, treatment, and fasting glucose value > 6.9 mmol/L (125 mg/dL). CKD was based on the estimated glomerular filtration rate (< 60 mL/min/1.73m²), calculated with the Modification in Diet in Renal Disease formula.

For the comparison short- and long-term outcomes in stable AMI patients with and without PEGASUS characteristics, we used a cohort study of consecutive AMI patients aged 35-74 years included in the REGICOR reference hospital in 2003-2009. To obtain a population of stable AMI patients similar to the population of the PEGASUS trial, we excluded patients younger than 50 years, patients who died or had a subsequent AMI in the year following the index event, patients with end-stage CKD (< 15 mL/min/1.73m²), patients who were classified at a very high risk of bleeding by the CRUSADE risk score, and patients with history of ischemic or non-classifiable stroke (before the AMI and during the first year post-AMI). Patients for whom the PEGASUS category could not be defined were also excluded. Baseline was defined as the index AMI date plus 1 year, and thus, the follow-up to determine the occurrence of cardiovascular events and death began 365 days after the index AMI. The REGICOR study complies with the Declaration of Helsinki and was approved by the local ethics committee. All AMI patients included were duly informed and signed a consent to participate in the registry.

Outcomes and Variables for Prognosis Analysis

Incidence of AMI, cardiovascular death, non-cardiovascular death, all-cause death, and the composite AMI/All-cause death, was analyzed at 1 year and at a median 4.7 years of follow-up in PEGASUS and non-PEGASUS stable AMI patients. Self-reported incidence of stroke was only examined in crude analysis, as the information was only available for 43% of the included patients.

Variables used for descriptive and/or adjustment purposes were: age, gender, hypertension (based on clinical history, treatment, and observed systolic/diastolic blood pressure > 140/90), hypercholesterolemia (based on clinical history, treatment, and observed total-cholesterol > 200 mg/dL), smoking (considered smokers if currently smoking or quit < 1 year ago), history of angina, heart failure (based on the New York Heart Association Functional Classification and considered if II-IV), ST segment elevation, angiography, reperfusion (including thrombolysis and percutaneous coronary intervention), post-AMI arrhythmia (including ventricular fibrillation and tachycardia), post-AMI angina, left ventricular ejection fraction, maximum Killip class, prescription of evidence-based drugs in-hospital and at discharge (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACE inhibitor/ARB), beta-blockers, lipid lowering drugs, antiplatelet drugs).

Statistical Analysis

IBERICA Registry estimates, adjusted for clustering and for the 2000 AMI definition change,¹¹ were used for the population aged 45-74 years, under the assumption that AMI incidence did not change substantially in the last 17 years.¹² The REGICOR Registry was used to estimate AMI incidence in the population > 74 years, which was weighted for the expected difference between incidence rates from Girona and Spain observed in the IBERICA Study (Table 1 of the supplementary material). AMI mortality rates were obtained from the REGICOR Registry, as Girona's AMI mortality estimates have demonstrated to be a robust estimate of Spanish AMI mortality¹ (Table 1 of the supplementary material). The annual number of hospitalized stable AMI patients ≥ 50 years was calculated using the estimated incidence rates and discounting mortality and bleeding rates. Bleeding rates were obtained by applying the CRUSADE¹³ and CARDIOCHUS¹⁴ scales to the REGICOR Registry patients

from 2003-2009 (Table 2 of the supplementary material). The percentage of hospitalized patients was obtained from the REGICOR Registry.¹

Prevalence of PEGASUS characteristics in stable AMI patients ≥ 50 years old (Tables 3 and 4 of the supplementary material) was obtained using REGICOR AMI patient admission data, excluding patients who died or had a subsequent AMI during the first year after the index AMI. It was assumed that prevalence did not change substantially in the first year post-AMI.

Exact 95% confidence intervals for incidence rates and population estimates were obtained using an exact method by assuming a Poisson distribution.

In the prognosis analysis, we first described the patients in the PEGASUS and the non-PEGASUS groups. Incidence of the defined outcomes was assessed at 1-year and at 4.7 years of median follow-up, after 1 year of stable disease, by Kaplan-Meier. Sensitivity analyses for the incidence of the assessed outcomes were performed by competing risk adjusted survival analysis (Table 5 of the supplementary material).¹⁵ Excess risk in PEGASUS patients was analyzed at the defined time points using Cox proportional hazards regression models. The proportional hazard assumption of the PEGASUS characteristic was confirmed graphically, by the non-crossing of the survival curves by PEGASUS category, and statistically, by the non-significance of the non-zero slope test. Adjustment variables in the models were selected if significantly associated with the outcome and with the PEGASUS variable in bivariate analyses ($P < .05$). To prevent multicollinearity the following variables were excluded from the models: PEGASUS characteristics (diabetes, previous AMI and CKD) if the PEGASUS variable was included; thrombolysis and percutaneous coronary intervention if reperfusion was included; left ventricular ejection fraction if maximum Killip class was included; and in-hospital medication if discharge medication was included, the latter was preferred as a proxy of follow-up medication. The C-statistics of the Cox models for the 4.7 years of median follow-up are shown in Table 6 of the supplementary material. Fully adjusted incidence was represented graphically by group (PEGASUS and non-PEGASUS). Predictors of outcome occurrence during the whole follow-up in stable PEGASUS patients were examined using Cox proportional hazard regression models. To

account for the effect of not including multivessel CHD in the PEGASUS definition we have done a sensitivity analysis using the variable when available (Table 7 of the supplementary material).

Statistical analyses were performed using R software version 3.2.1.¹⁶

RESULTS

Yearly Number of Stable Acute Myocardial Infarction Patients With PEGASUS Characteristics

It was estimated that the incidence of AMI, of hospitalized AMI, of stable AMI at 1 year, and of stable AMI without severe bleeding at 1 year was 534, 353, 286 and 241/100 000 inhabitants in individuals ≥ 50 years old (Table 1). These figures yielded an estimation of 91 639 incident AMI cases in individuals ≥ 50 years old in Spain in 2014. Of those, 60 528 were hospitalized, 49 007 were alive and stable at 1-year, and 41 311 had no severe bleeding events during the first year post-AMI (Figure 1, Table 8 of the supplementary material).

PEGASUS characteristics (diabetes, previous AMI and CKD), were highly prevalent in AMI patients ≥ 50 years old who did not have another AMI or died during the first year after the index AMI (Table 3 of the supplementary material). Diabetes was the most prevalent in both men and women (28.9% and 40.4%, respectively). The estimated annual incidence of stable AMI without severe bleeding at 1 year, and at least one PEGASUS characteristic was 131/100 000 inhabitants in individuals ≥ 50 years old (Table 2). If age ≥ 65 years was taken into account, incidence increased to 204/100 000 inhabitants in this population. These figures translated into an annual number of stable AMI patients with at least one PEGASUS characteristic of 22 493 and 34 981, respectively (Figure 1, Table 9 of the supplementary material).

It was also estimated that 191 491 individuals aged ≥ 50 years old who had an AMI within the preceding 3 years, were stable in Spain in 2014 (Table 10 of the supplementary material).

Outcome Analysis in PEGASUS Patients

The REGICOR reference hospital consecutively collected 1963 AMI patients aged 35-74 years in 2003-2009. Of those, 1391 patients were available for analysis (Figure 2), with a median follow-up of 4.7 years (25th-75th percentiles 3.2-5.7 years) after 1 year of stable disease.

At baseline, patients with at least one PEGASUS characteristic (including age $\geq$ 65 years) had a higher prevalence of hypertension and heart failure than non-PEGASUS patients (Table 3). During hospitalization, PEGASUS patients less frequently underwent reperfusion. On the other hand, PEGASUS patients had more often post-AMI arrhythmia, a lower left ventricular ejection fraction and a higher Killip class. Both during hospitalization and at discharge, PEGASUS patients were more often prescribed ACE inhibitor/ARBs, but less often received beta-blockers and lipid lowering drugs.

At 1 year of follow-up after 1 year of stable disease, PEGASUS patients had a higher incidence of all-cause death than non-PEGASUS patients. At a median 4.7 years of follow-up, incidence of all outcomes, except for AMI, was higher in PEGASUS patients (Table 4). A competing risk analysis of outcome incidence showed similar results (Table 5 of the supplementary material). At 3 years of follow-up crude incidence of all outcomes, except for AMI, was higher in PEGASUS patients (Table 11 of the supplementary material). At 3.1 years of median follow-up, there was no difference in crude self-reported incidence of stroke (1.1% vs 1.4%, in 174 non-PEGASUS and 446 PEGASUS patients, respectively).

At 1 year of follow-up, stable PEGASUS patients had a higher risk of all-cause death (hazard ratio= 4.4, 95% confidence interval 1.3-14.6) and of AMI/all-cause death (hazard ratio= 2.34; 95% confidence interval, 1.2-4.6), but only in unadjusted analysis (Table 12 of the supplementary material). At a median 4.7 years of follow-up, unadjusted hazard ratios showed that PEGASUS patients had a higher risk of death (cardiovascular, non-cardiovascular and all-cause) and of having an AMI/all-cause death than non-PEGASUS patients (Table 5). After adjustment for demographic and clinical history variables, cardiovascular and all-cause death remained significantly higher in PEGASUS patients (hazard ratio= 3.7 and 2.5; 95% confidence interval, 1.3-10.3 and 1.3-5.0, respectively). Further adjustment with discharge medication did not explain the higher risk of cardiovascular and

all-cause death observed in PEGASUS patients (Table 5 and Figure 3). In the sensitivity analysis including multivessel CHD in the PEGASUS definition, results at 4.7 years of follow-up were similar although the effects diminished (Table 7 of the supplementary material).

In PEGASUS patients, heart failure was the most significant predictor of cardiovascular and all-cause mortality, previous AMI and hypertension were the more significant predictors of AMI and no prescription of beta-blockers at discharge was the most significant predictor of non-cardiovascular death (Table 13 of the supplementary material).

DISCUSSION

We estimated that, in 2014, there were 41 311 AMI patients ≥ 50 years old in Spain who were stable and without bleeding events at 1-year post-AMI. Of those patients, 22 493 (54.4%) had diabetes, previous AMI or CKD.

Based on the findings of the PEGASUS trial, we would expect that treating these 22 493 patients for 1 year with aspirin and ticagrelor at 60-mg, would prevent 106 events (cardiovascular death, AMI or stroke) and would cause 78 major bleeding events.⁷ While the number of prevented cardiovascular events is higher than the number of caused bleeding events, the latter include intracranial bleeding, overt signs of hemorrhage and fatal bleeding. In the PEGASUS trial, patients receiving aspirin + ticagrelor had a significantly higher occurrence of bleeding events requiring transfusion or study-drug discontinuation, but not of fatal bleedings or intracranial hemorrhages.⁷ The high ratio of bleeding events caused to cardiovascular events prevented could probably be lowered by carefully considering the treatment of patients at a certain bleeding risk. Thus, the estimation of the bleeding risk in these patients is of paramount importance to define their treatment and should be estimated systematically by validated bleeding scores.

In this study, we found that the competing risk adjusted incidence of AMI/All-cause death in stable AMI patients during the second year after the index AMI was 5%. This incidence is between the 2% and the 9% reported by the CLARIFY registry and a nationwide observational study in Sweden,

respectively.^{17,18} One of the reasons for the incidence difference could be the age of the included patients. On the other hand, while 3-year crude incidence of AMI was almost the same in this study (4.4%) and in the PEGASUS trial (4.2%), compared to the PEGASUS trial, we found a higher incidence of cardiovascular and all-cause death (3.2% vs 2.6% and 6.3% vs 4.0%, respectively). These differences could be due to the higher prevalence of previous AMI and the lower prescription of beta/blockers in our study compared to the PEGASUS trial participants. In addition, a possible higher prevalence of heart failure in the PEGASUS patients of our study could also have had an impact on the higher incidence of cardiovascular and all-cause death.

Our adjusted analysis showed that PEGASUS patients had a higher risk of cardiovascular and all-cause death during the follow-up, compared to non-PEGASUS patients. In addition to the presence of PEGASUS characteristics, this result could be partially explained by the lower reperfusion, higher Killip class, higher percentage of non-ST segment elevation AMI and non-classifiable patients, and the higher prevalence of post-AMI arrhythmia in PEGASUS patients. The lower prescription of beta-blockers and lipid-lowering drugs likely contributed to the higher cardiovascular and all-cause death in PEGASUS patients. The presence of more patients with non-ST segment elevation AMI and non-classifiable AMI in the PEGASUS group reflects the more complex phenotype and the greater burden of comorbidities in patients with PEGASUS characteristics.¹⁹ The higher long-term mortality of patients with non-ST segment elevation compared to patients with ST segment elevation²⁰ could partially explain the higher mortality of PEGASUS patients in our study.

Regarding in-hospital management, AMI patients ≥ 50 years old with either diabetes, previous AMI or CKD received less revascularization and less prescription of guideline-recommended medication (except for ACE inhibitor/ARBs) than patients without these characteristics. Part of this differential management is presumably related to the older age of the PEGASUS patients.²¹ In the present study, cardiovascular and all-cause death risk differences between PEGASUS and non-PEGASUS patients were partially explained by clinical characteristics, in-hospital management and discharge medication. The persistent differences despite adjustment show the residual risk of these patients

even after treatment with evidence-based recommended care. From these results one also wonders if an increase in revascularization and guideline-recommended medication prescription, in addition to DAPT, would decrease even further the occurrence of cardiovascular events in PEGASUS patients.

As for the predictors of the composite AMI/All-cause death at long-term in stable PEGASUS patients, we observed an increased risk for older patients, and for those with diabetes, previous AMI or heart failure. The magnitude of the increased risks was comparable to that described in a nationwide study of stable AMI patients in Sweden.¹⁸ On the contrary, female gender was not associated with the composite AMI/all-cause death in our study. As for guideline-recommended medication, prescription of beta-blockers at discharge was inversely and independently associated with non-cardiovascular and all-cause death and with AMI/All-cause death in stable PEGASUS patients. These results are in line with previous studies showing that the use of beta-blockers and statins is associated with a reduced risk of all-cause mortality after AMI.²²

The duration of DAPT after acute coronary syndrome has been under debate for the last decade. On the one hand, recent registry studies and clinical trials have shown that premature discontinuation of DAPT (aspirin + clopidogrel / prasugrel) in acute coronary syndrome patients with stent implantation was associated with an increased risk of ischemic events,²³ and that aspirin + ticagrelor beyond 1 year was associated in AMI patients with a lower risk of cardiovascular events.⁷ On the other hand, recent randomized studies, with a lower number of patients, have shown that DAPT (aspirin + clopidogrel / ticagrelor / prasugrel) beyond 6 months did not provide additional benefit after stent implantation.^{24,25} Still, while DAPT beyond 1-year appears to be beneficial in terms of cardiovascular events prevented, at least in AMI patients, the increase in bleeding events calls for further analysis of these patients. In addition, the optimum total length of DAPT has yet to be determined. A recent study from the FAST-MI 2005 Registry has shown that aspirin + clopidogrel for 1- and 2-years had no impact on 5-year mortality,²⁶ highlighting the importance of assessing long-term outcomes in stable AMI patients to define the duration of DAPT.

To our knowledge, this is the first comparison of long-term outcomes in stable AMI patients with and without high-risk characteristics using real-world data. Two studies have previously reported outcomes in this population, the CLARIFY registry¹⁷ and a Swedish observational study¹⁸, however, these studies did not compare patients with and without high-risk features or analyzed long-term outcomes. In addition, this is the first study estimating the population prevalence of these patients.

Limitations

The estimation of the annual number of AMI patients ≥ 50 years old with PEGASUS characteristics in Spain has certain limitations. First, AMI incidence rates were obtained from IBERICA, carried out in the late 90s. These estimates, the most recent for Spain, although adjusted for clustering and updated by the 2000 AMI definition change, may differ from the real estimates. This limitation highlights the need of updated population estimates of AMI incidence and mortality in Europe. Second, due to data availability we used PEGASUS characteristics prevalence at hospitalization for the index AMI instead of at 1-year post-AMI. However, we would not expect a significant increase in risk factor prevalence during this year. Third, due to the high percentage of missing data on multivessel CHD (60%), we did not include it in the analysis. Based on preliminary data from the REGICOR hospital Registry, $> 50\%$ (70%) of AMI patients had multivessel CHD, and the inclusion of multivessel CHD would increase the number of patients with at least one PEGASUS characteristic by 14% (17%). Thus, we would expect an even higher number of stable AMI patients with at least one PEGASUS characteristic in Spain.

There are also limitations in the outcome analysis of PEGASUS and non-PEGASUS patients. First, this was an observational study, and potential confounding caused by measured and unmeasured variables may be present. Second, while we included all AMI patients aged 35-74 years from a reference area of approximately 600 000 inhabitants during 2003-2009, the study could not have sufficient power to detect differences in certain outcomes such as AMI. Third, we did not have information on prescribed or used medication during the follow-up; thus, we could only include

prescribed medication during hospitalization and at discharge. While medication at discharge could be considered as a proxy for follow-up medication, it is affected by the proportion of days covered which may vary considerably among the included patients. Fourth, we did not have information on bleeding events during follow-up so we could not analyze their incidence. Fifth, we did not include multivessel CHD in the PEGASUS definition due to data completeness. However, the sensitivity analysis including multivessel CHD in the PEGASUS definition, when available, showed similar results in the prognosis analysis but diminished effects. Sixth, while it is possible that changes in the management of AMI patients occurred in the last decade could affect the obtained results, the higher prescription of evidence-based medication observed in the included patients suggests that the modification would be moderate.

CONCLUSIONS

In 2014, there were 22 493 AMI patients ≥ 50 years old in Spain who had survived 1 year without bleeding events and had at least one PEGASUS characteristic (diabetes, previous AMI or CKD). Stable AMI patients aged 50-74 years with any PEGASUS characteristic had a higher risk of cardiovascular and all-cause death at 4.7 years, than those without any PEGASUS characteristic. The increased risk of death of AMI patients with PEGASUS characteristics indicates the need of strengthening secondary prevention and lifestyle modifications and of properly defining the required duration of DAPT in these patients.

ACKNOWLEDGEMENTS

The authors are grateful to Susanna Tello, Marta Cabañero, Leny Franco, and Isabel Ramió for project and data management. We also appreciate the revision of the English text by Elaine Lilly, Ph.D., of Writer's First Aid.

FUNDING

The REGICOR AMI Registry was supported by the *Instituto de Salud Carlos III*-FEDER (grant numbers RD06/0009, RD12/0042, FIS-90/0672, FIS-93/0568, FIS 94/0539, FIS96/0026-01, FIS99/0655, FIS99/0013-01, FIS 99/9342, PI081327, PI11/01801, CP12/03287 [MG], and IFI14/00007 [SSB]), the Catalan Agency for Management of University and Research Grants (grant numbers 2005SGR00577, 2009SGR1195, 2014SGR240), *Fundació La Marató TV3* (grant number ID#081630) and *Agència d'Informació, avaluació i qualitat en salut* (grant number AATRM 034/33/02). I.R. Dégano was funded by the RECERCAIXA Program, *Obra Social "La Caixa"* (grant number RE087465).

CONFLICTS OF INTEREST

J. Marrugat reports grants, consultancy fees, or honoraria from AstraZéneca, Sanofi, Shire, Gilead, Daichii-Sankyo, Gendiag and Ferrer.

REFERENCES

1. Dégano IR, Elosua R, Marrugat J. Epidemiology of acute coronary syndromes in Spain: estimation of the number of cases and trends from 2005 to 2049. *Rev Esp Cardiol.* 2013;66:472–81.
2. Bosch D, Masia R, Sala J, Vila J, Ramos R, Elosua R, et al. Effect of opening a new catheterization laboratory on 30-day and 2-year survival rates in myocardial infarction patients. *Rev Esp Cardiol.* 2011;64:96–104.
3. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001;345:494–502.
4. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med.* 2005;352:1179–89.
5. Wiviott S, Braunwald E, McCabe C, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357:2001–15.
6. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045–57.
7. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med.* 2015;372:1791–800.
8. Bonaca MP, Bhatt DL, Braunwald E, Cohen M, Steg PG, Storey RF, et al. Design and rationale for the prevention of cardiovascular events in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin-thrombolysis in myocardial infarction 54 (PEGASUS_TIMI 54) trial. *Am Heart J.* 2014;167:437–44.
9. Marrugat J, Elosua R, Aldasoro E, Tormo MJ, Vanaclocha H, Segura A, et al. Regional variability in population acute myocardial infarction cumulative incidence and mortality rates in Spain 1997 and 1998. *Eur J Epidemiol.* 2004;19:831–9.

10. Sala J, Marrugat J, Masiá R, Porta M. Improvement in survival after myocardial infarction between 1978-85 and 1986-88 in the REGICOR study. (Registre Glroni del COR) registry. *Eur Heart J*. 1995;16:779–84.
11. Agüero F, Marrugat J, Elosua R, Sala J, Masiá R, Ramos R, et al. New myocardial infarction definition affects incidence, mortality, hospitalization rates and prognosis. *Eur J Prev Cardiol*. 2015;22:1272–80.
12. Dégano IR, Salomaa V, Veronesi G, Ferrières J, Kirchberger I, Laks T, et al. Twenty-five-year trends in myocardial infarction attack and mortality rates, and case-fatality, in six European populations. *Heart*. 2015;101:1413–21.
13. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major bleeding in non-ST-segment elevation myocardial infarction: the CRUSADE bleeding score. *Circulation*. 2009;119:1873–82.
14. Raposeiras S, Abu-Assi E, Alvarez B, Gonzalez MC, Mazon-Ramos P, Virgós A, et al. Prediction of bleeding admission in the first year after acute coronary syndrome and prognostic impact: the cardiochus bleeding risk score [abstract]. *J Am Coll Cardiol*. 2014;63(Suppl12):A32.
15. Srucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. *Bone Marrow Transplant*. 2007;40:381–7.
16. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available at: <http://www.R-project.org/>
17. Steg PG, Greenlaw N, Tardif JC, Tendera M, Ford I, Kääb S, et al. Women and men with stable coronary artery disease have similar clinical outcomes: insights from the international prospective CLARIFY registry. *Eur Heart J*. 2012;33:2831–40.
18. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J*. 2015;36:1163–70.

19. Cohen M. Long-term outcomes in high-risk patients with non-ST-segment elevation myocardial infarction. *J Thromb Thrombolysis*. 2015 May 23. [Epub ahead of print].
20. Darling CE, Fisher KA, McManus DD, Coles AH, Spencer FA, Gore JM, et al. Survival after hospital discharge for ST-segment elevation and non-ST-segment elevation acute myocardial infarction : a population-based study. *Clin Epidemiol*. 2013;5:229–36.
21. Zaman MJ, Stirling S, Shepstone L, Ryding A, Flather M, Bachmann M, et al. The association between older age and receipt of care and outcomes in patients with acute coronary syndromes: a cohort study of the myocardial ischaemia national audit project (MINAP). *Eur Heart J*. 2014;35:1551–8.
22. Gunnell AS, Einarsdottir K, Sanfilippo F, Liew D, Holman CD, Briffa T. Improved long-term survival in patients on combination therapies following an incident acute myocardial infarction: a longitudinal population-based study. *Heart*. 2013;99:1353–8.
23. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet*. 2013;382:1714–22.
24. Collet JP, Silvain J, Barthélémy O, Rangé G, Cayla G, Van Belle E, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomized trial. *Lancet*. 2014;384:1577–85.
25. Gilard M, Barragan P, Noryani AA, Noor HA, Majwal T, Hovasse T, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. *J Am Coll Cardiol*. 2015;65:777–86.
26. Schiele F, Puymirat E, Bonello L, Dentan G, Meneveau N, Collet JP, et al. Impact of prolonged dual antiplatelet therapy after acute myocardial infarction on 5-year mortality in the FAST-MI 2005 registry. *Int J Cardiol*. 2015;187:354–60.

Table 1

Estimated Incident Rate of Acute Myocardial Infarction in Patients ≥ 50 years old (/100000 person-year), Stable and Without Bleeding Events at 1-year Follow-up, in Spain in 2014.

	Hospitalized AMI patients rate (95%CI)	Stable AMI patients at 1 year rate (95%CI)	Stable AMI patients without severe bleeding rate (95%CI)
50-64 years	136 (129; 143)	127 (120; 134)	116 (109; 123)
65-74 years	318 (307; 329)	270 (260; 281)	225 (216; 234)
75-84 years	836 (818; 854)	662 (646; 678)	542 (528; 557)
> 84 years	801 (784; 819)	526 (512; 540)	429 (416; 442)
≥ 50 years	353 (341; 365)	286 (276; 297)	241 (232; 251)

AMI, acute myocardial infarction; CI, confidence interval.

Table 2

Estimated Incident Rate of Acute Myocardial Infarction in Patients ≥ 50 Years Old (/100000 person-year), by Number of PEGASUS Criteria, in Spain in 2014.

	≥ 1 PEGASUS characteristic	≥ 2 PEGASUS characteristics	3 PEGASUS characteristics
	rate (95%CI)	rate (95%CI)	rate (95%CI)
50-64 years	43 (39; 47)	7.2 (5.7; 9.1)	2.0 (1.3; 3.0)
65-74 years	119 (113; 126)	32 (28; 35)	8.1 (6.5; 10.1)
75-84 years	313 (303; 325)	117 (110; 124)	26 (23; 29)
> 84 years	338 (327; 350)	179 (171; 188)	47 (43; 51)
≥ 50 years	131 (124; 138)	45 (41; 49)	11 (9.1; 13.3)

AMI, acute myocardial infarction; CI, confidence interval.

*PEGASUS criteria: diabetes, previous AMI and chronic disease.

Table 3

Characteristics of the 1391 Consecutive Acute Myocardial Infarction Patients Included, Aged 50-74 Years, by the Presence of at Least one PEGASUS Characteristic (age > 64 years, diabetes, previous Acute Myocardial Infarction or Chronic Kidney Disease).

	Non-PEGASUS (n=465)	PEGASUS (n=926)	<i>P</i>
Age, years	56.7 (4.3)	66.2 (6.5)	<.001
Female gender	76 (16.3%)	213 (23.0%)	.005
Hypertension	243 (53.2%)	635 (70.1%)	<.001
Hypercholesterolemia	252 (56.8%)	518 (60.0%)	.281
Smoking (current)	273 (59.7%)	274 (30.4%)	<.001
History of angina	156 (34.3%)	350 (39.6%)	.064
Heart failure	70 (15.8%)	211 (24.9%)	<.001
During hospitalization			
ST elevation	279 (60.7%)	463 (51.4%)	<.001
Angiography	384 (83.7%)	746 (80.9%)	.240
Reperfusion	348 (75.0%)	537 (58.5%)	<.001
Thrombolysis	149 (32.0%)	204 (22.1%)	<.001
PCI	285 (61.6%)	438 (47.7%)	<.001
Arrhythmia (VT, VF)	71 (15.5%)	181 (20.1%)	.046
Angina	41 (9.0%)	100 (11.1%)	.271
LVEF < 50%	104 (25.0%)	235 (31.6%)	.013
III-IV highest Killip class	19 (4.1%)	74 (8.1%)	.008
ACE inhibitor/ARB	353 (76.7%)	784 (86.6%)	<.001
Beta-blocker	436 (94.8%)	758 (83.0%)	<.001
Lipid lowering drugs	432 (93.5%)	794 (88.3%)	.003
Antiplatelet treatment	456 (99.8%)	910 (99.7%)	.999
4-drug combination	310 (68.4%)	581 (65.3%)	.274
At discharge			
ACE inhibitor/ARB	267 (58.3%)	678 (74.8%)	<.001
Beta-blocker	392 (85.2%)	668 (73.2%)	<.001
Lipid lowering drugs	418 (90.7%)	728 (81.0%)	<.001
Antiplatelet treatment	455 (99.3%)	871 (97.9%)	.071
4-drug combination	217 (47.3%)	427 (47.4%)	.999

ACE inhibitor, angiotensin-converting enzyme inhibitor; AML, acute myocardial infarction; ARB, angiotensin receptor

blocker; CKD, chronic kidney disease; PCI, percutaneous intervention; VT, ventricular tachycardia; VF, ventricular fibrillation,

LVEF, left ventricular ejection fraction.

Table 4

Incidence (x 100) of Events in Stable Acute Myocardial Infarction Patients With and Without PEGASUS Criteria Obtained by Survival Analysis

	Non-PEGASUS (n=465)	PEGASUS (n=926)	<i>P</i>
Annual incidence during the second year after the index AMI			
AMI	1.53 (0.40; 2.63)	2.73 (1.67; 3.77)	.162
CV death	0.22 (0.00; 0.64)	1.32 (0.57; 2.06)	.047
Non-CV death	0.43 (0.00; 1.03)	1.54 (0.74; 2.34)	.073
All-cause death	0.65 (0.00; 1.38)	2.84 (1.76; 3.91)	.008
AMI/All-cause death	2.18 (1.18; 3.95)	5.02 (3.73; 6.64)	.012
Incidence during a median follow-up of 4.7 years after 1 year of stable disease			
AMI	5.60 (3.16; 7.98)	6.25 (4.51; 7.95)	.272
CV death	1.28 (0.14; 2.39)	8.55 (6.49; 10.56)	<.001
Non-CV death	2.95 (0.68; 5.18)	6.24 (4.48; 7.96)	<.001
All-cause death	4.19 (1.68; 6.64)	14.00 (11.52; 16.40)	<.001
AMI/All-cause death	9.26 (5.97; 12.44)	17.70 (15.04; 20.35)	<.001

AMI, acute myocardial infarction; CV, cardiovascular

Table 5

Hazard Ratio of Outcomes During a 4.7 Years of Median Follow-up for Stable PEGASUS Acute Myocardial Infarction Patients

	Model 1	Model 2	Model 3	Model 4
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
AMI	1.31 (0.81, 2.12)	1.35 (0.72, 2.54)	1.35 (0.71, 2.58)	1.37 (0.72, 2.62)
CV death	7.43 (3.00, 18.4)*	3.70 (1.33, 10.32)*	3.71 (1.33, 10.38)*	3.44 (1.22, 9.74)*
Non-CV death	3.38 (1.67, 6.81)*	1.80 (0.72, 4.52)	1.52 (0.59, 3.92)	1.46 (0.56, 3.78)
All-cause death	4.82 (2.78, 8.37)*	2.53 (1.29, 4.97)*	2.38 (1.20, 4.70)*	2.21 (1.11, 4.42)*
AMI/All-cause death	2.40 (1.68, 3.44)*	1.59 (0.99, 2.55)†	1.57 (0.97, 2.53)†	1.50 (0.93, 2.44)†

AMI, acute myocardial infarction; CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Models: 1=Crude HR; 2=Adjusted for age, hypertension, smoking, heart failure; 3=As model 2 plus ST elevation, reperfusion, arrhythmia, maximum Killip class; 4=As model 3 plus beta-blockers and lipid-lowering drugs at discharge.

* $P < .05$; † $P < .1$

FIGURE LEGENDS

Figure 1. Estimated number (and 95% confidence interval) of annual stable acute myocardial infarction patients ≥ 50 years old with at least 1 PEGASUS characteristic, in Spain in 2014.

AMI, acute myocardial infarction.

Figure 2. Flow-chart of the study participants included in the outcome analysis.

AMI, acute myocardial infarction.

Figure 3. Incidence of outcomes in stable acute myocardial infarction patients by presence/absence of PEGASUS characteristics. The fully adjusted models presented in Table 5 are represented in this figure. Grey and black lines represent patients with and without any PEGASUS characteristic, respectively.

AMI, acute myocardial infarction; CV, cardiovascular.

AMI patients ≥ 50 years
91 639 (91 047; 92 234)

Hospitalized AMI
patients ≥ 50 years
60 528 (60 047; 61 012)

AMI patients ≥ 50 years
stable at 1 year
49 007 (48 575; 49 442)

Stable AMI patients ≥ 50
years without severe
bleeding events
41 311 (40 914; 41 711)

Patients with ≥ 1
PEGASUS characteristic
22 493 (22 200; 22 788)

Patients with ≥ 1
PEGASUS characteristic
(including age ≥ 65 years)
34 981 (34 616; 35 349)

Consecutive patients with a non-fatal AMI in the REGICOR hospital registry in 2003-2009 aged 35-74 years (n= 1963)

AMI

CV death

Non-CV death

All-cause death

AMI/All-cause death