Original Research

Do We Reperfuse Those in Most Need? Clinical Characteristics of ST-Elevation Myocardial Infarction Patients Receiving Reperfusion Therapy in the Countrywide Registry HELIOS

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Key words: **Acute myocardial infarction, primary PCI, fibrinolysis, registry.**

Introduction: We analysed the clinical profile of patients with an ST-elevation myocardial infarction (STEMI) who arrived in hospital within 12 hrs from pain onset and either received reperfusion therapy (PCI or fibrinolytic therapy) or remained without reperfusion.

Methods: The Hellenic Infarction Observation Study (HELIOS) was a countrywide registry of acute myocardial infarction, conducted during 2005-2006. The registry enrolled 1840 patients with myocardial infarction from 31 hospitals, with a proportional representation of all types of hospitals and all geographical areas.

Results: Of 870 patients with STEMI who were admitted within 12 hrs from pain onset, Group A received no reperfusion (n=289, 33.2%), group B underwent primary PCI (n=84, 9.7%) and group C received fibrinolysis (n=497, 57.1%). In groups A, B and C, respectively, mean age was 73 ± 13, 61 ± 12 and 62 ± 13 years (p<0.001). The prevalence of female sex was 33%, 14%, 18%, of diabetes 40%, 23%, 21%, of prior MI 23%, 10%, 11% and of Killip class 2-4 at admission 32%, 11%, 13%, respectively (all p<0.001). In a multivariate analysis, advanced Killip class, age, diabetes and pain to admission time >3 hrs were all independent variables related to no reperfusion therapy.

Conclusion: Reperfusion therapies are applied to relatively lower-risk patients. If a survival advantage is to be expected at the national level, more high-risk patients, such as the elderly, women, diabetics, and mainly those with advanced Killip class, should be considered for reperfusion strategies.

Manuscript received: March 7, 2010;
Accepted: May 28, 2010.

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Current guidelines for the management of patients with ST-segment elevation myocardial infarction (STEMI) who present within 12 hours from pain onset emphasise the importance of timely reperfusion, either with primary percutaneous coronary intervention (PPCI) or with fibrinolytic therapy.[1,2] In the collaborative meta-analysis of trials comparing fibrinolytic therapy with control treatment, it was evident that the absolute risk reduction in mortality with reperfusion (lives saved per patients treated) was larger in high-risk patients, such as those with anterior infarcts or left bundle branch block, those aged 65-75 years,

those with low blood pressure or tachycardia, or those with diabetes.[3] Similarly, in trials comparing PPCI with fibrinolysis, the greatest benefit from mechanical reperfusion was evident for patients considered to be at high risk.[4,5] It is, therefore, obvious that, in order to achieve the best outcome of patients with STEMI, we should aim to reduce the number of patients receiving no reperfusion and at the same time perform more PPCI in the higher-risk subset.

The Hellenic Infarction Observation Study (HELIOS) is a registry of patients with acute myocardial infarction, representing all types of hospitals and all geographical regions of the country.[6] Therefore, it offers an opportunity to assess the clinical profile of patients with STEMI who undergo PPCI, receive fibrinolytic therapy, or remain without reperfusion. These data would be important for the organisation of national strategies of reperfusion in STEMI.[7]

Methods

The HELIOS registry was organised by the Working Group of Epidemiology of the Hellenic Cardiological Society and ended recruitment in January 2006. Its methodology and main results have been published in detail.[6] In brief, we identified 31 hospitals with or without invasive facilities (proportional representation) from all geographical regions of the country. To obtain a representative cohort of patients that would accurately reflect the situation in the whole country, each hospital contributed relatively to the population of its region, taking into consideration seasonal changes between urban and rural areas. Patients enrolled had a discharge diagnosis of acute myocardial infarction (MI) as defined by the ESC/AHA in 2003.[8] We recorded demographic baseline characteristics, previous cardiac history with medical treatment before admission, time delays from pain onset to admission and to treatment, serial electrocardiograms, troponin, any treatment in hospital, important clinical events and mortality in hospital, and vital status at 30 days and 6 months. In order to ensure consistency among the participating centres, the definitions of all variables were clearly stated in the Clinical Record Form (CRF) booklet so that the investigators could easily refer to them.

The registry included 1840 patients who were admitted to 31 Greek hospitals from January 2005 to January 2006. In this report we have included 870 patients with STEMI who presented in hospital within 12 hours from pain onset, with an ECG that fulfilled the criteria for considering reperfusion therapy, as reviewed centrally. Of these patients 289 remained without reperfusion (33.2%, group A), 84 underwent PPCI (9.7%, group B) and 497 received fibrinolytic therapy (57.1%, group C).

Statistical analysis

Data are expressed as mean ± standard deviation for continuous variables and as percentages for categorical ones. The chi-square test for categorical variables and Student's t-test (ANOVA) for continuous variables were employed to compare the baseline characteristics of the groups of interest. Logistic multivariate regression analysis was employed to explore the variables related to no reperfusion therapy. All tests were considered to be significant at a 0.05 level of statistical significance. Statistical analyses were performed using the SPSS statistical software (version 15, SPSS, Chicago, IL, USA).

Results

The baseline characteristics of the three groups are shown in Table 1. Reperfused patients were younger, predominantly male, without diabetes or prior MI, and in Killip class I. Of the 299 patients who were admitted to an invasive hospital, the prevalence in the not-reperfused, the PPCI and the lysis patients (i.e. in groups A, B and C, respectively) were: for advanced Killip class 35%, 10% and 18% ($p=0.001$); for female gender 40%, 14% and 21% ($p<0.001$); and for prior MI 19%, 11% and 17% ($p=0.294$).

In a multivariate analysis, adjusted for the baseline characteristics that differed significantly between the study groups (age, gender, diabetes, prior MI, history of CAD, hypertension, smoking, obesity, Killip class 2-4, presentation after 3 hours), factors significantly and independently associated with no reperfusion treatment were: advanced Killip class (odds ratio [OR]=0.49, 95% confidence interval [CI]=0.32-0.76, $p=0.001$), age (per year) (OR=0.95, 95% CI=0.94-0.96, $p<0.001$), diabetes (OR=0.59, 95% CI=0.46-0.86, $p=0.006$) and pain to admission time >3 hrs (OR=0.53, 95% CI=0.38-0.74, $p<0.001$).

Of the 84 patients who underwent PPCI, 32 (38%) were younger than 75 years, presented within 3 hrs and had an anterior infarct; therefore, they could be considered as good candidates for fibrinolytic therapy.

Medical treatment in hospital and at discharge was also different between the groups, with patients

Table 1. Baseline characteristics of patients.

	Group A (n=289)	Group B (n=84)	Group C (n=497)	p
Age (years, mean ± SD)	73 ± 13	61 ± 12	62 ± 13	<0.001
Female (%)	33	14	18	<0.001
Diabetes (%)	40	23	21	<0.001
Ever smoker (%)	64	77	82	<0.001
Hypertension (%)	64	45	47	<0.001
Hyperlipidaemia (%)	49	60	47	0.093
Prior MI (%)	23	10	11	<0.001
History of CAD (%)	29	17	14	<0.001
Obesity (%)	17	21	26	0.024
Killip class 2-4 (%)	32	11	13	<0.001
Pain-door <3 hrs (%)	49	68	70	<0.001

MI – myocardial infarction; CAD – coronary artery disease.

who were not reperfused also receiving fewer secondary prevention therapies (Table 2).

Mortality in hospital was 12.1% in group A, 3.6% in group B and 4.6% in group C. Mortality at day 30 and at 6 months was 16.8% and 24.5% in group A, 7.2% and 11.3% in group B and 5.8% and 7.1% in group C, respectively.

Discussion

National registries for acute MI are important, as they provide data that are unique for the specific country and could contribute to the optimal use of reperfusion therapies, with the ultimate goal of reducing mortality.[9]

One of the findings of this report from the HELIOS registry is the confirmation that, in Greece, about one third of patients with STEMI who present within 12 hours and are candidates for reperfusion therapy according to current guidelines, in fact receive no such therapy. This is not different from the situation in other countries, since this reperfusion therapy shortfall is already known from multinational registries in Europe and other countries, and remains a problem.[10-12] In our study we did not include all STEMI patients, but excluded the 15% that presented more than 12 hours after pain onset.[13] This was appropriate, as these patients are not good candidates for reperfusion therapies and may have different characteristics. Late presenters have been found to have no mortality advantage with either lytic therapy or PPCI.[3,14] However, it would be important to reduce this percentage, in order to bring more patients into the reperfusion algorithms nationwide.

Our main finding is that patients who receive reperfusion have a relatively low risk profile, and this is particularly evident in the patients selected for PPCI. Undoubtedly, there are patients for whom it is appro-

Table 2. Treatment in hospital and at discharge.

	Group A	Group B	Group C	p
In hospital:				
Aspirin (%)	86	99	96	p<0.001
Clopidogrel (%)	60	98	66	p<0.001
Heparin (%)	34	79	71	p<0.001
LMWH (%)	80	31	73	p<0.001
GPI (%)	10	68	8	p<0.001
At discharge:				
Aspirin (%)	81	95	94	p<0.001
Clopidogrel (%)	60	93	68	p<0.001
ACEi/ARB (%)	73	86	71	p<0.01
Statin (%)	70	99	90	p<0.001
beta-blockers (%)	72	91	85	p<0.001

LMWH – low molecular weight heparin; GPI – glycoprotein IIb/IIIa inhibitors; ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker.

priate not to deliver reperfusion therapy, either because they arrive too late (for example after 9 hours) or are thought to have little to gain (no myocardium at risk to salvage). However, our results show that certain risk factors (advanced Killip class, increased age, diabetes) are associated with no reperfusion, while in fact patients with such characteristics would benefit most.[3] Moreover, patients who are considered to have a contraindication for fibrinolytic therapy, and would preferably be treated with PPCI instead, are those at increased bleeding risk, such as the elderly, females, hypertensives, diabetics and those who present after 2-3 hours.[15] One would expect, therefore, that PPCI patients should include such high-risk patients, resulting in a group with materially different characteristics compared to the fibrinolysis group. In our registry, however, PPCI patients had the same risk profile as fibrinolytic therapy patients, meaning that there may be a reluctance to perform PPCI in higher-risk patients. The SHOCK registry confirmed the advantage of PPCI over fibrinolysis in cardiogenic shock, yet in our data few patients with advanced Killip class underwent PPCI.[16] Also, it is known that the advantage of PPCI over fibrinolysis (pre-hospital or in-hospital) is more evident as time from pain onset increases.[17,18] In our series, patients treated with PPCI were no different from lysed patients with respect to time from pain onset. Moreover, more than one third of PPCI patients had the characteristics of a good fibrinolysis candidate.

One other observation from our data relates to the use of secondary prevention drug therapies at discharge. There was an underuse of statins, angiotensin-converting enzyme inhibitors, b-blockers and antiplatelet drugs in the group not receiving reperfusion. This could in part be explained by the different baseline characteristics and the possible presence of contraindications. Since mortality at 6 months is very high in this particular group of patients, efforts must be made to increase the use of secondary prevention drugs. Reports of under-utilisation of secondary prevention drug therapy and poorer outcomes have been published.[19,20] A finding that needs further exploration is the relatively high 6-month mortality in PPCI patients. It would be interesting to see whether premature discontinuation of dual antiplatelet therapy after stent placement might be responsible.[21]

There are some limitations in our study. HELIOS was specifically designed to have a cohort of acute MI patients with a proportional representation of all types of hospitals and of all geographical areas, and we believe that our study reflects accurately the way acute MI is treated in Greece, without selection bias. However, a larger registry with the participation of every single hospital admitting acute MI cases would certainly be more accurate and desirable. Also, since the collection of our data in 2006, the rates of PPCI in Greece have certainly increased and a PPCI programme is indeed implemented and under way.

At a national level, mortality in STEMI patients could be reduced through three complementary actions. First, it is very important to reduce the percentage of patients receiving no reperfusion therapy at all. Second, fibrinolysis should be administered as early as possible and ideally in the pre-hospital phase. This is important for non-invasive hospitals that do not have the possibility to transfer patients for PPCI within the recommended 90-120 minute time window. We have reported that outcomes are not significantly inferior in these hospitals.[22] Third, more high risk patients should be treated with PPCI in the invasive hospitals. The aim should be to treat with PPCI those STEMI patients who otherwise would receive no reperfusion, and those with a bleeding risk or those likely to have a poor result from fibrinolysis. Simply performing PPCI in patients who are ideal candidates for fibrinolysis offers less benefit. Our data suggest that it is important for authorities and organisations to monitor continuously the profile of STEMI patients who undergo reperfusion therapies or not, record outcomes and implement solutions, in order to obtain the most benefit from the available treatment strategies at a nationwide level.[23,24]

Acknowledgements

We are indebted to all the cardiologists and to the directors of the cardiac departments that participated in the study. The names of the study investigators are listed in the Appendix. Special thanks are due to the support provided by Associate Professor John Lekakis and Professor Harisios Boudoulas, who served as presidents of the Hellenic Cardiological Society during the design and the completion of the study. The study was kindly supported by Boehringer Ingelheim Ellas.

Appendix

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References

1. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J. 2008; 29: 2909-2945.
2. Silber S, Albertsson P, Avilés FF, et al. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Eur Heart J. 2005; 26: 804-847.
3. Fibrinolytic Therapy Trialists (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet. 1994; 343: 311-322.
4. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003; 361: 13-20.
5. De Luca G, Cassetti E, Marino P. Percutaneous coronary intervention-related time delay, patient's risk profile, and survival benefits of primary angioplasty vs lytic therapy in ST-segment elevation myocardial infarction. Am J Emerg Med. 2009; 27: 712-719.
6. Andrikopoulos G, Pipilis A, Goudevenos J, et al. Epidemiological characteristics, management and early outcome of acute myocardial infarction in Greece: the HELlenic Infarction Observation Study. Hellenic J Cardiol. 2007; 48: 325-334.
7. Pipilis A, Andrikopoulos G, Goudevenos J. Strategic steps to improve reperfusion in acute myocardial infarction in Greece. Hellenic J Cardiol. 2008; 49: 123-124.
8. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. Circulation. 2003; 108: 2543-2549.
9. Pipilis AG, Paschidi MD, Andrikopoulos GK, Goudevenos JA. Seven plus one reasons for surveys of acute myocardial infarction in Greece. Hellenic J Cardiol. 2006; 47: 194-197.
10. Eagle KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, López-Sendón J. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). Lancet. 2002; 359: 373-377.
11. Mandelzweig L, Battler A, Boyko V, et al. The second Euro Heart Survey on acute coronary syndromes: Characteristics, treatment and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. Eur Heart J. 2006; 27: 2285-2293.
12. Eagle KA, Nallamothu BK, Mehta RH, et al. Trends in acute reperfusion therapy for ST-segment elevation myocardial infarction from 1999 to 2006: we are getting better but we have got a long way to go. Eur Heart J. 2008; 29: 571-572.
13. Pipilis A, Andrikopoulos G, Lekakis J, et al. Temporal and spatial distribution of ST-elevation myocardial infarction admissions in a countrywide registry. Int J Cardiol. 2009; 142: 172-176.
14. Schömig A, Mehilli J, Antoniucci D, et al. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hrs from symptom onset: a randomized controlled trial. JAMA. 2005; 293: 2865-2872.
15. Fox KAA, Anderson FA, Dabbous OH, et al. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). Heart. 2007; 93: 177-182.
16. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med. 1999; 341: 625-634.
17. Stenestrand U, Lindbäck J, Wallentin L. Long-term outcome of primary percutaneous coronary intervention vs prehospital and in-hospital thrombolysis for patients with ST-elevation myocardial infarction. JAMA. 2006; 296: 1749-1756.
18. Steg PG, Bonnefoy E, Chabaud S, et al. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. Circulation. 2003; 108: 2851-2856.
19. Stenestrand U, Wallentin L; Swedish Register of Cardiac Intensive Care (RIKS-HIA). Early statin treatment following

acute myocardial infarction and 1 year survival. JAMA. 2001; 285: 430-436.
20. Norhammar A. Malberg K, Rydén L, Tornvall P, Stenestrand U, Wallentin L. Underutilisation of evidence based treatment partially explains for the unfavourable prognosis in diabetic patients with acute myocardial infarction. Eur Heart J 2003; 24: 838-844.
21. Kuchulakanti PK, Chu WW, Torguson R, et al. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation. 2006; 113: 1108-1113.
22. Pipilis A, Andrikopoulos G, Lekakis J, et al. Outcome of patients with acute myocardial infarction admitted in hospitals with or without catheterization laboratory: results from the HELIOS registry. Eur J Cardiovasc Prev Rehabil. 2009; 16: 85-90.
23. Bassand J-P, Danchin N, Filippatos G, et al. Implementation of reperfusion therapy in acute myocardial infarction. A policy statement from the European Society of Cardiology. Eur Heart J. 2005; 26: 2733-2741.
24. Le May MR, So DY, Dionne R, et al. A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2008; 358: 231-240.