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Economic Evaluation

Cost-Effectiveness of Posthospital Management of Acute Coronary Syndrome: A Real-World Investigation From Italy

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ABSTRACT

Objectives: This study aimed to assess the cost-effectiveness profile of adherence to recommendations for the community management of patients discharged with a diagnosis of acute coronary syndrome (ACS).

Methods: The cohort of 50 282 residents in the Lombardy Region (Italy) who were discharged with a diagnosis of ACS during 2011 to 2015 was followed up until 2018. Adherence to selected recommendations including drug therapies (DTs), outpatient controls, and rehabilitation, experienced during the first year after index discharge, was considered. Adherent and nonadherent cohort members were matched on high-dimensional propensity scores. Composite clinical outcomes (cardiovascular hospital admissions and all-cause mortality) and healthcare costs were assessed for a time horizon of 5 years. Cost-effectiveness profile of adherence to recommendations was measured through the incremental cost-effectiveness ratio, that is, the incremental cost for 1 day free from the composite clinical outcome.

Results: Adherence to DTs, outpatient controls, and rehabilitation, respectively, regarded 39%, 81%, and 3% of cohort members. Compared with nonadherent patients, those adherent to DTs, outpatient controls, and rehabilitation had (1) a delay in the occurrence of the composite clinical outcome of 50, 43, and 73 days, respectively, and (2) lower (on average, €199 per year for DTs) and higher costs (€292 and €1024 for outpatient controls and rehabilitation). Cost-effectiveness profiles were better for patients with myocardial infarction than those with angina and for patients with more severe clinical complexity than those with milder conditions.

Conclusions: Health-related and economic benefits are expected from improving adherence to international guidelines recommendations concerning outpatient treatments and monitoring of patients with ACS.

Keywords: acute coronary syndrome, cardiac rehabilitation, cost-effectiveness, evidence-based recommendations, healthcare cost, healthcare utilization database, real-world.

VALUE HEALTH. 2022; 25(2):185–193

Introduction

Acute coronary syndrome (ACS) includes acute myocardial infarction and unstable angina (UA). ACS involves nonobstructive coronary artery diseases[1] and abnormalities in coronary arteries characterized by acute rupture of unstable atherosclerotic plaques and subsequent obstruction of coronary artery lumina.[2]

Mortality from ACS has declined substantially in most developed countries.[3] In Italy during the 1990s, almost two-thirds of the decrease in coronary mortality was caused by a reduction in 28-day fatality[4] likely because, in the same period, pharmacologic and nonpharmacologic treatments led to impressive improvements.[5] Hence, compared with the past few decades, many more patients survive ACS nowadays, and their care after hospital discharge has become a major challenge for improving the long-term prognosis.[6]

According to randomized clinical trials and observational investigations, suitable care of patients with myocardial infarction after hospital discharge is considered effective for the secondary prevention of cardiovascular (CV) events and death[7-15] and, consequently, evidence-based guidelines have been developed.[16,17] These latter include cardiac rehabilitation (ie, a combination of physical exercises to alleviate the symptoms of the patient after surgery and improve outcomes), 4 main pharmacological treatments (ie, antiplatelets, statins, beta-blockers, and angiotensin-converting enzyme inhibitors [ACEi]/angiotensin receptor blockers [ARBs]), and out-of-hospital controls (ie, echocardiogram/electrocardiogram, cardiology visit, and lipid-profile test).

Nevertheless, real-world investigations have shown at least suboptimal adherence to current guidelines.[18-22] Few studies have addressed the implications of posthospital-discharge multiple interventions across ACS diagnostic categories and general clinical profiles. In addition, policy makers and stakeholders increasingly demand cost-effectiveness evidence to support their conclusions and decisions.[23] Indeed, albeit several authors assessed both medical and productivity costs of patients with ACS[24,25] and several studies were performed to estimating the cost-effectiveness profile of treatments such as the percutaneous coronary intervention,[26] the literature is scanty of investigations performed for evaluating the cost-effectiveness profile of adherence to recommendations for the out-of-hospital healthcare.

We wished to (1) assess the cost-effectiveness profile of adherence to recommendations for the posthospital-discharge care of patients with ACS from the perspective of the Italian National Health Service (NHS) and (2) identify key features that could modify the cost-effectiveness profile, such as diagnostic categories (ie, UA, myocardial infarction with and without ST elevation) and general clinical profile (surrogated from comorbidities).

Methods

Setting

The data used for this study were retrieved from the healthcare utilization (HCU) databases of Lombardy, a region that accounts for ~16% (~10 million) of the entire Italian population. All Italian citizens have equal access to healthcare services as part of the NHS. An automated system of HCU databases allows each Italian region to manage the local branch of the NHS. HCU data include information on (1) residents who receive NHS assistance (NHS beneficiaries), reporting demographic and administrative data, (2) the diagnosis upon discharge from public/private hospitals and performed procedures (coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification classification system), (3) outpatient drug prescriptions reimbursed by the NHS (coded according to the Anatomical Therapeutic Chemical classification system), and (4) specialist visits and diagnostic examinations reimbursable by the NHS. The cost of each single service supplied to an NHS beneficiary and reimbursed to a health provider (ie, direct healthcare cost for the Regional Health Authority) is also recorded routinely. Record linkage between databases is allowed through a single identification code. To preserve privacy, each identification code is anonymized, with the inverse process being allowed only for the regional authority upon request of judicial authorities. Details of HCU databases of Lombardy and of their use in CV diseases have been reported.[27-30] The authors of the present article were allowed access to these databases through an agreement with Lombardy Region for this study. Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.015 reports the codes used to identify hospitalizations, prescriptions, and information of interest in this study.

Our article was structured in accordance with the checklist items from the Consolidated Health Economic Evaluation Reporting Standards (see Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.015).

Cohort Selection and Follow-up

The target population consisted of all beneficiaries of the NHS resident in Lombardy aged 40 to 90 years. According to the Italian National Institute of Statistics, in 2015 this population totaled approximately 5.8 million inhabitants. Of this population, those who were hospitalized via emergency room with a diagnosis of ACS during 2011 to 2015 were identified. The dates of admission and discharge of the first hospitalization during this period were recorded as “index admission” and “index discharge,” respectively, with the “index hospital stay” being the period between hospital admission and hospital discharge. Transfers between departments (and even between hospitals) were considered to be part of the same hospital stay.

We excluded patients if they (1) were beneficiaries of the NHS from <5 years before the index hospital admission (because we were interested in characterizing each cohort member according to services received previously by the NHS), (2) already experienced at least 1 hospital admission for ACS within 5 years before the index hospital admission (because we aimed to include patients who had a common onset of the event that generated the beginning of the observation, that is, the first hospitalization for ACS), (3) died during the index hospital stay (because we aimed to investigate the healthcare supplied and the outcome that occurred after hospital discharge from the index hospital admission), (4) were transferred from the index hospital stay to a residential facility to undergo an inpatient cardiac rehabilitation program (because these patients likely experienced more severe clinical conditions that we were not able to detect), and (5) accumulated <1 year of follow-up (because we were interested in measuring adherence to recommendations during the first year after hospital discharge from the index hospital admission). The remaining patients were included in the study cohort.

Baseline Characteristics of the Cohort

The baseline characteristics of cohort members included those measured at the index hospital admission, such as sex, age, ACS type (UA, ST elevation myocardial infarction [STEMI], and non-STEMI [NSTEMI]), and selected comorbidities as detected from in-hospital diagnoses and drugs dispensed within 5 years before the index hospital admission. The Multisource Comorbidity Score, a new comorbidity index obtained from inpatient diagnostic information and outpatient drug prescriptions and validated using Italian data,[31] was calculated for each cohort member. Patients were categorized as having a “mild” (0-4), “medium” (5-9), or “severe” (≥10) clinical profile according to the Multisource Comorbidity Score. Finally, the number of contacts with the NHS of each cohort member in the year before the index hospital admission was recorded.

Adherence to Recommendations

We wished to outline the use of out-of-hospital healthcare in the first year after the date of the index hospital discharge. Hence, healthcare supplied to cohort members was assessed, such as the use of selected drugs, undertaking suitable controls, and issuing an outpatient cardiac rehabilitation program (OCRP). Adherence to each of these healthcare categories was investigated separately.

With regard to dispensed drug therapies (DTs), prescriptions of (1) agents that block the renin–angiotensin system, such as ACEi and ARBs; (2) beta-blockers; (3) statins; and (4) dual antiplatelet treatment (DAPT) were considered. The period covered by a prescription was calculated according to the metric of defined daily dose. Nevertheless, because beta-blockers after myocardial infarction are likely prescribed at doses lower than those established for treating hypertension,[32] the corresponding dose was chosen carefully by a working group of experts (see Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.015). For overlapping prescriptions, the individual was assumed to have completed the first prescription before starting the second. Adherence to DT was assessed as the cumulative number of days during which the medication was available divided by the number of days of follow-up (365 days), a quantity denoted as the “proportion of days covered” (PDC).[33] Overall, cohort members were considered adherent to DT if at least 3 of 4 of the considered drug classes had PDC of ≥75%.

With respect to outpatient controls and examinations (OCEs), cardiology visits, echocardiograms/electrocardiograms, and lipid-profile testing were considered. Cohort members were considered to be adherent to OCEs if at least 2 of the 3 of the considered services had been performed. Finally, OCRP issue during the first year after the index hospital discharge was considered.

Design for Matching of Propensity Scores

A high-dimensional propensity score (HDPS)-matching design was used. The HDPS algorithm empirically identified and prioritized covariates that were believed to be proxies for unmeasured confounders.[34] The predicted probability of being classified as "exposed" was estimated by regressing "all" covariates available from our databases against out-of-hospital healthcare. In particular, we separately used a HDPS-matching design for each healthcare category of interest by estimating a score predictive of DT adherence, OCE adherence, and OCRP issue. Briefly, this algorithm (1) identifies candidate covariates as all possible causes of hospitalization (3-digit International Classification of Diseases, Ninth Revision codes) experienced by the patients and all drugs prescribed (Anatomical Therapeutic Chemical codes, third level) to cohort members over the 5-year period before the index date and (2) prioritizes them according to their imbalance between groups (ie, adherent and nonadherent patients) and independently associated with the study outcome (ie, composite clinical outcome), assuming a multiplicative bias term.[34] The 200 most predictive covariates were selected and included in a logistic regression model to estimate the propensity score (to be adherent). For each cohort member who was classified as exposed to a given healthcare (eg, he or she was classified as OCE adherent), 1 cohort member who did not receive that service (eg, he or she was not OCE adherent) was selected randomly to be 1:1 matched for sex, age (±3 years), the number of previous contacts with the NHS, and HDPS through the nearest neighbor-matching algorithm.[35]

Health-Related Outcomes

Hospital admission for ACS, atherothrombotic events (ie, ischemic stroke and peripheral arterial disease), heart failure, any other CV disease, and all-cause mortality during follow-up among HDPS-matching paired cohort members adherent and not adherent to healthcare was compared separately. Follow-up started from the date corresponding to 1 year after the index hospital discharge until any outcome or censor (emigration, or endpoint of follow-up, ie, 5 years after entry) occurred. The probability of experiencing a specific outcome was estimated through the cause-specific cumulative incidence function,[36] a method that takes into account the competing nature of the considered outcomes. With this approach, an individual was assumed to experience the outcome only once, and the overall incidence at a given time was broken down into a sum of the individual cumulative incidence functions for each type of outcome.

Kaplan–Meier curves depicting time free from health-related outcomes until a time horizon of 5 years and corresponding 95% confidence interval (CI) profiles were calculated. The restricted mean survival time, calculated through the area under the Kaplan–Meier curve, represents the time free from health-related outcomes on average experienced by each cohort member.[37] In the current application, the corresponding measure was denoted as the average number of days free from health-related outcomes (DFHROs) experienced by each cohort member.

Healthcare Costs

The costs considered in the present analyses were assessed from the amount that the Regional Health Authority reimbursed to health providers for healthcare services and available in our databases. Costs included hospitalizations and access to emergency room (for CV diseases, or every other cause), drugs dispensed by the NHS (for ACS treatment, as well as every other agent), and outpatients services (related to control and examination of ACS, as well as every other service provided free-of-charge by the NHS, such as specialist visits, laboratory examinations, and instrument-based examinations). Healthcare costs accumulated by each cohort member started from the date of the index hospital discharge until death, migration, or end of follow-up (ie, 5 years after hospital discharge, regardless of which of these events came first). The time span accumulated during this period was denoted as "cost-related follow-up."

Healthcare costs accumulated during the time horizon of 5 years were calculated using the Bang and Tsiatis estimator,[38] a method that takes into account censored cost data. With the aim of expressing cost as a rate, healthcare costs accumulated overall by a given matched cohort were divided by the number of person-days accumulated from that cohort during the cost-related follow-up. The corresponding measure was denoted as the average daily healthcare cost and expressed in euros every person-day.

Cost-Effectiveness Profiles

When an intervention or treatment is clinically superior and cost saving than its comparator, it is referred to as an economically "dominant" strategy.[39] The opposite is called a "dominated" strategy. Nevertheless, the decision becomes more complex when 1 intervention or treatment is clinically superior but with higher costs than the other one. In these circumstances and to judge benefits relative to costs, the costs-effectiveness profile is usually investigated by means of the incremental cost-effectiveness ratio (ICER).[40]

In our study, the costs-effectiveness profile of adherence to each of the abovementioned healthcare categories (ie, DTs, outpatient controls, and rehabilitation) was investigated. Compared with nonadherence, the ICER represents the incremental cost for 1 day free from the composite clinical outcome associated with adherence. This measure was calculated by dividing the difference in the daily healthcare cost and DFHRO between groups (ie, HDPS-matched cohort pairs adherent and not adherent to each healthcare recommendation). A nonparametric bootstrap method based on 1000 resamples was used to explore the uncertainty in the cost-effectiveness estimates. The ICER was stratified according to ACS type (UA, STEMI, or NSTEMI) and clinical profile (mild, medium, or severe).

Sensitivity Analyses

To overcome the arbitrary nature of the thresholds used to define adherence to DTs and outpatient controls (ie, PDC ≥75% and 2 of 3 services), in secondary analyses, we used (1) more permissive (70%) and more restrictive (80%) categories of PDC to measure adherence to the drugs considered and (2) more restrictive definition of adherence to outpatient controls (all 3 services).

All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC). For all hypotheses tested, $P < .05$ (2-tailed) was considered significant.

Results

Patients

Among the 99 751 NHS beneficiaries from the Lombardy Region aged 40 to 90 years hospitalized for ACS during 2011 to 2015, a total of 50 282 met the inclusion criteria (see Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.015). At baseline, their mean age was ~67 years, 67% of them were men, nearly half of them had a diagnosis of STEMI, and just under 1 in 3 patients exhibited a severe clinical profile (Table 1).

Adherence to Recommendations

Table 2 shows that, 1 year after hospital discharge, more than one-third of cohort members adhered to at least 3 of 4 of the considered DTs (mainly to statins, less than half to beta-blockers, ACEi/ARBs, and DAPT) and 81% of them adhered to at least 2 of 3 OCEs (mainly echocardiograms/electrocardiograms and lipid-profile tests, and slightly fewer cardiology visits), but ~3% of them were issued OCRP.

HDPS-Matched Cohorts

Baseline characteristics were well balanced between HDPS-matched paired cohort members according to adherence or nonadherence to DTs, OCEs, and OCRP (see Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.015).

Health-Related Outcomes

The patients included in the final cohort accumulated 194 924 person-years (3.1 years per patient on average) and generated 7502 deaths, with an all-cause mortality rate of 46 every 1000 person-years.

At 5 years from the index hospital discharge, 21% versus 25%, 28% versus 29%, and 13% versus 18% of individuals adherent and nonadherent to DT, OCEs, and OCRP, respectively, experienced at least 1 health-related outcome (Fig. 1). The better prognosis of adherent patients was attributable mainly to an absolute reduction in the risk of all-cause mortality of 3%, 3%, and 2% associated with adherence to DT, OCEs, and OCRP, respectively. Details of individual health-related outcomes experienced from adherent and nonadherent individuals according to diagnostic categories are reported in Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.015.

Compared with nonadherent patients, those adherent to DT, OCEs, and OCRP had an outcome delay of 47, 33, and 69 days, respectively.

Healthcare Costs

At 5 years from the index hospital discharge, adherent and nonadherent individuals to DT, OCEs, and OCRP, respectively, accumulated healthcare costs of €4056 versus €4255, €4023 versus €3731, and €4714 versus €3690 per year (Table 3).

Cost-Effectiveness Profiles

Cost-effectiveness was affected by the type of healthcare provided during the first year after the index hospital discharge (Table 4). Adherence to DT is dominant, that is, patients who adhered to DT experienced a gain in DFHROs with respect to patients who did not adhere to DT (positive differential effectiveness) and a saving of costs (negative healthcare costs differential). With respect to adherence to OCEs and OCRP, adherent individuals experienced a positive differential effectiveness but at the expense of increased cost (positive healthcare costs differential), with ICER of 12.1 (95% CI 7.4-15.9) and 16.6 (95% CI 9.5-36.2), respectively.

Cost-effectiveness was also affected by the baseline characteristics of patients, such as their ACS type and clinical profile at the index hospital discharge (Fig. 2). Regarding adherence to DT, a more advantageous cost-effectiveness profile was reached for patients with STEMI and NSTEMI and for those with medium and severe clinical profiles, rather than for those with UA and a mild clinical profile.

UA, STEMI, and NSTEMI patients adherent to OCEs had, on average, a positive differential effectiveness, but with a positive healthcare costs differential, and an ICER (money on average expended for each day without a health-related outcome) of 11.0 (−46.7 to 67.3), 12.9 (7.1-30.5) and 31.0 (3.8-11.7), respectively. There was no evidence that the clinical profile affected the

Table 1. Baseline characteristics of the 50 282 patients who were discharged with a diagnosis of acute coronary syndrome (Lombardy Region and Italy, 2011-2015).

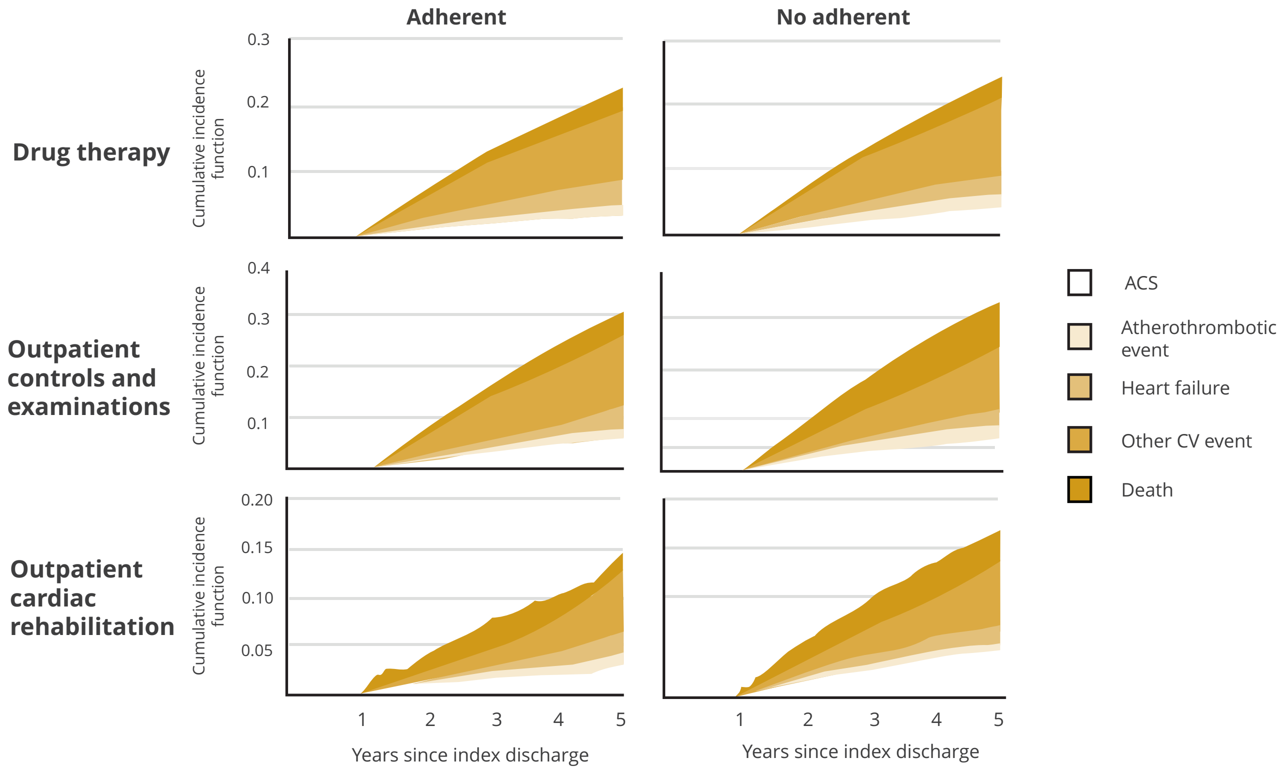
Characteristics	n (%)
Age (y) – mean (SD)	67.4 (12.2)
Male sex	33 805 (67.2)
Diagnosis at the index hospitalization	
Myocardial infarction (STEMI)	22 629 (45.0)
Myocardial infarction (NSTEMI)	16 416 (32.6)
Unstable angina	11 237 (22.4)
Comorbidities	
Hypertension	34 017 (67.7)
Cerebrovascular disease	2561 (5.1)
Dyslipidemia	17 855 (35.5)
Diabetes	9329 (18.6)
Chronic renal failure	363 (0.7)
Chronic obstructive pulmonary disease	14 417 (28.7)
Malignancies	2838 (5.6)
Depression	8090 (16.1)
Clinical profile	
Mild	18 645 (37.1)
Medium	17 273 (34.3)
Severe	14 364 (28.6)

NSTEMI indicates non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction.

Table 2. Adherence to healthcare management strategies in the first year after discharge from the index hospital admission for acute coronary syndrome (Lombardy Region and Italy, 2011 to 2015).

Adherence to	n (%)
Drug dispensation	
Beta-blockers	23 463 (46.7)
Statins	31 671 (63.0)
Renin–angiotensin system blockade	23 506 (46.7)
Dual antiplatelet treatment	23 001 (45.7)
3 of 4	19 360 (38.5)
Cardiac controls	
Cardiologic visits	36 863 (73.3)
Echocardiogram/electrocardiograms	40 631 (80.8)
Test for lipid profile	40 455 (80.5)
2 of 3	40 869 (81.3)
Cardiac rehabilitation	
No	48 853 (97.2)
Yes	1429 (2.8)

Figure 1. Time free from health-related outcomes among high-dimensional propensity score 1:1 matched cohort members differentiated according to whether they adhered or did not adhere to drug therapy, outpatient controls, and cardiac rehabilitation.



ACS indicates acute coronary syndrome; CV, cardiovascular.

outpatient services cost-effectiveness profile because the ICER was €40.0 (−364.8 to 333.8), €13.8 (7.53-39.4), and €11.0 (5.3-40.1) for mild, medium, and severe clinical profiles, respectively.

With respect to adherence to OCRP, the ICER was €11.0 (−46.7 to 67.3), €12.9 (7.1-30.5), and €30.9 (−262.9 to 340.5) for UA, STEMI, and NSTEMI, respectively, and €39.9 (−364.7 to 333.8), €13.8 (7.5-39.4), and €11.0 (5.3-40.1) for mild, medium, and severe clinical profiles, respectively.

The main findings did not change substantially by modifying the threshold used to define adherence to DTs and outpatient controls (see Appendix Table 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.07.015).

Discussion

This study provides real-world evidence on health-related outcomes and healthcare costs for the outpatient care of patients discharged from hospital with ACS. With the exception of OCEs provided to patients with UA, patients who adhered to all other healthcare showed relevant clinical benefits compared with those who did not adhere to it. For example, patients who in the first year after hospital discharge adhered to DT, OCEs, and OCRP had an absolute reduction in the prevalence of health-related outcomes of 4%, 1%, and 5%, respectively, in the following 4 years. Nevertheless, even though €54 every patient-year had been saved among those adherent to DT, additional costs of €407 and €1169 were spent among those adherent to OCEs and OCRP, respectively. Hence, with respect to adherence to DT, a less favorable cost-effectiveness profile ensued from OCEs and rehabilitation; their additional costs ranged from €6 (OCEs of patients with STEMI, NSTEMI, or a mild clinical profile) to €40 (OCRP of patients with mild clinical profile) for every day gained without a health-related outcome. These findings support decision makers by informing them that the additional healthcare cost that the payer should bear by ensuring adherence to healthcare recommendations was a maximum of €14 500 per year gained free from health-related outcomes. It is difficult to find a reference from the literature for these cost-effectiveness profiles. For example, the willingness-to-pay threshold per year of life gained frequently adopted by western countries is €50 000 to €100 000,[41] and the Italy's gross domestic product per capita is approximately €35 000.[42] Nevertheless, because our ICERs consider the event-free survival time instead of quality-adjusted life-year and have a shorter time horizon (5 years instead of lifetime), our findings cannot be directly compared with these thresholds.

Evidence suggests that combined therapy with an ACEi or ARB, beta-blocker, statin, and DAPT can help to reduce CV morbidity and mortality in patients with ACS,[43] which is consistent with recommendations from the American College of Cardiology, American Heart Association, and European Society of Cardiology.[17,44] Our study confirms such evidence and also confirms previous observations that, in real-life settings, adherence to evidence-based therapy is 40% to 60%.[45,46] As a novel and original finding, our study showed that greater clinical and economic benefits were aligned with the greater clinical complexity of patients. The monetary saving associated with a 1-year delay in health-related outcome was from €256 to €475 among patients

Table 3. Average annual healthcare cost (euros) per patient accumulated during a time horizon of 5 years (or up to the end of follow-up), according to adherence to healthcare in the first year after index discharge.

Healthcare services	Drug therapy (11 296 matched pairs)		Outpatient controls (7385 matched pairs)		Cardiac rehabilitation (1253 matched pairs)	
	Adherent	Nonadherent	Adherent	Nonadherent	Adherent	Nonadherent
Hospital admissions						
Cardiovascular events	814	885	885	839	644	675
All other causes together	498	580	580	600	408	465
Accesses to emergency room						
Cardiovascular events	6	6	7	5	5	5
All other causes together	57	66	72	55	47	53
Drug dispensed						
Specific agents	472	308	367	285	461	394
All other dispensations together	572	566	600	504	561	510
Outpatient services						
Specific services	114	90	101	41	1101	70
All other services together	528	612	575	453	536	422
Total	3061	3115	3188	2781	3764	2595

with NSTEMI and STEMI and from €402 to €840 among patients with mild and severe clinical profiles, respectively.

Despite their widespread use, the association between cardiac noninvasive diagnostic tests and outcomes is controversial.[47] Our study helps to support the notion that adherence to selected outpatient diagnostic tests is associated with a lower prevalence of CV morbidity and all-cause mortality, although adherence to these healthcare instruments involves additional costs.

Cardiac rehabilitation is an effective strategy to improve clinical outcomes.[48,49] Several medical societies include cardiac rehabilitation as a class IA recommendation for stable patients after ACS.[16,50,51] In accordance with other large observational population studies,[52] our findings reinforce these recommendations and add that OCRP among patients who survived the first hospital admission for myocardial infarction was associated with a reduction in mortality and hospital readmission for CV outcomes. According to common formulas to assess the population attributable fraction,[53] we estimate that 27% of health-related outcomes observed in our setting could have been avoided if patients with ACS had participated in OCRP. Nevertheless, a surprisingly low participation in OCRPs was observed in our setting (3%), much lower than that reported from other European countries.[54] Nevertheless, it should be considered that 21% of patients discharged with a diagnosis of ACS underwent residential cardiac rehabilitation programs, but that these patients were excluded from our study because their clinical conditions are likely not comparable with those of the investigated patients.

Our study had 3 main strengths. First, our study was based on a very large unselected population, which was made possible because the healthcare system in Italy is free (or almost free) of cost for virtually all citizens. Second, the HCU database generates accurate data because all services claimed by health providers to obtain reimbursement by the Regional Health Authority are checked, and incorrect reports may have legal consequences. Third, precise information about the actual costs of the entire path that the patients experienced can be searched out. This allows to perform an economic evaluation that includes also most fragile patients, who are usually excluded from trials. Moreover, real-world analysis usually allows to include long-term clinical and economic benefits that can be hard to observe using a randomized controlled trial design, and it can also be used for setting where it is not possible/feasible to conduct a randomized controlled trial (eg, narcotic abuse).[55] Finally, because this approach is based on a retrospective evaluation, no model is needed to predict the future (clinical and economic) outcomes, usually based on input gathered from the literature.

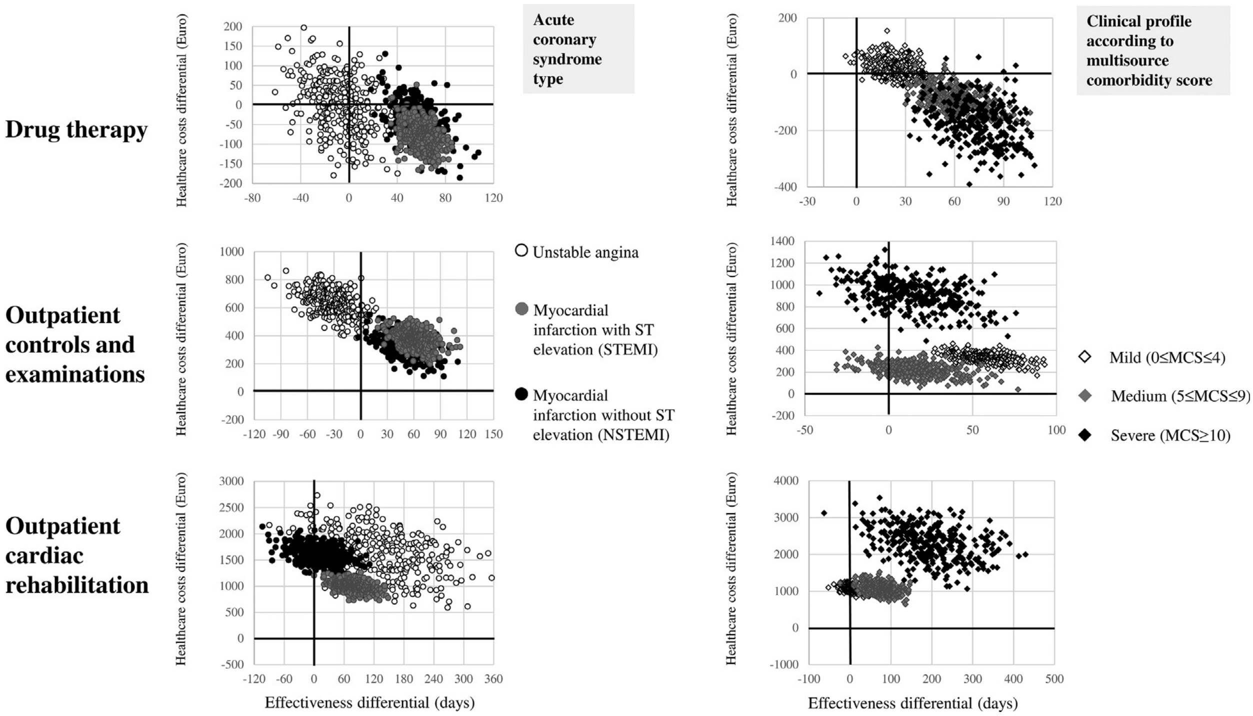
In contrast, we also recognize the limitations of real-world data for economic evaluations, because the findings obtained through these data could be affected by several sources of bias. Indeed, our study had several limitations. First, the generalizability of our findings to patients treated in other healthcare systems (eg, other Italian regions or outside Italy) or with different ages (<40 or >90 years) requires caution. Second, owing to the lack of data on quality of life in our database, we could not measure endpoints such as quality-adjusted life-years and therefore the cost-utility profile. Third, exposure misclassification may have affected our findings in several ways. For example, adherence during the first year after hospital discharge was assumed to be a proxy of adherence during follow-up, which may not be the case. In addition, adherence to DT may have been misclassified because of

Table 4. Differences in healthcare costs and health-related outcomes and ICERs comparing high-dimensional propensity score 1:1 matched cohorts.

Adherence to	Effectiveness differential	Healthcare costs differential	ICER
Drug therapies	46.83	−57.05	Dominant strategy
Outpatient controls	33.36	406.67	12.08 (7.36; 25.91)
Outpatient rehabilitation	71.18	1168.28	16.58 (9.49; 36.17)

ICER indicates incremental cost-effectiveness ratio.

Figure 2. ICER scatterplots representing cost-effectiveness profiles obtained by comparing high-dimensional propensity score 1:1 matched cohorts differentiated according to whether they adhered or did not adhere to drug therapy, outpatient controls, and cardiac rehabilitation. Data were stratified according to the type of acute coronary syndrome (UA, STEMI, or NSTEMI) and MCS (mild, medium, or severe clinical profile). The ICER was measured by dividing the differences in healthcare costs and health-related outcomes between 2 matched cohorts (ie, between adherent and nonadherent patients). Nonparametric bootstrap method based on 1000 resamples was used to explore the uncertainty in the estimates of cost-effectiveness.



ICER indicates incremental cost-effectiveness ratio; MCS, Multisource Comorbidity Score; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; UA, unstable angina.

over-the-counter drug dispensing. Finally, patients with more frequent examinations (as recommended by guidelines) are expected to have different clinical features to those with fewer examinations, so our results could have been affected by confounding by indication. For example, patients who develop progressive frailty could be less adherent to all forms of care and at a higher risk of adverse outcomes. For these reasons, the reduction in health-related outcomes associated with better adherence might have been generated by uncontrolled factors that were accompanied by adherence. To minimize the potential for residual confounding, we used multiple approaches, including the use of HDPS-matching design. This strategy does not avoid confounding entirely, one aspect of which is that, because adherence may be a surrogate for overall health-seeking behavior, more adherent patients might also have followed healthy lifestyle advices and treatment indications more regularly.[56] Nevertheless, because adherent and nonadherent cohort members were matched also for the intensity of their previous contacts with the NHS, it is unlikely that a healthy adherent effect would have affected our findings robustly. Nevertheless, as an observational study, confounding cannot be ruled out, and future high-quality investigations are needed to confirm these findings.

Conclusions

Benefits for patients and healthcare systems are expected from improving adherence to guidelines-driven recommendations. Hence, appropriate care of patients discharged with a diagnosis of ACS through regular outpatient DT, controls, and examinations and cardiac rehabilitation must be considered the cornerstone of national guidance, national audits, and schemes to aid quality improvement.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2021.07.015.

Article and Author Information

Accepted for Publication: July 26, 2021

Published Online: September 4, 2021

doi: https://doi.org/10.1016/j.jval.2021.07.015

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Conflict of Interest Disclosures: Dr Corrao reported receiving grants or contracts from the European Community; the Italian Agency of Drug; the Italian Ministry of Education, University, and Research; Novartis; GlaxoSmithKline; Roche, Amgen; and Bristol-Myers Squibb during the conduct of this study and honoraria as a member of the Advisory Board from Roche. No other disclosures were reported.

Funding/Support: This work was supported by a grant from the Italian Ministry of Health ("Ricerca Finalizzata 2016," NET-2016-02363853).

Role of Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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