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Comparison of Days Alive Out of Hospital With Initial Invasive vs Conservative Management
A Prespecified Analysis of the ISCHEMIA Trial

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IMPORTANCE Traditional time-to-event analyses rate events occurring early as more important than later events, even if later events are more severe, eg, death. Days alive out of hospital (DAOH) adds a patient-focused perspective beyond trial end points.

OBJECTIVE To compare DAOH between invasive management and conservative management, including invasive protocol–assigned stays, in the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) randomized clinical trial.

DESIGN, SETTING, AND PARTICIPANTS In this prespecified analysis of the ISCHEMIA trial, DAOH was compared between 5179 patients with stable coronary disease and moderate or severe ischemia randomized to invasive management or conservative management. Participants were recruited from 320 sites in 37 countries. Stays included overnight stays in hospital or extended care facility (skilled nursing facility, rehabilitation, or nursing home). DAOH was separately analyzed excluding invasive protocol–assigned procedures. Data were collected from July 2012 to June 2019, and data were analyzed from July 2020 to April 2021.

INTERVENTIONS Invasive management with angiography and revascularization if feasible or conservative management, with both groups receiving optimal medical therapy.

MAIN OUTCOMES AND MEASURES The hypothesis was formulated before data lock in July 2020. The primary end point was mean DAOH per patient between randomization and 4 years. Initial stays for invasive protocol–assigned procedures were prespecified to be excluded.

RESULTS Of 5179 included patients, 1168 (22.6%) were female, and the median (interquartile range) age was 64 (58-70) years. The average DAOH was higher in the conservative management group compared with the invasive management group at 1 month (30.8 vs 28.4 days; *P* < .001), 1 year (362.2 vs 355.9 days; *P* < .001), and 2 years (718.4 vs 712.1 days; *P* = .001). At 4 years, the 2 groups' DAOH were not significantly different (1415.0 vs 1412.2 days; *P* = .65). In the invasive management group, 2434 of 4002 stays (60.8%) were for protocol-assigned procedures. There were no clear differences at any time point in DAOH when protocol-assigned procedures were excluded from the invasive management group. There were more hospital and extended care stays in the invasive management vs conservative management group during follow-up (4002 vs 1897; *P* < .001). Excluding protocol-assigned procedures, there were fewer stays in the invasive vs conservative group (1568 vs 1897; *P* = .001). Cardiovascular stays following the initial assigned procedures were lower in the invasive management group (685 of 4002 [17.1%] vs 1095 of 1897 [57.8%]; *P* < .001) due to decreased spontaneous myocardial infarction stays (65 [1.6%] vs 123 [6.5%]; *P* < .001) and unstable angina stays (119 [3.0%] vs 216 [11.4%]; *P* < .001).

CONCLUSIONS AND RELEVANCE DAOH was higher for patients in the conservative management group in the first 2 years but not different at 4 years. DAOH was decreased early in the invasive management group due to protocol-assigned procedures. Hospital stays for myocardial infarction and unstable angina during follow-up were lower in the invasive management group. DAOH provides a patient-focused metric that can be used by clinicians and patients in shared decision-making for management of stable coronary artery disease.

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+ **Supplemental content**

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I n the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) randomized clinical trial, patients with stable coronary disease and moderate or severe myocardial ischemia on stress testing were randomized to initial invasive or conservative management strategies.[1] After a median follow-up of 3.2 years, the invasive management strategy did not reduce the composite primary end point of cardiovascular mortality, myocardial infarction (MI), or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest, but it did lessen the occurrence of angina.[2]

In the ISCHEMIA trial, the primary end point analysis used time to composite event, the usual analysis in clinical trials. This type of analysis has many limitations. First, it does not fully consider the balance of efficacy and adverse events, such as bleeding. Second, in composite end point trials, time-to-event analysis rates an event of lesser severity occurring early, such as hospitalization for unstable angina, as more important than an event of greater severity occurring later, such as death. Each component of the composite end point is given equal importance and counted only at its first occurrence. Third, time-to-event analysis does not account for multiple events. Fourth, hospitalizations may not meet trial definitions so are not counted in a traditional end point-focused approach. A total-event analysis can provide a clinically important estimation of risk reduction from a randomized treatment, but discontinuation of treatment or waning effectiveness after an initial event are known challenges.[3] An alternative end point is days alive out of hospital (DAOH).[4-8] DAOH is a global measure that includes death and days out of hospital collectively. It is most reflective of the patient experience as opposed to only capturing single trial-defined primary and secondary end points, since all hospitalized days are counted. DAOH provides an indirect measure of event severity by incorporating length of stay in the metric and incorporates timing of a participant's death. In this prespecified analysis of the ISCHEMIA trial, DAOH was compared between patients in the invasive management group and the conservative management group.

We hypothesized that there would be less DAOH in the invasive management group initially taking into account invasive protocol-assigned procedures but that there may be a benefit later on with increased DAOH due to reduction in hospitalization or extended care related to reduction in needs for further revascularization and/or reductions in acute coronary syndromes (ACS).

Methods

The study design, baseline characteristics, and main results of the ISCHEMIA trial have been published previously.[2,9,10] The protocol was approved by the Institutional Review Board at the New York University Grossman School of Medicine (the clinical coordinating center) and by the institutional review board or ethics committee at each participating site and can be found in Supplement 1. Trial personnel can be found in Supplement 2. All patients provided written informed consent. This

Key Points

Question Is the patient-focused metric days alive out of hospital (DAOH) different in patients randomized to invasive management compared with conservative management in the ISCHEMIA randomized clinical trial?

Findings This prespecified analysis of the ISCHEMIA trial analyzed 5179 patients with stable coronary disease and moderate or severe ischemia randomized to invasive or conservative management. Compared with the invasive management group, DAOH was higher in the conservative management group at 1 month (difference, 2.4 days), 1 year (difference, 6.4 days), and 2 years (difference, 6.4 days); at 4 years, DAOH was similar in both groups.

Meaning DAOH can inform patient decisions about trade-offs, with higher DAOH earlier with conservative management but similar DAOH to invasive management at 4 years.

study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Patients with stable coronary disease and moderate or severe myocardial ischemia as determined by imaging and severe ischemia by exercise tolerance testing[9] were randomly assigned at 320 sites in 37 countries to an initial invasive management strategy with catheterization, angiography, and revascularization if feasible plus optimal medical therapy or to a conservative management strategy with optimal medical therapy alone and angiography reserved for failure of medical therapy due to refractory angina or an event. In the 2588 patients randomized to the invasive management strategy, cardiac catheterization was performed in 2475 patients (95.6%) and revascularization in 2054 patients (79.4%). The revascularization method was percutaneous coronary intervention (PCI) in 1524 of 2054 patients (74.2%) and coronary artery bypass grafting (CABG) in 530 of 2054 patients (25.8%). End point definitions of the primary composite outcome have been published previously.[9]

All randomized patients were included in an intention-to-treat basis. The prespecified primary end point before database lock for analysis was mean DAOH per patient from randomization to 4 years. Stays in hospital or extended care and the resulting discharge diagnoses were investigator reported. Stays were defined as an overnight stay in a hospital or extended care facility (skilled nursing facility, rehabilitation, or nursing home). Initial stays for invasive protocol-assigned procedures were included.

Identification of Stays

The algorithm used to identify stays in the ISCHEMIA database is summarized in the CONSORT diagram (**Figure 1**), which identifies stays that were not counted, including single-day stays, emergency department stays, and stays with a length of stay of 365 days or greater, which were likely data entry errors and missing data.

Classification of Patient Stay Types

Patient stay records were classified into the following mutually exclusive categories: invasive protocol-assigned procedures, cardiovascular discharge diagnosis, noncardiovascu-

lar discharge diagnoses, no discharge diagnosis data, and extended care. Cardiovascular diagnoses included ACS with spontaneous MI (types 1, 2, 4b, and 4c),[11] procedural MI (types 4a and 5), or unstable angina, heart failure, resuscitated cardiac arrest, stroke, and other cardiovascular events. This analysis includes investigator-reported hospital or extended care patient stays by type and discharge diagnoses, which were not adjudicated.

Statistical Analysis

In descriptive analysis, we tabulated the number of stays and the number of days spent in hospital or extended care by treatment group overall and for specific reasons during follow-up without adjustment for censoring. We compared the number of stays per patient across treatment groups using the Mantel-Haenszel χ^2 test with mean scores. The number of days spent in hospital or extended care per patient was compared in a similar manner. We separately analyzed the role of stays for invasive protocol-assigned procedures on DAOH.

Formal statistical analysis estimated the cumulative mean number of days alive and out of hospital or extended care (DAOH) per patient by treatment group with adjustment for censoring over a 4-year time horizon. Follow-up began at the time of randomization and included initial stays for invasive treatment. Analysis was based on the temporal process regression framework of Zhan and Schaubel.[12] To account for nonproportional hazards, we fit the model in each treatment group separately and without covariates. This was equivalent to performing a fully nonparametric analysis. For additional perspective, we also applied the Zhan and Schaubel methodology[12] to additional end points that are related to DAOH. These included the number of distinct admissions to a hospital or extended care facility over 4 years, the total number of days spent in a hospital or extended care facility over 4 years, and the number of days that a patient was alive over 4 years beginning at randomization.

To assess heterogeneity of treatment effect, we estimated the difference in mean DAOH over 4 years for invasive and conservative groups across levels of the following baseline risk factors, as prespecified: age (younger than 65 years, 65 to 74 years, 75 years and older), sex, race/ethnicity, region, prior MI, prior heart failure, modified Duke prognostic score, and multicomorbidity (3 or more vs less than 3 of the following: prior MI, prior PCI, prior CABG, stroke, valvular heart disease, heart failure, atrial fibrillation, diabetes, current smoking, or glomerular filtration rate less than 60 mL/min/1.73 m^2). Tests of covariate by treatment interaction were based on the null hypothesis that difference in cumulative mean DAOH for invasive management minus conservative management at 4 years was constant across all levels of baseline factors.

We performed a landmark analysis from 30 days. We also analyzed DAOH across categories of Seattle Angina Questionnaire 7-Angina Frequency (SAQ7-AF) within each treatment group. SAQ7-AF scores of 0 to 30, 31 to 60, 61 to 99, and 100 have been shown to validly reflect angina that occurs daily, weekly, several times per month ("monthly"), and no angina, respectively, as assessed with daily diaries.[13]

Figure 1. CONSORT Diagram of Identification of Patient Stays
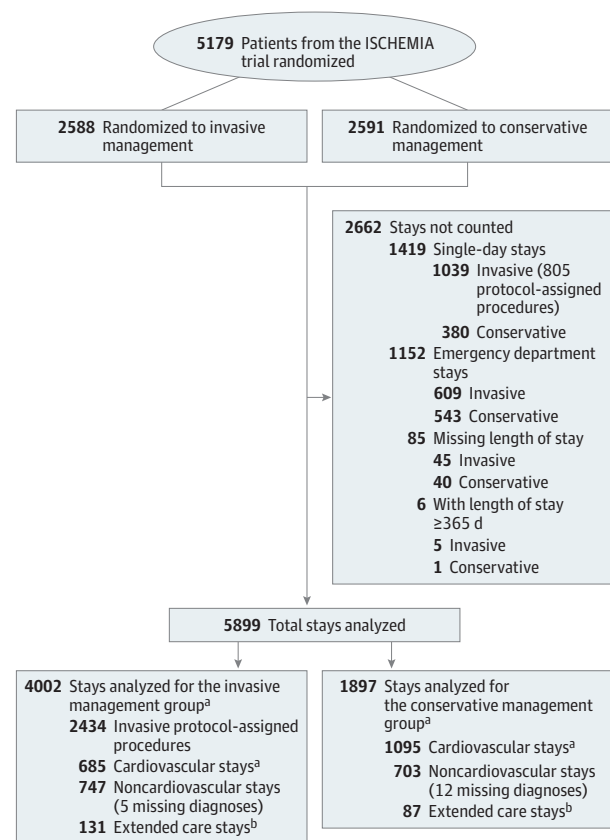
Extended care included stays at a skilled nursing facility, rehabilitation, or nursing home. ISCHEMIA indicates International Study of Comparative Health Effectiveness with Medical and Invasive Approaches.

[a] P < .001 for comparison of invasive management stays vs conservative management stays.

[b] P = .01 for comparison of invasive management stays vs conservative management stays.

Two-tailed P values were used without adjustment for multiplicity, and P values less than .05 were considered significant. Analyses were performed using SAS version 9.4 (SAS Institute) and R Open version 3.5.3 (The R Foundation).

Results

All 5179 patients were included in this analysis. Of these, 1168 (22.6%) were female, and the median (interquartile range) age was 64 (58-70) years. A total of 5899 stays were analyzed (Figure 1).

Estimated Cumulative Mean DAOH

Estimated cumulative mean DAOH after 1 month were 2.4 days more in patients randomized to conservative management compared with invasive management (30.8 vs 28.4; difference, 2.4; 95% CI, 2.2-2.6; P < .001). The mean additional DAOH for the conservative management group compared with the

Table 1. Estimated Cumulative Mean Days Alive Out of Hospital or Extended Care (DAOH)
Over Time by Treatment Group

Time point from randomization	Days, mean (95% CI)			
	Invasive management	Conservative management	Difference	P value
Mean DAOH				
1 mo	28.4 (28.3 to 28.6)	30.8 (30.8 to 30.9)	−2.4 (−2.6 to −2.2)	<.001
1 y	355.9 (354.7 to 357.1)	362.2 (361.4 to 363.0)	−6.3 (−7.7 to −4.8)	<.001
2 y	712.1 (709.1 to 715.1)	718.4 (716.0 to 720.9)	−6.3 (−10.2 to −2.4)	.001
3 y	1065.4 (1060.1 to 1070.8)	1070.0 (1065.0 to 1075.0)	−4.6 (−11.9 to 2.8)	.22
4 y	1412.2 (1403.8 to 1420.6)	1415.0 (1406.6 to 1423.4)	−2.8 (−14.6 to 9.1)	.65
Mean DAOH excluding days related to invasive protocol-assigned procedures				
1 mo	30.8 (30.8 to 30.9)	30.8 (30.8 to 30.9)	−0 (−0.1 to 0.1)	.66
1 y	361.1 (360.0 to 362.2)	362.2 (361.4 to 363.0)	−1.1 (−2.5 to 0.3)	.11
2 y	717.3 (714.4 to 720.3)	718.4 (716.0 to 720.9)	−1.1 (−4.9 to 2.8)	.58
3 y	1070.6 (1065.3 to 1075.9)	1070.0 (1065.0 to 1075.0)	0.7 (−6.6 to 7.9)	.86
4 y	1417.5 (1409.1 to 1425.8)	1415.0 (1406.6 to 1423.4)	2.4 (−9.4 to 14.3)	.69

Figure 2. Proportion of Days Alive Out of Hospital (DAOH) With Follow-up Up to 4 Years Among Randomized Participants
vs Those Excluding Protocol-Assigned Procedures
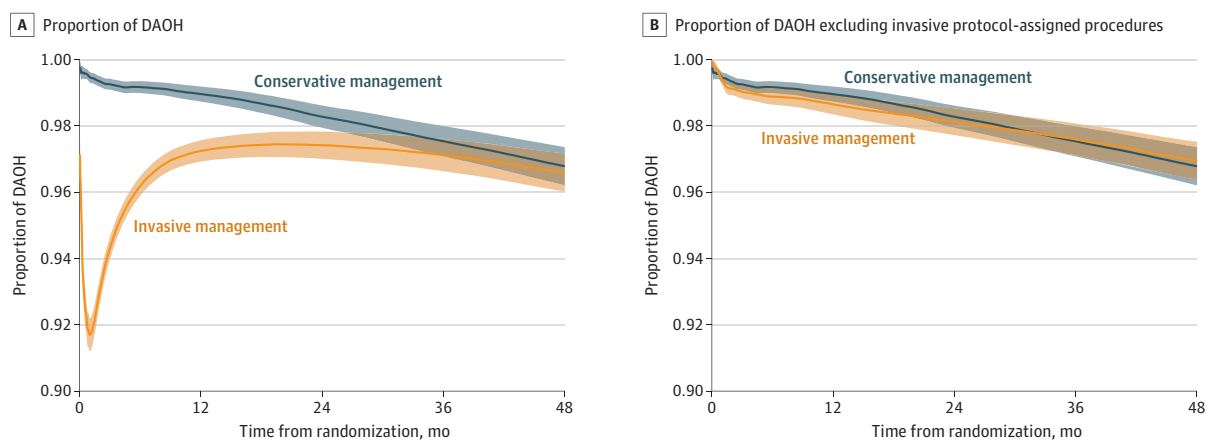
A, Proportion of DAOH for assigned patients, with follow-up up to 4 years. B, Proportion of DAOH excluding protocol-assigned procedures for assigned patients, with follow-up up to 4 years. The shaded areas indicate 95% CIs.

invasive management group was 6.3 days (362.2 vs 355.9; difference, 6.3; 95% CI, 4.8-7.7; *P* < .001) after 1 year, 6.3 days (718.4 vs 712.1; difference, 6.3; 95% CI, 2.4-10.2; *P* = .001) after 2 years, 4.6 days (1065.4 vs 1070.0; difference, 4.6; 95% CI, 2.8-11.9; *P* = .22) after 3 years, and 2.8 days (1415.0 vs 1412.2; difference, 2.8; 95% CI, 9.1-14.6; *P* = .65) after 4 years (**Table 1**) (**Figure 2**). There were no statistically significant differences (between 0 and 2.4 DAOH) at any time point when invasive protocol-assigned procedures were excluded from the analysis (Table 1).

Landmark analysis excluding the first 30 days after randomization (eTable 1 in Supplement 3) showed a difference of 3.9 DAOH at 1 year favoring the conservative management group, with a similar difference of 3.9 DAOH at 2 years and no significant difference at 4 years.

Relationship of DAOH With Angina Symptoms
eTable 2 and eFigure 1 in Supplement 3 show the SAQ7-AF with DAOH at 4 years in both groups. There was no relationship of angina with DAOH.

Subgroups for DAOH
eFigure 2 in Supplement 3 shows a forest plot for 10 prespecified subgroups for DAOH. There were no significant treatment differences in any subgroup. eTable 3 in Supplement 3 shows that patients 75 years and older had fewer DAOH at 4 years than patients younger than 65 years, both within the invasive management group (1358 [32.4%] vs 1429 [34.0%]; *P* < .001) and the conservative management group (1355 [32.3%] vs 1430 [34.0%]; *P* < .001). eTable 3 in Supplement 3 also shows DAOH according to region at 4 years. There were no differences between geographic regions (Asia, Latin America, North America, and other regions) compared with the reference group of Europe.

eTable 4 in Supplement 3 shows DAOH according to age and region excluding invasive protocol-assigned procedures. There were no significant differences between the groups.

Stays in Hospital or Extended Care
There were 4002 stays in hospital or extended care facilities in the invasive management group and 1897 stays in the

Table 2. Number of Stays and Reasons for Hospital or Extended Care Stays by Treatment Group

Reason	No.			P value
	Overall (N = 5179)	Invasive management (n = 2588)	Conservative management (n = 2591)	
No. of stays overall	5899	4002	1897	<.001
Invasive protocol-assigned procedure stays	NA	2434	NA	NA
First revascularization				
PCI	NA	1568	NA	NA
CABG	NA	652	NA	NA
None[a]	NA	214	NA	NA
Excluding protocol-assigned procedure stays	3465	1568	1897	.001
Cardiovascular stays	1780	685	1095	<.001
MI/unstable angina[b]	595	200	395	<.001
Spontaneous MI[c]	188	65	123	<.001
Procedural MI[d]	18	5	13	.07
Unstable angina	335	119	216	<.001
Missing site-reported event type	54	11	43	<.001
Heart failure[e]	132	74	58	.29
Resuscitated cardiac arrest	18	10	8	.64
Stroke	72	38	34	.65
Other cardiovascular	1025	388	637	<.001
Noncardiovascular stays	1450	747	703	.47
Infection	198	111	87	.20
Malignancy	214	137	77	.08
Bleeding	93	49	44	.65
Noncardiac chest pain	65	25	40	.09
Pneumonia	53	26	27	.91
Kidney failure	43	23	20	.69
Other	941	465	476	.79
Missing discharge diagnoses	17	5	12	.11
Extended care stays				
Nursing/rehabilitation	218	131	87	.01
Transfer	152	94	58	.02
Direct admit	66	37	29	.36
Skilled nursing	74	48	26	.049
Rehabilitation	123	72	51	.08
Nursing home	8	6	2	.16
Unknown type	13	5	8	.49

Abbreviations: CABG, coronary artery bypass graft; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention.

[a] Includes patients who were randomized to revascularization but who did not receive it because of nonsignificant coronary artery disease or extensive coronary disease not suitable for revascularization.

[b] MI and unstable angina types are based on site-reported data, as described in the Methods section.

[c] Spontaneous MI indicates MI types 1, 2, 4b, and 4c.[11]

[d] Procedural MI indicates MI types 4a and 5.

[e] Investigator-reported stays for heart failure include recurrent admissions. The primary ISCHEMIA trial article[1] reported only first heart failure events.

conservative management group (*P* < .001) (Figure 2A) (**Table 2**). In the invasive management group, 2434 stays (60.8%) were due to the invasive protocol-assigned procedures (Figure 2B) (**Table 3**). When invasive protocol-assigned procedures were excluded, there were fewer stays in the invasive management group than in the conservative management group (1568 vs 1897; *P* = .001).

Stays in Hospital or Extended Care per Patient
The mean number of stays in a hospital or extended care during follow-up per patient was higher in the invasive management group (mean [SD], 1.5 [1.6] vs 0.7 [1.4]; *P* < .001) (Table 3). Excluding invasive protocol-assigned procedures, the mean number of stays in hospital or extended care per patient was

lower in the invasive management group (mean [SD], 0.6 [1.4] vs 0.7 [1.4]; *P* = .001). More patients had zero stays in the conservative group (409 [20.0%] vs 1635 [80.0%]; *P* < .001). Recurrent stays were higher in the invasive group compared with the conservative group (957 [36.9%] vs 446 [17.2%]; *P* < .001).

Cumulative Stays in Hospital or Extended Care at 4 Years
eTable 5 in Supplement 3 shows that the cumulative mean number of stays in hospital or extended care per patient at 4 years was higher for the invasive management group (1.61 vs 0.81; difference, 0.80; 95% CI, 0.71-0.89; *P* < .001) but lower for the invasive management group if invasive protocol-assigned procedures were excluded (0.69 vs 0.81; difference, −0.12; 95% CI, −0.21 to −0.03; *P* = .007).

Table 3. Number of Stays and Days Spent in Hospital or Extended Care per Patient by Treatment Group

Measure	Overall (N = 5179)	Invasive management (n = 2588)	Conservative management (n = 2591)	P value
Stays				
Stays per patient, No.				
Mean (SD)	1.1 (1.5)	1.5 (1.6)	0.7 (1.4)	<.001
Median (IQR)	1 (0-2)	1 (1-2)	0 (0-1)	
Invasive protocol–assigned procedures				
Mean (SD)	NA	0.9 (0.6)	NA	NA
Median (IQR)	NA	1 (1-1)	NA	NA
Excluding invasive protocol–assigned procedures				
Mean (SD)	0.7 (1.4)	0.6 (1.4)	0.7 (1.4)	.001
Median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	
Stays per patient including recurrent stays, No.				
0	2044	409	1635	
1	1732	1222	510	
2	796	563	233	<.001
3	314	214	100	
≥4	293	180	113	
Days spent in hospital or extended care				
Days spent in hospital or extended care per patient				
Mean (SD)	7.3 (17.1)	9.1 (18.6)	5.4 (15.3)	<.001
Median (IQR)	2 (0-8)	4 (1-10)	0 (0-4)	
Invasive protocol–assigned procedures				
Total				
Mean (SD)	NA	4.4 (6.6)	NA	NA
Median (IQR)	NA	2 (1-6)	NA	NA
First revascularization				
PCI[a]				
Mean (SD)	NA	2.9 (3.6)	NA	NA
Median (IQR)	NA	2 (1-4)	NA	NA
CABG[b]				
Mean (SD)	NA	12 (9.8)	NA	NA
Median (IQR)	NA	9 (7-14)	NA	NA
None[c]				
Mean (SD)	NA	1.2 (3.2)	NA	NA
Median (IQR)	NA	0 (0-2)	NA	NA
Excluding invasive protocol–assigned procedures				
Mean (SD)	5.1 (15.7)	4.7 (16.1)	5.4 (15.3)	.10
Median (IQR)	0 (0-3)	0 (0-2)	0 (0-4)	NA

Abbreviations: CABG, coronary artery bypass graft; IQR, interquartile range; NA, not applicable; PCI, percutaneous coronary intervention.

[a] n = 1524.

[b] n = 530.

[c] n = 534. Includes patients who were randomized to revascularization but who did not receive it because of nonsignificant coronary artery disease or extensive coronary disease not suitable for revascularization.

Reasons for Stays in Hospital or Extended Care

Table 2 shows the discharge diagnoses according to randomized group. eFigure 3 in Supplement 3 illustrates differences between the groups for reasons for patient stays. Cardiovascular stays following the invasive protocol-assigned procedures were lower in the invasive management group (685 of 4002 [17.1%] vs 1095 of 1897 [57.8%]; P < .001), including fewer stays for spontaneous MIs (65 [1.6%] vs 123 [6.5%]; P < .001) and for unstable angina (119 [3.0%] vs 216 [11.4%]; P < .001). Noncardiovascular stays were similar in both groups.

Extended care stays were higher in the invasive management group compared with the conservative management group (131 [3.3%] vs 87 [4.6%]; P = .01) (eFigure 4 in Supple-

ment 3), with 37 of 72 stays (51%) in the invasive management group being transfers from a CABG stay.

Days Spent in Hospital or Extended Care per Patient

The number of days spent in hospital or extended care per patient was higher in the invasive management group compared with the conservative management group (mean [SD], 9.1 [18.6] vs 5.4 [15.3]; P < .001) (Table 3). When invasive protocol-assigned procedures were excluded, there was no significant difference (mean [SD], 4.7 [16.1] vs 5.4 [15.3]; P = .10).

Patients randomized to the invasive management group who underwent initial CABG (n = 530) stayed a mean (SD) 11.8 (9.8) days spent in hospital or extended care, and those ran-

domized to initial PCI (n = 1524) stayed a mean (SD) 2.9 (3.6) days (*P* < .001) (eTable 6 in Supplement 3).

Cumulative Days Spent in Hospital or Extended Care

eTable 5 in Supplement 3 shows that 4-year cumulative mean days spent in hospital or extended care per patient was higher in the invasive management group than in the conservative management group (11.16 vs 6.75; difference, 4.41; 95% CI, 3.32-5.50; *P* < .001). Excluding invasive protocol-assigned procedures, the findings were similar (5.95 vs 6.75; difference, −0.80; 95% CI, −1.82 to 0.22; *P* = .13).

Compared with the conservative management group, the estimated mean cumulative number of days spent in hospital or extended care per patient over time was greater in the invasive management group by 2.4 days (95% CI, 2.3-2.6; *P* < .001) at 1 month, 5.0 days (95% CI, 4.5-5.6; *P* < .001) at 1 year, 4.2 days (95% CI, 3.5-4.9; *P* < .001) at 2 years, 4.5 days (95% CI, 3.6-5.5; *P* < .001) at 3 years, and 4.4 days (95% CI, 3.3-5.5; *P* < .001) at 4 years (eTable 7 in Supplement 3). There was no differences when invasive protocol-assigned procedures were excluded (eTable 8 in Supplement 3).

Days Alive

The estimated cumulative mean days alive at 4 years was similar for the 2 treatment groups (invasive management, 1423 days; 95% CI, 1415-1432; conservative management, 1422 days; 95% CI, 1413-1430; *P* = .78) (eTable 9 in Supplement 3).

Mortality

Time to death was similar in both groups. Number of deaths were similar in both groups for all-cause, cardiovascular, and noncardiovascular death.[9]

Discussion

This analysis of DAOH in the ISCHEMIA trial showed that randomization to the conservative management group compared with the invasive management group was associated with significantly more DAOH during the first 2 years, with no significant difference beyond 2 years. The differences were small and no greater than 6.3 days at any analyzed time point. Based on 95% CIs, the likely true difference in the 4-year cumulative mean DAOH is between 14.6 days in favor of the conservative group and 9.1 days in favor of the invasive group.

Decreased DAOH in the first 2 years in the invasive management group was largely due to protocol-assigned procedures. Landmark analysis excluding the first 30 days showed decreased DAOH in the invasive management group of 3.9 days over the first 2 years.

DAOH is an additional metric to inform patient-centered discussions, taking into account the timing and duration of hospitalization or admission to extended care facilities for patients with stable coronary disease. Patients generally prefer to be out of hospital and to spend more time with family, friends, in recreation, or at work.[14,15]

All other prespecified end points were higher in the invasive management group, including total stays, stays per patient, cumulative stays, total days, days per patient, and cumulative days spent in hospital or extended care. We predicted that there would be an upfront cost in the invasive management group with decreased DAOH and increased other prespecified end points due to time spent in hospital or extended care in relation to invasive protocol-assigned procedures but hypothesized that these differences might be more than offset in later follow-up due to decreased admissions for revascularization and/or ACS. However, we did not find this.

Particular strengths of the current study include prespecification of this analysis, the large number of events (5899 patient stays), the inclusion of stays in extended care settings, and the inclusion of reasons for stays.

There was more than a 2-fold higher number of stays in hospital or extended care in patients assigned to the invasive management group compared with the conservative management group, largely due to more stays relating to invasive protocol-assigned procedures. More patients in the invasive management group were admitted to extended care stay, of which half were attributable to CABG procedures. When stays related to invasive protocol-assigned procedures were excluded, there was similar DAOH in both groups.

As expected in a population at high risk of ischemic events, most hospital and extended care stays excluding assigned procedures were for cardiovascular causes. Patients in the invasive management group had fewer stays related to cardiovascular causes due to lower rates of stays for spontaneous MI and unstable angina. Stays for stroke, heart failure, and bleeding were infrequent and not different between the groups.

Several other aspects of our study are worth noting. First, older patients had fewer DAOH overall than younger patients, as may have been expected due to greater burden of comorbidities. DAOH was similar across regions.

Importance for Patients

For patients, the importance of a diagnosis may not be captured by the diagnosis alone but by the associated morbidity and treatment cascade it causes. Patients generally want to avoid extra days spent in hospital or extended care. More time spent away from home is time that could have been spent with family, at work, or in recreation. Several studies have reported that patients would rather be at home than in health care facilities,[14] and in a study where frail older patients were asked, "What is most important to you," the priority that emerged was "time spent at home."[15] The possibility of increased stays in the first 2 years with an invasive management strategy compared with a conservative management strategy could be mentioned in a patient-centered discussion about choice of management strategies.

Perspectives of Previous Studies of DAOH

DAOH have been reported in previous clinical trials in heart failure and ACS[4-6] and in cohort studies.[7,8] These studies provide a framework for assessing the role of treatments in optimizing time spent alive and out of hospital across strategies. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial,[4] the

methodology of using DAOH was first illustrated in 7599 patients with symptomatic heart failure. Over a median follow-up of 38 months, patients randomized to receive candesartan compared with placebo had more DAOH (difference, 24.1 days; $P < .001$).

Conversely, in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial,[5] which compared prasugrel with clopidogrel after non-ST elevation ACS in patients without revascularization, there were no differences in DAOH overall, reflecting the neutral trial results. In the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY) trial,[6] DAOH were significantly higher in patients randomized to alirocumab compared with placebo; however, the differences were small (3 days; $P = .05$). DAOH (home time) has also been calculated in administrative claims data for community-dwelling Medicare beneficiaries, and decreased DAOH was associated with poor self-rated health, less mobility impairment, worse depression, limited social activity, and difficulty in self-care.[16]

Implications

The ISCHEMIA trial reported that an initial invasive strategy compared with a conservative management strategy did not reduce the primary major adverse cardiac events end point or the secondary end point of all-cause death.[1] There were greater improvements in angina-related health status as assessed by the SAQ7-AF in patients with angina at baseline in the invasive management group.[2] This improvement in quality of life needs to be interpreted in light of no effect on the primary composite outcome in the ISCHEMIA trial and, in the present analysis, decreased DAOH in the first 2 years in patients allocated to invasive management, largely due to protocol-assigned procedures, but similar DAOH at 4 years with either management strategy.

Limitations

This study had limitations. In the overall ISCHEMIA trial, enrollment was less than originally planned, and the event rate was lower than anticipated. In this analysis, stays were grouped as cardiovascular or noncardiovascular based on investigator-reported discharge diagnoses. It is possible that stays were underreported or misclassified by type. We did not assess patient preferences for early stays for an elective procedure as opposed to later stays for an urgent indication, nor did we assess whether patients would prefer to have decreased angina compared with decreased DAOH in the first 2 years with an invasive strategy.

DAOH does not consider symptoms, health status, functional status, or quality of life and does not include single-day stays or emergency department visits. Our analysis showed no relationship of angina with DAOH. Also, single-day visits were significantly higher and emergency department visits were nominally higher in the invasive management group, indicating that DAOH including these 2 variables would be lower in the invasive management group.

Individual symptom burden may have impacted stays (ie, angina frequency); however, we found no association between angina frequency and DAOH. Longer stays for CABG compared with PCI or no revascularization in invasive management group were expected, but the choice of revascularization was investigator determined and part of the strategy comparison.

Conclusions

In this prespecified analysis of the ISCHEMIA trial, DAOH was higher for patients in the conservative management group compared with the invasive management group in the first 2 years but not significantly different at 4 years. This highlights trade-offs between management strategies, with DAOH being decreased early in the invasive management group due to protocol-assigned procedures and similar in both groups later. Hospital and extended care stays for MI and unstable angina during follow-up were lower in the invasive management group. DAOH provides a patient-focused metric that can be used by clinicians and patients in shared decision-making for the management of stable coronary artery disease.

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