

Risk Score for Future Myocardial Infarction After an Acute Coronary Syndrome and Pharmacogenetic Response to Dalcetrapib

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BACKGROUND

Acute coronary syndrome (ACS) survivors have heightened risk for subsequent cardiovascular (CV) events, particularly myocardial infarction (MI).

METHODS

All baseline characteristics collected in both the Dal-Outcomes and Dal-GenE trials, such as demographics, prior CV history, medications, vital signs, and blood markers including lipids and hs-CRP, were considered as potential risk markers. A risk score for subsequent fatal and non-fatal MI following ACS was developed using Cox proportional hazards modeling with backward variable selection on data from Dal-Outcomes placebo patients (n=7086). Variables not reaching the significance level of 0.15 were removed. This risk score was then applied in all Dal-GenE participants (n=5989) to determine whether the reduction in MI observed with dalcetrapib (versus placebo) in patients with the AA genotype at rs1967309 in the ADCY9 gene remained significant, independent of the other markers integrated in the risk score.

RESULTS

Of the 36 baseline variables considered as potential risk markers, 18 contributed to the risk score with a C-statistic of 0.72 (95% CI, 0.69-0.75) in Dal-Outcomes placebo patients. In these ACS survivors, prior history of coronary events (CABG, PCI, ACS and MI) as well as higher LDL-C, blood pressure, hemoglobin A1c and hs-CRP, current smoking and older age were contributors. The risk score was strongly predictive when applied to the 5989 AA genotype patients from Dal-GenE, with an increased risk of MI of 1.92 (95%CI: 1.78-2.08) for one standard deviation increase of the score. When assessing the effect of random assignment to treatment while adjusting for the risk score, dalcetrapib (versus placebo) reduced the risk of MI by 23% (HR:0.77, 95% CI, 0.63-0.94) in Dal-GenE.

CONCLUSION

Despite the standard of care for ACS survivors, history of prior coronary events as well as on-treatment values for blood pressure, LDL-C, A1c and hs-CRP remain determinants of future MI. In the Dal-GenE AA genotype patients, dalcetrapib significantly reduced the rate of future fatal and non-fatal MI, independently of a risk score including those variables. The ongoing Dal-GenE 2 trial is designed to confirm this pharmacogenetic hypothesis.

Table 1.1: Baseline Characteristics of Patients With and Without Fatal or non-fatal MI - Dal-Outcomes (Placebo)

Characteristic	Overall (n=7933)	Patients without Fatal/Non-Fatal MI (n=7517)	Patients with Fatal/Non-Fatal MI (n=416)	P-value
Characteristic				
Age - yr	60.3 ± 9.3	60.0 ± 9.0	62.8 ± 9.9	<0.0001
Male sex	6436 (81)	6108 (81)	328 (80)	0.5626
Race				0.3729
White	7015 (88)	6638 (88)	377 (92)	
Asian	602 (8)	579 (8)	23 (6)	
Black	182 (2)	182 (2)	0	
Other	133 (2)	118 (2)	15 (4)	
Ethnicity				0.6760
Hispanic or Latino	810/7926 (10)	770/7510 (10)	40/416 (10)	
Not Hispanic or Latino	7126/7926 (90)	6740/7510 (90)	376/416 (90)	
Body mass index - kg/m ²	26.8 ± 4.3	26.8 ± 4.3	26.8 ± 4.2	0.0059
Region of enrollment				0.1834
Europe	3854 (50)	3750 (50)	104 (27)	
North America	2521 (32)	2366 (32)	155 (38)	
South America	439 (6)	407 (6)	32 (8)	
Asia, Australia, New Zealand or South Africa	819 (10)	792 (10)	27 (7)	
Cardiovascular disease history				<0.0001
Myocardial infarction	1196 (15)	1045 (14)	151 (36)	
PCI	1150 (14)	1002 (13)	148 (36)	
CABG	462 (6)	381 (5)	81 (20)	
Stroke	272 (3)	254 (3)	18 (4)	
TIA	109 (1)	103 (1)	6 (1)	
Angina pectoris	1271 (16)	1127 (15)	144 (35)	
Hospitalization for unstable angina	304 (4)	304 (4)	0	
Peripheral vascular disease	583/7794 (7)	521/7588 (7)	62/406 (15)	
NVA class I congestive heart failure	1018/7940 (13)	981/7431 (13)	37/409 (9)	
NVA class II congestive heart failure	250/7862 (3)	229/7452 (3)	21/410 (5)	
Cardiovascular risk factors				<0.0001
Hypertension	5419/7909 (69)	5091/7494 (68)	328/415 (79)	
Diabetes	1852/7714 (24)	1807/7501 (24)	44/413 (11)	
Hypercholesterolemia	5753/7797 (74)	5410/7587 (73)	333/410 (82)	
Current smoker	1851/7931 (23)	1555/7515 (21)	296/416 (73)	
ACS index diagnosis				0.8500
Spontaneous myocardial infarction	6717/7930 (85)	6358/7514 (85)	359/416 (86)	
Myocardial infarction related to PCI	149	147 (15)	2 (1)	
Unstable angina without elevated biomarkers	1064/7930 (13)	1014/7514 (14)	50/416 (12)	
Time from index event to randomization - days	61 ± 16	61 ± 16	60 ± 16	0.4290
Vital signs				
SBP - mmHg	127.6 ± 16.9	127.4 ± 16.8	130.4 ± 18.1	0.0015
DBP - mmHg	76.8 ± 9.7	76.8 ± 9.6	76.5 ± 10.9	0.5485
Pulse rate - bpm	64.4 ± 10.0	64.3 ± 10.0	66.0 ± 10.1	0.0005

Table 1.3: Baseline Characteristics of Patients With and Without Fatal or non-fatal MI - Dal-Outcomes (Placebo)

Characteristic	Overall (n=7933)	Patients without Fatal/Non-Fatal MI (n=7517)	Patients with Fatal/Non-Fatal MI (n=416)	P-value
Characteristic				
Medications				
Statin	7736 (98)	7331 (98)	405 (97)	0.3876
Aspirin	7624 (97)	7238 (97)	386 (93)	0.0278
Other anti-platelet agents	7050 (89)	6693 (89)	357 (87)	0.6042
Beta blocker	6946 (88)	6381 (88)	565 (14)	0.0496
ACE inhibitor or ARB	6271 (79)	5936 (79)	335 (81)	0.4463
Lipids - mg/dL				
LDL cholesterol	76.8 ± 25.9	76.4 ± 25.6	81.3 ± 29.5	<0.0001
HDL cholesterol	42.2 ± 11.5	42.1 ± 11.5	42.8 ± 12.0	0.3883
Triglycerides	115 [86 - 150]	115 [86 - 150] (n=7493)	115 [87 - 172]	0.0203
Glycated hemoglobin - %	5.8 [5.5 - 6.2]	5.8 [5.5 - 6.2] (n=7494)	6.0 [5.6 - 6.5]	<0.0001
Creatinine clearance - mL/min/1.73 m ²	81.8 ± 18.4	81.9 ± 18.2	78.8 ± 20.6	0.0031
C-reactive protein - mg/liter	1.5 [0.8 - 3.6]	1.5 [0.8 - 3.5]	2.2 [0.9 - 4.6]	<0.0001

Notes: Categorical variables are presented as no./total no. (%), while numerical variables are presented as mean±standard deviation with the exception of Triglycerides, Glycated hemoglobin and C-reactive protein that are presented as median [interquartile range]. For the calculation of percentage, the denominator (total no.) is always 7933 overall, 7517 for patients without event and 416 for patients with an event, unless otherwise specified. P-value from Chi-square test, Student's t-test or Wilcoxon two-sample test.

Table 1.2b: CV Risk Model for Fatal or Non-Fatal MI - Dal-Outcomes Placebo (n=7086) [In Decreasing Order of Chi-Square Statistic]

	Chi-Square ^(a)	β	HR (95% CI)	P-value
History of CABG	26.2120	0.76935	2.158 (1.608-2.898)	<0.0001
Prior hospitalization for UA	12.3640	0.51311	1.670 (1.255-2.224)	0.0004
History of PCI	12.1545	0.51490	1.673 (1.253-2.235)	0.0005
LDL cholesterol (per mg/dL increase)	12.0222	0.00695	1.006 (1.003-1.010)	0.0005
DBP (per mmHg increase)	11.8513	-0.15457	0.857 (0.785-0.936)	0.0006
DBP ² (per mmHg ² increase)	10.5379	0.00095	1.001 (1.000-1.002)	0.0012
Age (per year increase)	9.3645	0.02011	1.020 (1.007-1.034)	0.0022
History of myocardial infarction	7.2618	0.38171	1.465 (1.110-1.934)	0.0070
Current smoker	5.8684	0.30545	1.359 (1.056-1.748)	0.0173
Log glycated hemoglobin (per log % increase)	4.9207	0.84375	2.325 (1.103-4.900)	0.0265
ACS index diagnosis	6.1033 (2)			0.0473
Spontaneous MI	4.3925	0.34394	1.410 (1.023-1.946)	
MI related to PCI	0.3151	-0.24590	0.782 (0.331-1.845)	
History of peripheral vascular disease	2.9521	0.26938	1.309 (0.963-1.780)	0.0858
Male sex	2.9499	0.24345	1.276 (0.966-1.684)	0.0859
SBP (per mmHg increase)	2.8351	0.00695	1.007 (0.999-1.015)	0.0622
NVA class I congestive heart failure	2.6681	0.22468	1.252 (0.956-1.639)	0.1024
Log C-reactive protein (per log mg/liter increase)	2.5786	0.07740	1.080 (0.983-1.188)	0.1083
Pulse rate (per bpm increase)	2.5479	0.00867	1.009 (0.998-1.019)	0.1104
Body mass index (per kg/m ² increase)	2.5298	0.01667	1.017 (0.996-1.038)	0.1117
NVA class II congestive heart failure	2.1172	0.34386	1.410 (0.893-2.227)	0.1401

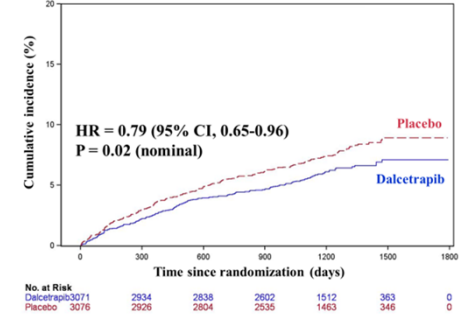
^(a) When not equal to 1, degrees of freedom are presented in parentheses. Harrell c-index of multivariable CV risk model=0.7205

Table 1.3: CV Risk Model for Fatal or Non-Fatal MI Applied to Dal-GenE-1 Patients (n=5989)

	Model Without Treatment			Model Including Treatment		
	β	HR (95% CI)	P-value	β	HR (95% CI)	P-value
Risk Score	0.83933	2.315 (2.093 - 2.561)	<0.0001	0.83860	2.313 (2.091 - 2.559)	<0.0001
Treatment (Dal vs. Pbo)	---	---	---	-0.26436	0.768 (0.629 - 0.937)	0.0094
Harrell c-index of model without treatment=0.6845						
Harrell c-index of model including treatment=0.6882						

FIGURE 1

Fatal or non-fatal MI (ITT population) in the Dal-GenE-1 trial



CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; MI, myocardial infarction.

DISCUSSION

- Despite the standard of care for ACS survivors, history of prior coronary events as well as on-treatment values for blood pressure, LDL-C, HbA1c and hs-CRP remain determinants of future myocardial infarction.
- In the Dal-GenE AA genotype patients, dalcetrapib significantly reduced the rate of future fatal and non-fatal MI, independently of a risk score including those variables.
- The ongoing Dal-GenE 2 trial is designed to confirm this pharmacogenetic hypothesis.

FIGURE 2

Confirmatory Dal-GenE-2 trial

Primary Endpoint: Time to first occurrence of a non-fatal or fatal MI event
Secondary Endpoints: Composites of first and recurrent all-cause death, resuscitated cardiac arrest, non-fatal MI and stroke and first and recurrent fatal and non-fatal MIs



- 73% power for HR=0.70 with an alpha of 0.056 with 200 primary endpoint events and minimum detectable HR= 0.763
- Interim analysis at 120 events with an alpha of 0.002 to allow early stopping

CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction. <https://dalcorpharma.com/dal-gene-2-trial>

DISCLOSURE INFORMATION

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