SUPPLEMENTAL MATERIAL

Detailed Methods

Cell preparation and infusion

CAP-1002 consists of 25 million human allogeneic CDCs in 10 ml of a cryogenic cell preservation solution (CryoStor® CS10; Biolife Solutions, Bothell, WA, USA), which contains 10% dimethyl sulfoxide (DMSO), with heparin added. The placebo consisted of 11.5 ml of cryopreservation solution containing 10% DMSO, heparin (1,800 U total), and nitroglycerin (450 µg total). CAP-1002 or placebo were administered inracoronarily using over the wire balloon angioplasty catheter using stop flow technique in the culprit artery[1].

Safety follow-up protocol

Participants were followed-up for the primary safety endpoint of the study which included the occurrence of any of the following within 1 month after intracoronary infusion: myocarditis, ventricular tachycardia-related or ventricular fibrillation-related sudden unexpected death or major cardiovascular events (composite of death, non-fatal recurrent myocardial infarction, hospital admission or emergency room treatment for heart failure or need for left ventricular assist device or heart transplant).

Cardiac MRI

Cine images using steady-state free precession (SSFP) with retrospective gating were utilized for quantification of LV volumes, LVEF and myocardial strain and included 4-chamber, 2-chamber, and a stack of 12 short axis slices covering the entire LV. For assessment of myocardial scar, high resolution late gadolinium enhancement (LGE) images were acquired using breath-hold inversion recovery-prepared gated TurboFLASH sequence 15 minutes after IV administration of 0.2 mmol/kg gadolinium contrast. LGE images were also acquired as 4 and 2-chamber views, in addition to a stack of 12 short axis slices from the same location as the cine images. MRI image acquisition for patients who received implantable cardioverter defibrillators (ICD) due to clinical indications over the course of the study was performed according to a stringent protocol to maintain safety [2, 3]. In these patients, cine images were acquired using fast gradient echo pulse sequence and LGE images were acquired using wideband sequence to avoid device induced artifacts [4].

De-identified MRI images were analyzed by a single experienced reader in the MRI Core Laboratory at Johns Hopkins Hospital. LV volumes and LVEF were quantified by manual delineation of endo- and epicardial LV borders in contiguous cine slices using FDA approved software (QMass 7.4, Medis medical imaging systems, The Netherlands). Sphericity volume index was calculated as LV volume/(LV length^3 $\times\pi/6$)[5]. For myocardial scar quantification from LGE images, the endo- and epicardial borders were contoured using QMass 7.4 and the boundaries of the scar were determined using full width half maximum method as described elsewhere[6]. The LV scar was presented as the percentage of the total myocardial mass. Multimodality Tissue Tracking software (MTT 6.1, Toshiba, Japan) was used to obtain the circumferential strain (Ecc) from short axis cine images. This method utilizes a pixel-to-pixel matching technique by defining angle-independent motion vectors from multiple tracking points to find identical voxels in successive frame.[7] LV endocardial and epicardial borders were manually drawn at a reference frame in which the MTT software recorded a characteristic pixel pattern and propagated that pixel pattern throughout the cardiac cycle to generate the strain curve. The mid-wall peak systolic circumferential strain (Ecc) was determined from strain curves, with lower Ecc values representing greater systolic myocardial contraction. The segmental myocardial scar and circumferential strain were obtained according to the American Heart Association 16-segment model [8].

Supplementary table 1. Endpoint analysis of global and segmental circumferential strain between baseline and 6-month in patients with recent index myocardial infarction.

	Mean (SD)		Coefficient (Between-group p value)			
	Placebo	CDC group	Unadjusted	Adjusted for LV scar percent	Adjusted for LVEDVi	Adjusted for LVEDVi and scar percent
All segments						
Segmental Ecc at baseline, %	-9.7(5.5)	-9.7(5.4)	-0.63(0.20)	-0.49(0.26)	-0.57(0.25)	-0.47(0.29)
Segmental Ecc at 6-month, %	-9.5(5.7)	-10.1(5.2)				
Within-group p value	0.35	**0.03**				
Change in segmental Ecc, %	0.2(4.4)	-0.4(4.1)				
Remote segments						
Segmental Ecc at baseline, %	-12.1(5.7)	-12.4(5.3)	-0.33(0.65)	-	-0.37(0.62)	-
Segmental Ecc at 6-month, %	-11.8(6.0)	-12.4(5.5)				
Within-group p value	0.62	0.84				
Change in segmental Ecc, %	0.2(4.5)	-0.05(4.7)				
Infarcted segments						
Segmental Ecc at baseline, %	-8.3(5.0)	-8.0(4.4)	-0.84(0.1)	-	-0.77(0.14)	-
Segmental Ecc at 6-month, %	-8.02(4.9)	-8.5(4.4)				
Within-group p value	0.42	**0.004**				
Change in segmental Ecc, %	0.3(4.4)	-0.5(3.7)				
Global Ecc at baseline, %	-8.4(2.6)	-8.1(3.4)	-0.69(0.35)	-0.61(0.41)	-0.62(0.41)	-0.59(0.43)
Global Ecc at 6-month, %	-8.3(2.9)	-8.6(3.0)				
Within-group p value	0.82	0.24				
Change in global Ecc, %	0.1(2.3)	-0.5(2.7)				

LVEDVi: Left ventricular end-diastolic volume index; Ecc: Circumferential strain

*The regression coefficients represent the relative difference in the slope of change from baseline to 6-month between CAP-1002 and placebo groups.

Supplementary table 2. Endpoint analysis of global and segmental circumferential strain between baseline and 6-month in patients with chronic index myocardial infarction.

	Mean (SD)		Coefficient (Between-group p value)			
	Placebo	CDC group	Unadjusted	Adjusted for LV scar percent	Adjusted for LVEDVi	Adjusted for LVEDVi and scar percent
All segments						
Segmental Ecc at baseline, %	-9.7(4.7)	-10.0(5.0)	-0.57(0.13)	**-0.73(0.03)**	-0.47(0.22)	-0.57(0.10)
Segmental Ecc at 6-month, %	-9.6(4.5)	-10.6(5.3)				
Within-group p value	0.51	**<0.001**				
Change in segmental Ecc, %	0.1(3.2)	-0.6(3.9)				
Remote segments						
Segmental Ecc at baseline, %	-12.3(4.6)	-12.5(4.7)	-0.73(0.21)	-	-0.77(0.20)	-
Segmental Ecc at 6-month, %	-11.8(4.6)	-12.9(5.5)				
Within-group p value	0.07	0.13				
Change in segmental Ecc, %	0.5(3.3)	-0.4(4.4)				
Infarcted segments						
Segmental Ecc at baseline, %	-8.3(4.1)	-8.2(4.3)	-0.51(0.19)	-	-0.38(0.35)	-
Segmental Ecc at 6-month, %	-8.4(3.9)	-9.0(4.6)				
Within-group p value	0.55	**<0.001**				
Change in segmental Ecc, %	-0.12(3.1)	-0.7(3.4)				
Global Ecc at baseline, %	-8.4(2.2)	-8.4(2.4)	-0.61(0.26)	-0.72(0.19)	-0.5(0.37)	-0.59(0.28)
Global Ecc at 6-month, %	-8.3(2.3)	-9.1(3.0)				
Within-group p value	0.66	0.07				
Change in global Ecc, %	0.1(1.5)	-0.7(2.5)				

LVEDVi: Left ventricular end-diastolic volume index; Ecc: Circumferential strain

*The regression coefficients represent the relative difference in the slope of change from baseline to 6-month between CAP-1002 and placebo groups.

Supplementary table 3. Endpoint analysis of global and segmental circumferential strain between baseline and 12-month in whole cohort

	Mean (SD)		Coefficient (Between-group p value)			
	Placebo (n=22)	**CAP-1002 group (n=44)**	**Unadjusted**	**Adjusted for LV scar percent**	**Adjusted for LVEDVi**	**Adjusted for LVEDVi and scar percent**
All segments						
Segmental Ecc at baseline, %	-10.0(5.1)	-10.0(5.3)	0.19(0.58)	0.31(0.40)	0.42(0.31)	0.36(0.35)
Segmental Ecc at 12-month, %	-10.3(5.0)	-9.9(5.3)				
Within-group p value	0.32	0.70				
Change in segmental Ecc, %	-0.2(4.1)	0.05(3.9)				
Remote segments						
Segmental Ecc at baseline, %	-12.3(5.1)	-11.7(5.4)	0.68(0.19)	-	0.86(0.14)	-
Segmental Ecc at 12-month, %	-12.0(5.4)	-12.7(4.9)				
Within-group p value	0.49	<0.001				
Change in segmental Ecc, %	0.25(4.4)	0.9(4.1)				
Infarcted segments						
Segmental Ecc at baseline, %	-8.3(4.4)	-8.1(4.8)	0.50	-	-0.04(0.94)	-
Segmental Ecc at 12-month, %	-8.9(4.2)	-8.7(4.9)				
Within-group p value	**0.03**	**<0.001**				
Change in segmental Ecc, %	-0.6(3.8)	-0.6(3.7)				
Global Ecc at baseline, %	-8.6(2.6)	-8.3(3.2)	0.09(0.87)	0.42(0.45)	0.44(0.47)	0.44(0.45)
Global Ecc at 21-month, %	-9.0(2.7)	-8.4(3.3)				
Within-group p value	0.47	0.75				
Change in global Ecc, %	-0.4(2.5)	-0.1(2.3)				

LVEDVi: Left ventricular end-diastolic volume index; Ecc: Circumferential strain

*The regression coefficients represent the relative difference in the slope of change from baseline to 12-month between CAP-1002 and placebo groups.

Supplemental References

References

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