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META-ANALYSIS

Autologous CD34$^+$ cell therapy improves exercise capacity, angina frequency and reduces mortality in no-option refractory angina: a patient-level pooled analysis of randomized double-blinded trials

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Aims Autologous CD34$^+$ (auto-CD34$^+$) cells represent an attractive option for the treatment of refractory angina. Three double-blinded randomized trials ($n = 304$) compared intramyocardial (IM) auto-CD34$^+$ cells with IM placebo injections to affect total exercise time (TET), angina frequency (AF), and major adverse cardiac events (MACE). Patient-level data were pooled from the Phase I, Phase II ACT-34, ACT-34 extension, and Phase III RENEW trials to determine the efficacy and safety of auto-CD34$^+$ cells.

Methods and results Treatment effects for TET were analysed using an analysis of covariance mixed-effects model and for AF using Poisson regression in a log linear model with repeated measures. The Kaplan–Meier rate estimates for MACE were compared using the log-rank test. Autologous CD34$^+$ cell therapy improved TET by 46.6 s [3 months, 95% confidence interval (CI) 13.0 s–80.3 s; $P = 0.007$], 49.5 s (6 months, 95% CI 9.3–89.7; $P = 0.016$), and 44.7 s (12 months, 95% CI - 2.7 s–92.1 s; $P = 0.065$). The relative frequency of angina was 0.78 (95% CI 0.63–0.98; $P = 0.032$), 0.66 (0.48–0.91; $P = 0.012$), and 0.58 (0.38–0.88; $P = 0.011$) at 3-, 6- and 12-months in auto-CD34$^+$ compared with placebo patients. Results remained concordant when analysed by treatment received and when confined to the Phase III dose of 1×10^5 cells/kg. Autologous CD34 + cell therapy significantly decreased mortality (12.1% vs. 2.5%; $P = 0.0025$) and numerically reduced MACE (38.9% vs. 30.0; $P = 0.14$) at 24 months.

Conclusion Treatment with auto-CD34$^+$ cells resulted in clinically meaningful durable improvements in TET and AF at 3-, 6- and 12-months, as well as a reduction in 24-month mortality in this patient-level meta-analysis.

Keywords Refractory angina • Stem cell therapy • CD34$^+$

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Introduction

An increasing number of patients with advanced coronary artery disease become suboptimal candidates for further revascularization, and continue to have symptoms despite best medical management.[1–6] The treatment options available for these patients with refractory angina (RA) are limited to risk factor modification, antianginal medication, enhanced external counter pulsation (EECP), and novel interventional techniques including new approaches to chronic total occlusions and the coronary sinus reducer.[3–8] Up to 15% of patients undergoing cardiac catheterization have ischaemia or angina and are suboptimal candidates for revascularization and this population is growing by up to 100 000 patients per year in the US.[1–6] Although, previously associated with high mortality, the prognosis of RA has improved but mortality remains approximately 3–5% per year,[9–11] and resource utilization is extremely high.[10] These observations reflect the dire need for novel therapies for these patients.

Cell therapy utilizing autologous CD34$^+$ (auto-CD34$^+$) cells is a promising therapy for RA patients.[3–6] CD34$^+$ was the original marker used to identify and isolate endothelial progenitor cells, a cell which can generate new blood vessels *in vitro* and promote angiogenesis *in vivo*.[12,13] In the US, the auto-CD34$^+$ cell therapy program was initially developed through two early phase clinical trials, which established the feasibility[14] and dose-response[15] for intramyocardial (IM) delivered auto-CD34$^+$ cells to improve exercise capacity. A Phase III pivotal trial was initiated[16] but terminated prematurely by the sponsor solely for financial reasons. As a result, no single trial was adequately powered to conclusively define the efficacy of this therapy.[17]

Since each of these three trials enrolled nearly identical patient populations and used similar designs and outcome measures, we performed a patient-level pooled analysis to compare the efficacy and safety of auto-CD34$^+$ therapy for patients with Canadian Cardiovascular Society Class III or IV RA with placebo.[14–18]

Methods

The complete details of Phase I [NCT00081913], Phase II ACT-34 [NCT00300053; NCT00545610], and Phase III RENEW [NCT 01508910] trials have been presented previously,[14–18] and are summarized in Supplementary material online, *Table S1*. The Phase I and Phase II ACT-34 trials randomized patients to IM auto-CD34$^+$ injection vs. IM placebo injections in a 3:1 and 2:1 ratio, respectively.[14,15] The Phase III RENEW trial randomized patients using a 2:1:1 ratio representing IM auto-CD34$^+$ injection, placebo injection, and open-label standard of care (SOC) group mandated by the Food and Drug Administration (FDA), respectively. Placebo patients underwent the same procedures as treated subjects including mobilization of bone marrow with granulocyte colony-stimulating factor (GCSF), apheresis to collect mobilized mononuclear cells and IM injection with the exact same diluent used to suspend CD34$^+$ cells for the active treatment arm.[14–18] Because participants assigned to open-label SOC received no trial specific therapy, they did not undergo assessment of efficacy endpoints.[16,17] The SOC arm was included only in the RENEW trial and was associated with a significantly higher major adverse cardiac events (MACE) rate as previously reported, and is therefore not included in this analysis.[17] Follow-up from the Phase I trial was censored at 6 months because patient treatment assignments were unblinded at this time point, and subsequent treatment group crossover was allowed. Complete trial datasets were obtained from the sponsor for each trial, and patient-level data was abstracted at longest available follow-up.

Definition of endpoints

Patients in each study underwent standardized exercise treadmill testing using either a Bruce (Phase I) or modified Bruce (ACT-34 and RENEW) protocol. All patients were required to experience angina-limited exercise capacity of 1–6 min (Phase I, Bruce protocol) or 3–10 min (ACT-34 and RENEW, modified Bruce), thus the change in exercise time in each trial fell at the same gradations of exercise. Total exercise time (TET) was assessed at baseline and 3-month time points in Phase I, and at baseline, 3-, 6-, and 12-months in the ACT-34 and RENEW trials. Exercise treadmill tests from ACT-34 and RENEW were interpreted and quantified by an independent core laboratory (Harvard University).

Self-reported angina was collected in each study utilizing paper diaries in Phase I, an interactive voice response system daily diary in ACT-34, and an electronic tablet based capture system in RENEW, in which patients entered daily angina episodes. Angina frequency was collected at baseline, 3- and 6-month time points in each study, and also at 12-month in the ACT-34 and RENEW trials.

All-cause death, myocardial infarction (MI), stroke, and cardiovascular hospitalizations were collected to 6-months in Phase I, to 12-months in ACT-34, and to 24-months in the ACT-34 extension and RENEW studies. Events were investigator-reported in the Phase I trial, but were centrally adjudicated by an independent group in the ACT-34/ACT-34 extension, and RENEW trials.

Statistical methods

Efficacy results were analysed both as intent-to-treat (ITT) (as randomized) and as-treated populations, in which patients were analysed according to treatment actually received. Efficacy analysis excluded seven participants from the ACT34 trial, because of compliance issues at a study site, as originally reported.[15]

In total, four patients randomized to auto-CD34$^+$ cell therapy received substituted placebo injections because of manufacturing issues with the cell product. Patients (auto-CD34$^+$ $n = 4$ and placebo $n = 2$) who did not receive injections, and were unblinded did not undergo follow-up efficacy assessments.

Summary statistics for patient characteristics, procedures, and outcomes are presented by treatment group (auto-CD34$^+$ and placebo) and by trial. At each follow-up time point, within-patient changes from baseline (post-baseline) were calculated for TET and angina frequency. Continuous variables are presented using median (interquartile range) and compared using analysis of variance or Kruskal–Wallis, as appropriate. Categorical variables are presented using frequencies (percentages) and compared using the χ^2 test or the Fisher's exact test, as appropriate.

Treatment effects in change for TET were tested in an analysis of covariance mixed-effects model with repeated measures, assuming an unstructured variance/covariance matrix for measurements within a patient. Change in TET was the dependent variable. The independent fixed-effect parameters were treatment group, visit, and the interaction between treatment group and visit. Trial and the individual baseline value of TET were included as baseline covariates. At each time point, least squares means and standard errors and the treatment effect (mean difference in change for TET between auto-CD34$^+$ and placebo groups) was estimated from the repeated measures model and reported with a 95% confidence interval and *P*-value.

Treatment effects on angina frequency (AF) were tested using the prespecified Poisson regression as well as a negative binomial regression, both utilizing a log-linear model with repeated measures (see Supplementary material online, *Appendix* for detailed methology).

Table 1 Total patient distribution by trial and cell dose including standard of care arm in RENEW

	Placebo ($n = 89$)	Auto-CD34$^+$ 1×10^4/kg ($n = 6$)	Auto-CD34$^+$ 1×10^5/kg ($n = 119$)	Auto-CD34$^+$ 5×10^5/kg ($n = 62$)	Any auto-CD34$^+$ ($n = 187$)	SOC ($n = 28$)	Total ($n = 304$)
Trials							
Phase I, *n* (%)	6 (6.7)	6/6 (100)	6 (5.0)	6 (9.7)	18 (9.6)	0	24 (7.9)
ACT34, *n* (%)	56 (62.9)	0	56 (47.1)	56 (90.3)	112 (59.9)	0	168 (55.3%)
RENEW, *n* (%)	27 (30.3)	0	57 (47.9)	0	57 (30.5)	28 (100.0)	112 (36.8)

Auto-CD34$^+$, autologous CD34$^+$; SOC, standard of care.

The Kaplan–Meier rate estimates for individual MACE (MI, stroke, CV-hospitalization, and all-cause death), as well as the composite, were presented for auto-CD34$^+$ and placebo groups through 24 months. The log-rank test was used to compare the time-to-event distributions between the auto-CD34$^+$ and Placebo groups.

A *P*-value <0.05 was considered statistically significant and no adjustment was made for multiple comparisons. Statistical analyses were performed by Duke Clinical Research Institute, (Durham, NC, USA) using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The relative contribution of each trial to the overall analysis as well as the number of patients receiving each dose of auto-CD34$^+$ cells studied is shown in *Table 1*. Over 50% of the patients came from the ACT-34 trial[15] with another 37% from the RENEW study.[17]

Patient characteristics and medical therapy were consistent across the treatment strategies (*Table 2*) and across trials (see Supplementary material online, *Table S2*), and are notable for a median age of 63 years, a large proportion of Caucasian males and with a high prevalence of cardiovascular risk factors, including over 50% with diabetes. These patients also had an extensive history of previous revascularization with nearly 90% of patients having undergone prior coronary artery bypass grafting and/or percutaneous coronary intervention. The use of anti-anginal therapies was also high (*Table 3*). Notably, ranolazine was approved in the US midway during the conduct of the ACT-34 Phase II trial and therefore varied across trials from 0% in the Phase I trial, to 27.4% in ACT34, to 59.8% in RENEW.

Exercise capacity

Patients randomized to placebo improved their TET by 31–50 s across the 3- to 12-month points (*Table 3*, *Figure 1A*, see Supplementary material online, *Table S3*). Patients randomized to auto-CD34$^+$ cell therapy improved their TET by 77–99 s, which outperformed placebo by a consistent 45–50 s throughout the 3–12 month period. Results were consistent when analysed as-treated with similar increases in treatment effect (45–53 s), findings which were statistically significant at each time point. (*Table 3* and *Figure 1B*).

Angina frequency

Patients in each trial, including those treated with placebo injections, reported significant reductions in angina with up to an 80% reduction in angina in the RENEW trial (see Supplementary material online, *Table S4*). Auto-CD34$^+$ cell therapy was associated with a statistically significant lower frequency of angina at each time point when analysed as prespecified using a Poisson regression in both the ITT and as-treated analysis (*Table 4* and *Figure 2*). Due to overdispersion observed as well as a few individual patients with high influence on the Poisson regression results, additional analyses were performed using a negative binomial regression (see Supplementary material online, *Table S5*) and also by refitting the Poisson analysis excluding three potentially influential patients (Pearson residual >20 or Cluster Cook's D >0.5) (see Supplementary material online, *Table S6*). Utilizing the more conservative, but *post hoc*, negative binomial analysis, Auto-CD34$^+$ cells were associated with a 10–20% reduction in the frequency of angina which was not statistically significant. These analyses demonstrated consistent reductions in angina, with a statistically significant reduction observed utilizing the prespecified statistical methodology agreed upon with regulators.

Dose sensitivity

To assess the efficacy of the targeted cell dose, we compared patients randomized to 1×10^5 cells/kg with those randomized to placebo. Cell therapy with the dose of 1×10^5 cells significantly and consistently improved both TET and AF up to 12 months with effects that were similar to those observed in the overall analysis, both when analysed as ITT and as treated (see Supplementary material online, *Table S7 and S8*).

Mortality and major adverse cardiac events

Compared with placebo, auto-CD34$^+$ cell therapy significantly decreased all-cause mortality at 24 months (12.1% vs. 2.5%; $P = 0.0025$) (*Table 5* and *Figure 3*). Although not significant, auto-CD34$^+$ cell therapy was also associated with a clinically meaningful reduction in MACE (38.9% vs. 30.0%; $P = 0.14$) which was driven by a reduction in all-cause death and CV-hospitalizations. The results remained robust when analysed as treated (mortality 11.8% vs 2.6%, $P = 0.0038$, MACE 38.2% vs. 29.9%, $P = 0.15$).

Discussion

Despite the growing numbers of patients with non-revascularizable coronary artery disease, only two new therapies have been approved for the treatment of RA in the last 40 years. Ranolazine was approved

Table 2 Patient demographics

	Placebo ($n = 89$)	Auto-CD34$^+$ ($n = 187$)	Total ($n = 276$)	*P*-value
Trial				
Phase I	6 (6.7)	18 (9.6)	24 (8.7)	0.72
ACT34	56 (62.9)	112 (59.9)	168 (60.9)	
RENEW	27 (30.3)	57 (30.5)	84 (30.4)	
Patient characteristics				
Age (years)	64 (56–69)	62 (56–68)	63 (56–68)	0.35
Female	11 (12.4)	30 (16.0)	41 (14.9)	0.42
Race				0.43
White	80 (89.9)	171 (91.4)	251 (90.9)	
Black	2 (2.2)	8 (4.3)	10 (3.6)	
Asian	3 (3.4)	2 (1.1)	5 (1.8)	
Other	4 (4.5)	6 (3.2)	10 (3.6)	
Height (cm)	174 (168–180)	175 (169–180)	175 (168–180)	0.70
Weight (kg)	98 (90–110)	96 (82–108)	96 (86–108)	0.30
BMI (kg/m^2)	32 (29–36)	31 (28–35)	31 (28–36)	0.35
Comorbidities				
Diabetes	50 (56.2)	95 (50.8)	145 (52.5)	0.40
Hypertension	81 (91.0)	176 (94.1)	257 (93.1)	0.34
CHF	31 (34.8)	50 (26.7)	81 (29.3)	0.17
Angina, CCS Class III or IV	84 (94.4)	183 (97.9)	267 (96.7)	0.15
PCI	78 (87.6)	162 (86.6)	240 (87.0)	0.82
CABG	80 (89.9)	173 (92.5)	253 (91.7)	0.46
Hyperlipidaemia	74 (83.1)	154 (82.4)	228 (82.6)	0.87
PVD	24 (27.0)	44 (23.5)	68 (24.6)	0.54
Smoking history				0.25
Never used	21 (23.6)	55 (29.4)	76 (27.5)	
Former user	63 (70.8)	114 (61.0)	177 (64.1)	
Current user	5 (5.6)	18 (9.6)	23 (8.3)	
Prior therapy				
Beta blockers	82 (92.1)	169 (90.4)	251 (90.9)	0.63
Long-acting nitrates	70 (78.7)	138 (73.8)	208 (75.4)	0.38
Ranolazine	29 (32.6)	66 (35.3)	95 (34.4)	0.66
Calcium channel Blockers	34 (38.2)	79 (42.2)	113 (40.9)	0.52
ACE/ARB	47 (52.8)	104 (55.6)	151 (54.7)	0.66
Statins	70 (78.7)	154 (82.4)	224 (81.2)	0.46
EECP	19 (21.3)	28 (15.0)	47 (17.0)	0.19

Data presented as median, (IQR) for continuous variables; *n* (%) for discrete variables. SOC patients excluded from table.
ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; Auto-CD34$^+$, autologous CD34$^+$; BMI, body mass index; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; EECP, enhanced external counterpulsation; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

based on studies in stable angina patients on single or no medical therapy,[19] and EECP demonstrated improvement in time-to-ST depression but not overall exercise capacity in a RA population.[20] More recently, the effectiveness of ranolazine has been questioned.[21,22] Given the lack of effective options, regenerative therapies, especially potent angiogenic populations, may represent a particularly attractive approach for the treatment of these patients.

CD34$^+$ was the original cell-surface marker used to identify and isolate endothelial progenitor cells, a cell with potent *in vivo* angiogenic capabilities.[12,13] In humans lower levels of circulating CD34$^+$ cells predict more advanced coronary disease,[23,24] worse outcomes after MI,[25] decreased physical function both at baseline as well as change over time,[26,27] and most compellingly, increased mortality.[28] In preclinical MI models, isolated CD34$^+$ cells were significantly more potent than unselected bone marrow cells, showing improvements in overall myocardial performance and regional wall motion, as well as in moderating fibrosis and increasing angiogenesis, even when CD34$^+$ cell dose was normalized.[13] Thus, pre-clinical as well as clinical data points to the importance of this cell population in angiogenesis and ongoing vascular repair.

Table 3 Comparative effect of autologous CD34$^+$ cell therapy vs. placebo in exercise tolerance time (seconds)

Visit	Auto-CD34$^+$ cell	Placebo	Treatment effect difference (95% CI)	*P*-value
Intent-to treat-population				
Month 3	77.3 (12.2)	30.7 (16.0)	46.6 (13.0 to 80.3)	0.007
Month 6	99.3 (13.9)	49.8 (18.7)	49.5 (9.3 to 89.7)	0.016
Month 12	87.0 (15.5)	42.3 (21.5)	44.7 (-2.7 to 92.1)	0.065
As-treated population				
Month 3	79.8 (12.2)	27.4 (15.7)	52.5 (19.2 to 85.7)	0.002
Month 6	100.9 (14.0)	48.4 (18.3)	52.5 (12.8 to 92.2)	0.010
Month 12	89.2 (15.6)	39.4 (21.1)	49.9 (3.1 to 96.7)	0.037

Least squares means (and standard errors) are reported for each treatment group.
Auto-CD34$^+$, autologous CD34$^+$; CI, confidence interval.

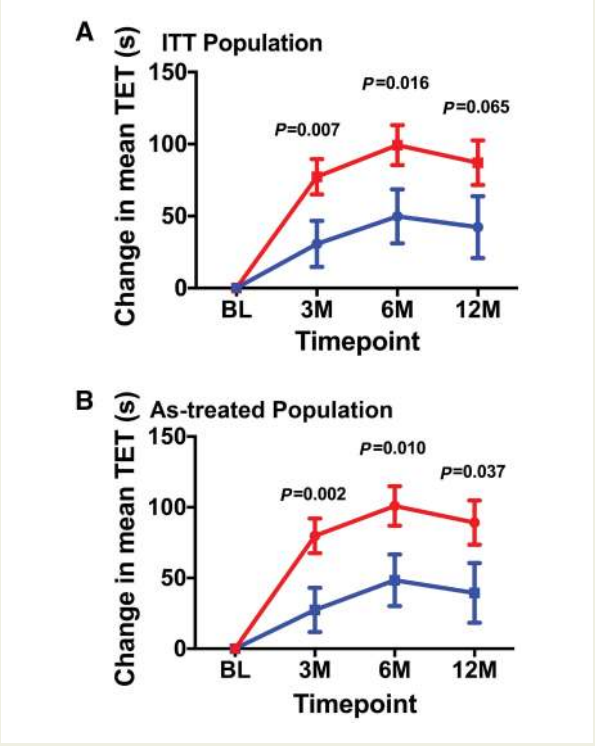


Figure 1 (*A*) Change from baseline in exercise tolerance time (seconds), intent-to-treat population. Least squares mean changes (±standard error) are plotted for each post-baseline time point. (*B*) Change from baseline in exercise tolerance time (seconds), as-treated population. Least squares mean changes (±standard error) are plotted for each post-baseline time point. Red colour indicates autologous CD34$^+$ and blue colour indicates placebo. ITT, intent-to-treat; TET, total exercise time.

Table 4 Comparative effect of autologous CD34$^+$ cell therapy vs. placebo on relative frequency of angina: (the estimated ratio of the mean angina frequency in the CD34+ group to the mean angina frequency in the placebo group)

Visit	Relative frequency of angina (auto-CD34$^+$/ placebo), with 95% CI	*P*-value
Intent-to treat-population		
Month 3	0.78 (0.63–0.98)	0.032
Month 6	0.66 (0.48–0.91)	0.012
Month 12	0.58 (0.38–0.88)	0.011
As-treated population		
Month 3	0.78 (0.63–0.98)	0.031
Month 6	0.66 (0.48–0.92)	0.013
Month 12	0.57 (0.38–0.87)	0.009

Auto-CD34$^+$, autologous CD34$^+$; CI, confidence interval.

Based on these pre-clinical and human observations, a clinical development program spanning 12 years evaluated the utility of auto-CD34$^+$ cells for the treatment of RA.[14–18] Three trials each demonstrated improvements in exercise capacity, AF, as well as lower rates of MACE, including mortality in auto-CD34$^+$ treated patients. Unfortunately, the Phase III RENEW trial was stopped early based solely on business considerations by the sponsor.[17] The RENEW trial was powered at greater than 90% with 200 evaluable patients randomized to auto-CD34$^+$ therapy vs. 100 patients treated with IM placebo injections.[16,17] Our current analysis encompassing 187 patients randomized to auto-CD34$^+$ therapy and 89 to placebo demonstrated statistically significant improvements in TET and AF at each time point, demonstrating a durable response to a single treatment with auto-CD34$^+$ cells. This analysis suggests that had a trial of adequate size like RENEW been completed, this therapy may have met the standard for approval in the US.

Although the individual studies were not powered to demonstrate a mortality benefit, a statistically significant improvement in mortality was observed in this combined patient-level analysis. While it is conceivable that the mortality difference observed is secondary to harm from placebo injections, the observed mortality in the placebo arm mirrors that observed in contemporary observations from registries, suggesting that the observed mortality benefit is more likely ascribable to benefit in CD34$^+$ treated patients.[10,11] Our results at

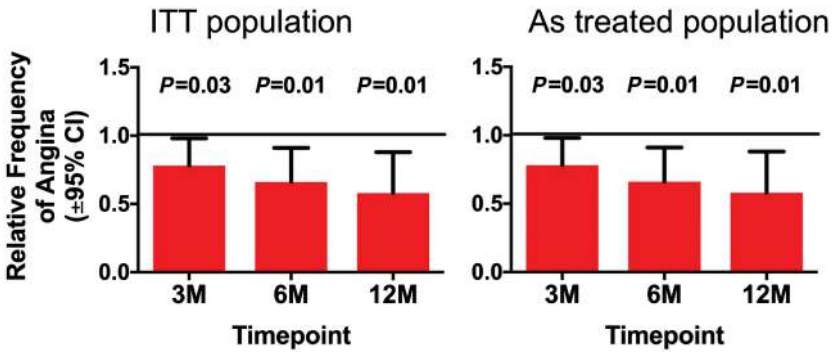


Figure 2 Relative frequency of angina (autologous CD34$^+$ vs. placebo) in intent-to-treat and as-treated populations. Relative frequency is the estimated ratio of the mean angina frequency in the CD34$^+$ group, to the mean angina frequency in the placebo group. CI, confidence interval; ITT, intent-to-treat.

Table 5 K-M rates for major adverse cardiac events at 2 years in intent-to-treat population

MACE	Placebo group $n = 89$ (K-M rate)	Auto-CD34$^+$ group $n = 187$ (K-M rate)	*P*-value
Death	9 (12.1)	4 (2.5)	0.0025
MI	10 (14.4)	21 (12.9)	0.80
Stroke	1 (1.4)	4 (2.5)	0.60
CV-hospitalization	20 (25.3)	33 (20.0)	0.20
Any MACE	31 (38.9)	50 (30.0)	0.14

Table reports number with event (cumulative %) by 2 years.
Auto-CD34$^+$, autologous CD34$^+$; CV, cardiovascular; K-M, Kaplan-Meier; MACE, major adverse cardiac events; MI, myocardial infarction.

minimum definitively support the safety of this approach, adding to the large body of data in this regard.

Cell therapy reduced AF compared with blinded placebo injection when analysed using the prespecified methodology agreed to with FDA regulators in a statistical analysis plan submitted prior to initiation of RENEW. Notably, this is a higher reduction than what was achieved with Ranolazine or EECP. The sensitivity of these analyses to the model used point to the difficulty of utilizing angina counts as an endpoint in clinical trials and may arise from differences in the methodologies used to collect angina across the three trials. Notably in RENEW, while patients remained blinded to treatment assignment, they were also made aware of the decision of the sponsor to prematurely terminate the trial. In RENEW, the median number of angina episodes decreased from 18 at baseline to three at 12-month follow-up, raising the possibility that patients abandoned their reporting efforts thereby diluting any treatment effect.

Comparisons of the high CV-hospitalization and composite MACE rates observed in the small number of patients in the SOC arm as reported in the RENEW trial[17] support the previous registry observations made in much larger patient populations regarding resource utilization in these patients when treatment options are absent.[10,11] More importantly, we believe the wide divergence in the rates of MACE in both the placebo and cell-treated patients as confirmed in this meta-analysis (reported Kaplan-Meier rate in RENEW SOC arm 72.5% at 24 months vs. 38.9% in the placebo arm and 30.0% in the auto-CD34$^+$ arm) compared with those not offered full participation in a trial illustrates the unmet need for the development of novel treatments for these patients.[14–18] In addition, it highlights the effectiveness of blinding in these studies, adding credence to the observations regarding exercise capacity which may be impacted by knowledge of treatment assignment, and validating the choice of a fully double-blinded control arm in RA studies.

Finally, it is worth noting that our results are consistent with several large meta-analyses of cell therapy in no option patients with refractory ischaemia [29–32] as well as with the results of intracoronary auto-CD34$^+$cells used in trials of RA, acute MI, and heart failure.[33–35]

Limitations

Patients randomized to IM placebo injections underwent stem cell mobilization and collection with daily GCSF injections and apheresis. We cannot exclude that these treatments either have a beneficial effect or impart some risk; however, it must be noted that the SOC arm in the RENEW trial had the highest MACE rate,[17] obviating concern in this regard and that the overall MACE rate in the ACT-34 study was modest and consistent with contemporaneous data in similar populations. No pre-clinical data suggest that transient mobilization of auto-CD34$^+$ cells in the setting of chronic myocardial ischaemia is an effective therapy. If cell mobilization into the circulation is an effective treatment option, the effectiveness of IM auto-CD34$^+$ is even more notable. While it is possible that the improvement in mortality observed is due to risk incurred by placebo injections, the observed mortality rate in the placebo arm is consistent with that reported in registry studies of populations that would have qualified for these trials and the mortality rate in the auto-CD34$^+$ groups was lower than reported in the previous observations made in similar patient populations.[11] Notably, the mortality curves continue to separate over time, suggesting that early procedural complications were not responsible for this result. Despite the aggregate experience from three trials in this work, the numbers of clinical events remain small, and the overall analysis remains underpowered to definitively define a treatment

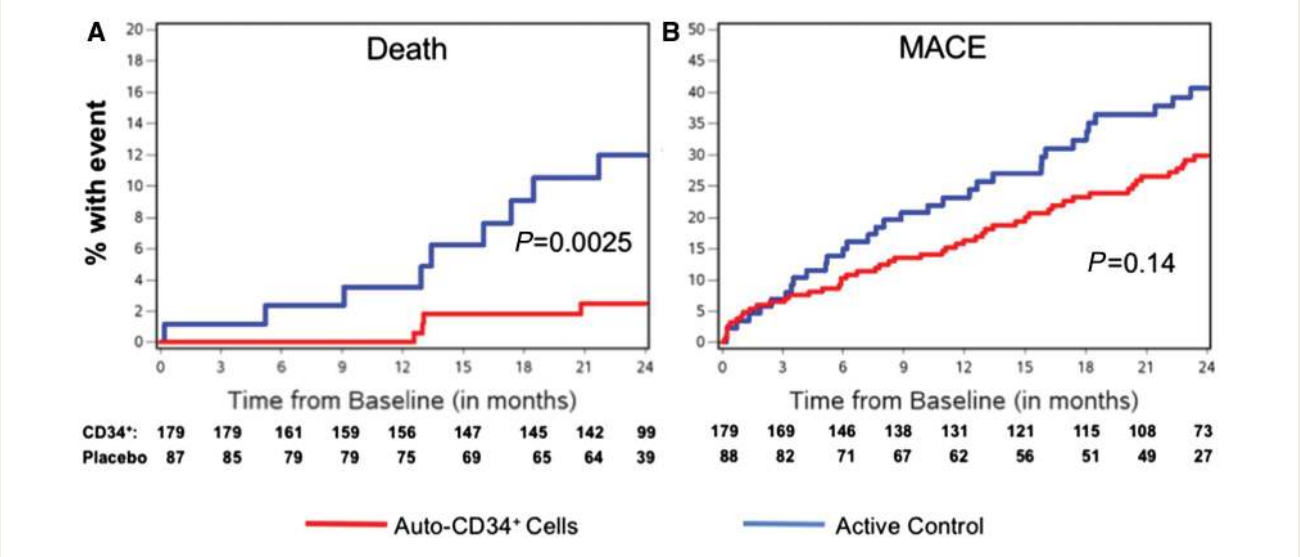
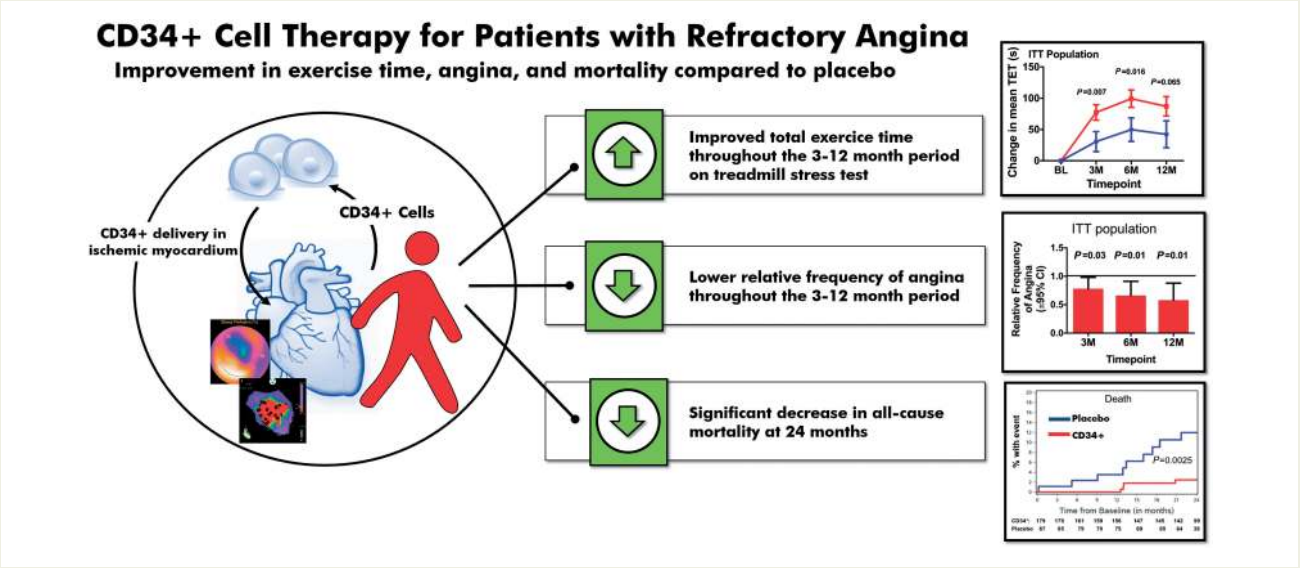


Figure 3 The Kaplan–Meier analysis for clinical events: (*A*) mortality (*B*) composite of death, myocardial infarction, stroke, and CV-hospitalization. CV, cardiovascular; MACE, major adverse cardiac events.



Take home figure Explanations for medical illustrator—on the left-side, you see a human figure, from which the CD34^{+} cells come from, and then you see a big heart in the background, in the lower left corner, you see an ischaemic heart based on a SPECT image and a NOGA mapping showing sites where the cells are injected. The site of injection and the ischaemic zone need to be concordant—the right-sided panel is easier to understand. SPECT, single photon emission computed tomography.

effect on clinical outcomes. The AF data had evidence of overdispersion, nonetheless, the point estimate was consistently in favour of cell therapy with a relative risk of at least 0.8, an effect that would be highly clinically impactful.

Conclusions

A combined patient-level analysis of three sequential double-blind clinical trials enrolling Class III and IV RA patients encompassing over a decade of enrollment demonstrated consistent and durable improvements in exercise capacity, AF, and mortality. These findings suggest that had RENEW been run to completion, a viable regenerative approach to the treatment of RA might have met criteria for clinical approval. These findings point to the promise and need for additional study of this therapy, and serve as a cautionary note of the potential loss to the medical and clinical/patient communities of the premature termination of clinical studies. Given the significant unmet clinical need for these no option patients, approaches to more rapid and cost efficient appraisal of such therapies are needed.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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CARDIOVASCULAR FLASHLIGHT

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Arteritis of Takayasu in Western man of 31 years

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We present the case of a 31-year-old Caucasian male, which was being studied in the emergency department for two episodes of syncope. The patient had a history of pain, coldness and paraesthesia of the right arm, jaw claudication, and intense headaches. He was being treated with two antihypertensive drugs due to arterial hypertension. Physical examination showed a differential arterial blood pressure between the arms (right 95/40, left 170/100), carotid systolic murmur in both sides of the neck, both supraclavicular spaces, and mesogastrium as well. Carotid and radial arteries pulses amplitude was diminished. Doppler sonography revealed several lesions in different vascular territories so the patient was sent for magnetic resonance angiography and a computed tomography angiography, revealing obstructions in the brachiocephalic artery, subclavian and vertebral arteries of both vascular territories which are marked with arrows (*Panel A*). *Panel B* shows that the carotid arteries are supplied by circulatory collateral through the polygon of Willis. The descending aorta was not affected (*Panel C*), but the right renal artery and the lower renal lobe the arteries had severe obstructions (*Panel D*). The wall of the aortic arch marked with an arrow shows an increase in thickness due to inflammation (*Panel E*). After several tests patient was diagnosed of Takayasu arteritis. He was treated with corticosteroids and percutaneous peripheral arteries interventions with good result and excellent clinical outcome. We report this case because the uncommon nature of Takayasu arteritis in western men, and its extensive vascular damage.