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CD34+ Cell Therapy for No-Option Refractory Disabling Angina: Time for FDA Approval?

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Significant improvements in revascularization techniques and adjunctive therapy have resulted in improved outcomes in patients with coronary artery disease. However, a sub-population of these patients continues to have disabling, chronic refractory angina. Refractory angina has been defined as three or more months of angina due to demonstrated coronary insufficiency that persists despite optimal medical therapy [1]. No-option refractory angina describes patients no longer amenable to further revascularization by either percutaneous or surgical revascularization [2]. Anatomic reasons which may preclude revascularization for refractory angina include diffuse, distal or side-branch disease, recurrent restenosis, degenerated vein grafts, poor distal target lesions, lack of conduits or other patient-related factors including extra-cardiac disease and frailty [2]. A smaller sub-population of no-option refractory angina patients have Canadian Cardiovascular Society (CCS) functional Class III or IV angina resulting in severe limitation in their ability to perform activities of daily living.

Finally, an even smaller sub-population of the no-option, CCS Class III/IV population are those who meet the Institute of Medicine definition of cardiovascular disability by being able to exercise less than five metabolic equivalents (METS) [3]. In this issue of *Cardiovascular Revascularization Medicine*, Velagapudi et al. provide a careful meta-analysis of clinical trials evaluating CD34+ cell therapy for this precisely defined sub-population of disabling, no-option, refractory angina [4]. Accordingly, it is critical to understand the patient population enrolled in the trials. To distinguish these patients from the more broadly defined and much larger populations described above, we propose to refer to these precisely defined subjects as having no-option refractory disabling angina (NORDA).

The exact prevalence of patients living with NORDA is unknown but can be estimated from a number of sources. Unfortunately, there are inadequate codes to identify patients from claims data. Older registry studies identified the prevalence of angina not amenable to revascularization from 6% to 14% of patients undergoing coronary angiography; however, these data do not account for angina severity or cardiovascular disability [5–8]. A retrospective study by Mukherjee et al. of consecutive patients undergoing coronary angiography at the Cleveland Clinic reported 12% of patients with coronary artery disease not amenable to revascularization [5]. A Swedish survey conducted in 1994–1995 identified a prevalence of 9.6% of patients with stable angina who were not candidates for revascularization [6]. More recently, Lenzen et al. noted a prevalence of 14% of patients in the European Heart Survey who were ineligible for traditional revascularization [7]. Finally, Williams et al. assessed 493 consecutive patients, of whom 6.7% were on optimal medical therapy and not candidates for revascularization, and were thus termed "no option" patients [8]. Again, these anatomic definitions do not account for angina severity or cardiovascular disability, which were both precisely defined requirements for entry into the clinical trials that are the subject of the meta-analysis by Velagapudi [4].

The true prevalence of NORDA can be estimated from the multiple sources in the literature. According to data from NHANES 2011 to 2014 (unpublished NHLBI tabulation), the overall prevalence for angina is 3.4% in adults ≥20 years of age, which is approximately 8,700,000 people in the United States (US) [9]. Data from Pichlhofer et al. [10], the CADENCE [11] and AVANCE [12] studies indicates that approximately 7.6–15% of patients with angina have CCS Class III/IV symptoms (662,000–1,305,000 patients). Data from Pichlhofer et al. also demonstrates that only 4% of subjects experience >7 episodes of angina per week, which was required in all 3 clinical trials [4]. This analysis suggests the prevalence of NORDA in the US is between 26,000 and 52,000, an orphan-sized population that explains the challenges experienced in identifying patients for the three CD34+ clinical trials described by Velagapudi et al. [4,13–17].

Another important issue is the natural history of coronary artery disease not amenable to revascularization with today's contemporary climate of medical therapy. While earlier registries reported high mortality rates [5,18,19], recent data indicates that one-year mortality rates are between 4% and 6% per year [20,21], which is consistent with the outcomes of the CD34+ clinical studies which demonstrated a 2-year all-cause mortality of ~12% in placebo subjects vs. ~2.5% in treated patients [13–17].

Despite improvements in mortality, the impact on quality of life for patients with NORDA cannot be underestimated [2,20,21]. It is also an expensive problem, with frequent re-hospitalizations and high utilization of medical care [21].

Traditional medical therapy in these patients employs anti-anginal agents, including nitrates, beta-blockers, calcium channel blockers and ranolazine [2]. After exhausting these medications, treatment options for refractory angina are limited, with enhanced external counterpulsation (EECP) and transmyocardial laser revascularization as the only approved options [2]. Since the primary problem in refractory angina is inadequate myocardial perfusion, autologous cell-based therapy has emerged as an

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enticing option by improving coronary microcirculation and enhancing the natural process of collateral development [2]. Tse et al. were the first to demonstrate that intramyocardial infusion of bone marrow cells could induce neovascularization and improve cardiac function in humans [22]. Preclinical studies have shown that the CD34+ marker can be used to identify and isolate endothelial progenitor cells which are capable of stimulating the regrowth of damaged microvessels in the myocardium [23]. Lower levels of circulating CD34+ cells have been associated with increased risk of poor cardiovascular outcomes including need for revascularization and death from cardiovascular causes [24]. CD34+ cells extracted from peripheral blood have been shown to promote angiogenesis and myocardial repair after ischemic injury [23]. The feasibility and safety of intra-myocardial transplantation of autologous CD34+ stem cells for refractory angina was first assessed in a phase 1 trial of 24 patients with reduction of angina [13]. The ACT34-CMI trial was a phase II study of 167 patients to establish dose-responsiveness of autologous CD34+ cells and demonstrated significant improvement in angina frequency and exercise tolerance at 6 and 12 months [14], with persistent improvement at two years [15]. RENEW was a phase III clinical trial designed for FDA approval with planned enrollment of 444 patients randomized to intramyocardial injection of CD34+ versus placebo or standard of care therapy. It was powered to assess the efficacy of CD34+ cells on exercise treadmill time, with important secondary endpoints including frequency of angina and major adverse cardiac events [16]. Unfortunately, RENEW was terminated prematurely due to financial considerations and, therefore, remained inadequately powered to meet its primary endpoints [17]. Accordingly, the 168-patient phase 2 study remains the largest completed study able to conclusively assess the efficacy of CD34+ cell therapy in patients with NORDA. Given the orphan size of the NORDA population, we therefore must consider the totality of evidence in this context and examine the rationale for ongoing study in this desperately ill population.

In this issue of *CRM*, Velagapudi et al. perform a meta-analysis of the three randomized, double-blind, placebo-controlled clinical trials conducted to determine the effect of CD34+ cells as compared to placebo for patients with NORDA. The three trials, ACT, ACT34-CMI, and RENEW, enrolled 269 patients, of whom 179 were randomized to CD34+ therapy and 90 to blinded placebo. The authors selected their primary outcomes as change in angina frequency and exercise time. In addition, they looked at major adverse cardiovascular events including myocardial infarction, stroke, and death. They report that intra-myocardial administration of CD34+ cells was associated with significantly lower frequency of angina, with an odds ratio of angina frequency with autologous CD34+ cells as compared to placebo of -2.91 (95% CI -4.57 to -1.25, $p = 0.0006$). The authors also note an improvement in exercise time by 58.62 s over the study period (95% CI 21.19–96.06, $p = 0.002$). Although there was no statistical difference in risk of myocardial infarction or stroke between the two groups, all-cause mortality was significantly lower in the CD34+ treated patients (OR 0.24, 95% CI 0.08–0.73, $p = 0.01$). The authors conclude that the pooled results of this meta-analysis support the utilization of autologous CD34+ cell therapy as a safe therapy in the NORDA population defined in all 3 studies [4].

These findings echo a recent patient-level meta-analysis by Henry et al. using the same three trials, which confirmed a significant improvement in exercise time and reduction in angina frequency [25]. Most compelling, the investigators found that overall mortality at 24 months was 2.5% in the treated group, as compared to 12.1% in the placebo arm [25].

Accordingly, the completed phase 2 ACT-34 study and the two meta-analyses demonstrate that therapy with CD34+ stem cells is safe and efficacious in reduction of angina, improvement in exercise capacity, and strongly suggests an improvement in mortality.

On the basis of these trials, CD34+ cell therapy has received the FDA regenerative medicine advanced therapy designation for use in no-option refractory angina. This designation addresses the potential of CD34+ cell therapy in treatment of this challenging condition and is a critical step in expediting the approval of CD34+ therapy as a viable treatment option in this patient population. An appreciation of the orphan size of this patient population raises the important question as to whether the existing evidence is sufficient for approval of this therapy for this desperately ill, disabled patient population.

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