SUPPLEMENTARY DATA

Supplementary Information on Flow Cytometry: Blood cells were gated based on forward and side laser light scattering, and nucleated cells were segregated from debris by DRAQ5 DNA staining. As discussed in the Methods section of the paper, the majority of studies were performed using a triple laser flow cytometer MACSQuant (Miltenyi Biotec Corp., Auburn, CA) that can simultaneously detect up to 8 colors using the manufacturers' acquisition software. Fluorescence signals from the three (404, 488 and 635 nm) excitation lasers using five band-pass filters (450/50-nm, 525/50-nm, 585/40-nm, 655-730-nm and 750 nm LP) were quantified based on the Fluorescence-Minus-One (FMO) method to determine cytometer boundaries for acceptance of an event as a SPCs and potential marker interactions. The approach removes operator-dependent judgements for selecting gating parameters and provides an objective way to place the boundary for non-staining cells in a channel versus an arbitrary pre-set decision of acceptance based on a signal-to-noise ratio (44). Because the compensation corrections differ in part based on amounts of the various reagents within cells in different subsets (*e.g.* those used for the various HIF measurements) use of FMO determines the boundary between positive and negative cells for each subset. Representative flow cytometry analyses are shown in the text and are analogous to those described and illustrated in prior publications (14, 15, 34).

Supplementary Table 1. Medications patients taking during the study. Subjects had been taking their medications prior to study entry and there were no deletions or additions during the study interval. Medications listed include insulin, metformin (Met.), sulfonylureas (Sulf), angiotensin converting enzyme inhibitors ACE), angiotensin receptor blockers (ARB), calcium channel blockers ($C^{++}B$), β-blockers (β-b), statin agents, clopidogrel (Clopid), a steroid and various ingested antibiotics (Ab).

	Insulin	Met.	Sulf	ACE	ARB	Ca++B	β-b	Statin	Clopid.	Steroid	Ab
Heal (37)	25	10	6	13	2	6	11	18	4	0	8
Not heal (63)	60	25	18	29	2	13	26	37	7	3	31

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SUPPLEMENTARY DATA

Supplementary Table 2. Wound management. In addition to materials shown in the table, during the 8 week interval of the study wounds for one person in each group (healed and not healed) were treated with a compression dressing, negative pressure wound therapy, hyperbaric oxygen therapy and a cell-based skin substitute. Two in the healed group received a honey-based dressing and two in the non-healed group had becaplermin applied.

	Iodo- or Silver-ointment	Carboxy-methyl-cellulose (CMC)	CMC +collagen + silver	Collagenase ointment	TCC	Antibiotic Ointment	xenograft	Extracell. matrix	Gauze
Heal (37)	9	4	8	4	6	3	1	2	2
Not heal (63)	27	7	6	9	7	9	10	5	4

Supplementary Table 3. Correlation coefficients for intracellular HIF ratios. The ratio**,** (HIF-1 + HIF-2)/HIF-3 was evaluated for circulating SPCs defined as CD34+ and CD45-dim. The (n) for each measurement is the same as shown in Figure 1 caption. Where p values are shown, correlations are statistically significant when corrected for multiple comparisons and these values are in bold.

	Day 1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
Day 1		**0.489 p<0.0001**	**0.593 p<0.0001**	0.217	**0.259**	**0.458 p=0.001**	-0.101	-0.440
Week 1			**0.540 p<0.0001**	**0.512 p<0.0001**	**0.597 p<0.0001**	**0.560 p<0.0001**	**0.888 p<0.0001**	**0.838 p=0.0002**
Week 2				**0.410 p=0.0001**	**0.426 p=0.0008**	**0.457 p=0.0009**	0.265	0.372
Week 3					**0.687 p<0.0001**	**0.755 p<0.0001**	**0.626 p=0.0002**	**0.681 p=0.002**
Week 4						**0.535 p<0.0001**	0.399	**0.916 p<0.0001**
Week 5							**0.492 p<0.007**	**0.749 p<0.0004**
Week 6								**0.947 p<0.0001**

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