Do Statins Have a Role in the Promotion of Postoperative Wound Healing in Cardiac Surgical Patients?

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Cardiac surgical patients often have associated comorbidities that can impede normal wound healing; however, statin therapy has the potential to improve this process through augmentation of the normal inflammatory response. Outcomes included a 30% earlier rate of wound epithelialization and an 80% greater wound-breaking strength combined with faster wound healing rates (13.0 days vs 18.7 days, $p < 0.0001$). Inhibition of farnesyl pyrophosphate may hold a key role in the mediation of such advantageous effects. This systematic review suggests that there is sufficient evidence to warrant completion of a human trial to assess the effects of statins on wound healing.

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REVIEW

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, commonly termed statins, are amongst the most widely prescribed medications in the world and are mainly used to lower plasma cholesterol levels with a resultant reduction in cardiovascular morbidity and mortality [1–3]. They act through competitive inhibition of HMG-CoA reductase, thereby preventing conversion of HMG-CoA to mevalonate, a rate-limiting step early in the pathway of cholesterol biosynthesis [4, 5]. The result is a reduction in low-density lipoprotein and an increase in high-density lipoprotein, with the clinical benefit of a significant reduction in cardiovascular and cerebrovascular events as well as improved survival rates in patients with coronary artery disease [4].

Recent evidence has further suggested that these drugs may have more wide-ranging effects through modulation of the normal inflammatory milieu. The inhibition of mevalonate formation early in the pathway prevents the production of many other nonsteroidal isoprenoidic compounds, an action that may account for the potential pleiotropic effect of statins [6]. Indeed, Node and colleagues [7] (2003) reported that pravastatin led to reductions in plasma inflammatory cytokines, including interleukin (IL)-6 and tumor necrosis factor-α (TNF-α), and various statins have also demonstrated an improvement in clinical outcomes in patients with sepsis and a reduction in rejection rates after organ transplantation [4, 7–10]. Although there has been some initial research into the potential role of statins in the promotion of wound healing and effect on wound infection rates, individually the results to date have been limited.

Wound healing normally occurs in a well-orchestrated series of four phases, namely, hemostasis, inflammation, proliferation, and remodelling (Fig 1) [11, 12]. For this cascade of events to occur and normal wound healing to progress, various inflammatory mediators are involved (Fig 2). Powerful vasoconstrictors (thromboxane A2 and prostaglandin 2-α) are initially released by the injured cell membrane, a fibrin clot forms, and its constituents (platelets, collagen, and thrombin) release cytokines and growth factors that enable progression to the inflammatory phase [13]. Chemotactic agents including IL-1, TNF-α, and transforming growth factor (TGF)-β attract neutrophils and monocytes to the injured area and enable the conversion of monocytes to macrophages [13].

Angiogenesis is also a critical component of normal wound healing and is stimulated by vascular endothelial growth factor (VEGF), resulting in increased vascular permeability, endothelial cell migration, and capillary formation [14]. Epithelialization and granulation tissue formation occur during the proliferative phase, mediated by platelets and macrophages through production of epidermal growth factor (EGF), TGF-α, and platelet-derived growth factor (PDGF) [13]. The resultant wound continues to undergo remodelling for up to a year as the collagen is reorganized and tensile strength improves [13].

Modern cardiac surgical practice encompasses a patient population with significant comorbidities that can

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Abbreviations and Acronyms

bFGF	=	basic fibroplastic growth factor
EGF	=	epidermal growth factor
eNOS	=	endothelial nitric oxide synthase
FPP	=	farnesyl pyrophosphate
HMG-CoA	=	3-hydroxy-3-methylglutaryl-coenzyme A
IFN-γ	=	interferon-γ
IGF	=	insulin-like growth factor
IL	=	interleukin
KGF	=	keratinocyte growth factor
NO	=	nitric oxide
PDGF	=	platelet-derived growth factor
TGF	=	transforming growth factor
VEGF	=	vascular endothelial growth factor

impair this normal wound-healing process. Although mainly elective in nature, patients are generally exposed to two significant incisions during coronary artery bypass grafting through their sternotomy and lower limb saphenous vein harvest. The overall rate of sternal wound infections remains low, at approximately 1%, but there remain a significant number of cardiac surgical patients whose wounds heal slowly due to their underlying comorbidities [15].

Wound-healing problems are even more prominent in the lower limb vein harvest site, where complication rates of between 10% and 20% have been reported [15]. Subsequent management of these wound complications affects patient quality of life and imposes a significant economic burden on health care providers, particularly

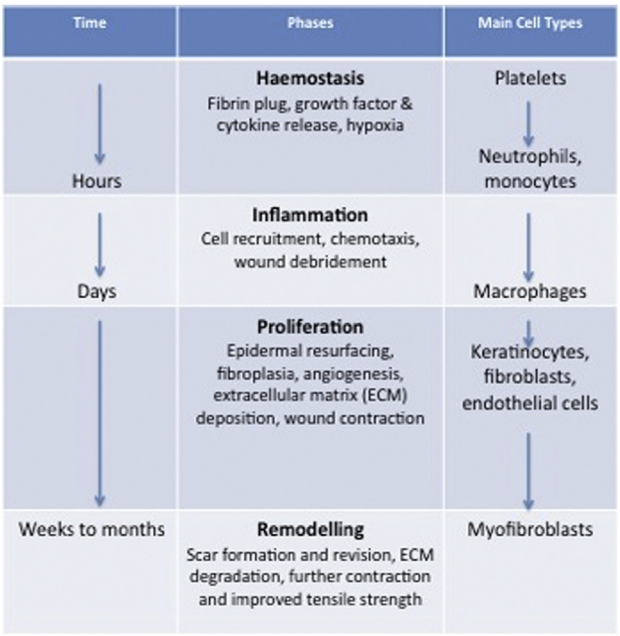

Fig 1. An overview of the phases of normal wound healing, including the main cell types involved. (Reprinted from Lancet, Vol. 366, Falanga V, Wound healing and its impairment in the diabetic foot, pages 1736–43. Copyright 2005, with permission from Elsevier [11].)

with delays in patient discharge, the cost of wound care, including the use of devices such as vacuum-assisted closure, and community nursing care costs [15]. Multiple perioperative processes have been modulated in recent years to improve wound healing and reduce postoperative infection rates, such as the administration of prophylactic antibiotics at the induction of anesthesia and optimal postoperative glycemic control. Although most wounds resolve satisfactorily, even after a delay, any mechanism that could potentially improve wound-healing rates merits exploration.

The aim of this study was to evaluate the potential role of statins, both topical and systemic, in the promotion of postoperative wound healing to elucidate more clearly a potential mechanism of action for statin augmentation of wound healing. The results would hope to enable consolidation of the current evidence base and allow a recommendation of whether further, more extensive trials, up to and including clinical trials, would be appropriate to directly evaluate the effect of statin use in the promotion of postoperative wound healing.

Material and Methods

A systematic review was conducted using MEDLINE, The Cochrane Library (in its entirety), Embase, and the Ovid gateway with the keywords "statins" and "wound," and "statins" and "neutrophil migration." These keywords were selected because they were broad ranging and would identify the maximum number of articles relevant to the chosen topic. The search was limited to the English language and to journal articles only, because these represent the most up-to-date clinical repository. A dedicated search of the "gray literature" (unpublished trials, theses, reports, technical, and conference notes) was not undertaken because sufficient contemporaneous data was obtained through the conventional literature search. There were no restrictions to the study design and no time limitations up to and including August 24, 2011.

The articles were critiqued using the Critical Appraisal Skills Programme appraisal tools [16], a standard critiquing tool used to assess articles by their methodology. The focus is on three key areas: the validity of the trial, the results, and whether the results will assist in patient care locally. A number of questions are used to assess each particular study's methodology, which provides a standardized technique to evaluate each article [16]. The hierarchy of evidence was standardized as outlined by the Oxford Centre for Evidence Based Medicine [17] (2009).

Results

We identified 326 articles through the combined search engines. The main author (G.J.F.) independently reviewed each abstract only and excluded any article that did not specifically relate to wounds, or the effect of statins on wound healing, or the effect of statins on the mediators of inflammation relevant to wound healing. There were no other specific exclusion criteria. A total of