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Endothelial Progenitor Cell Number: A Convergence of Cardiovascular Risk Factors

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1. Introduction

The bone marrow of adult humans is a source of endothelial progenitor cells (EPCs) that circulate in the blood and repair damaged endothelium. The number and function of EPCs is predictive of endothelial function and cardiovascular events. Herein we discuss the impact of individual risk factors on EPC numbers and discuss the potential utility of EPC number as a cardiovascular risk-assessment tool that integrates traditional and emerging cardiovascular risk factors.

2. The systemic basis of cardiovascular disease

Cardiovascular disease the leading cause of mortality in the Western world and manifests as coronary disease, peripheral vascular disease, or ischemic stroke depending on the vascular territory affected. The ageing population and projected increases in prevalence and costs of care have highlighted the need for more effective prevention of cardiovascular disease (Heidenreich, Trogon et al. 2011). These manifestations of cardiovascular disease share common risk factors of age, hypertension, diabetes, hypercholesterolemia and smoking (Roger, Go et al. 2011). Endothelial dysfunction is the precursor lesion to atherosclerosis and reflects depressed nitric oxide (NO) release from the endothelium (Furchgott 1996; Valgimigli, Merli et al. 2003). Basal release of NO from the endothelium regulates vascular tone and antagonizes the actions of vasoconstrictor substances. Further, NO possesses anti-platelet actions and down-regulates adhesion molecules that attract inflammatory cells to the endothelium (Deanfield, Halcox et al. 2007). The degree of endothelial dysfunction shows a graded response to the number of cardiac risk factors present (Bonetti, Lerman et al. 2003; Davignon and Ganz 2004) and is predictive of clinical events (Bonetti, Lerman et al. 2003; Davignon and Ganz 2004; Deanfield, Halcox et al. 2007). Since endothelial dysfunction occurs systemically, the atherosclerotic process involves a large portion of the arterial tree before it becomes clinically manifest (Deanfield, Halcox et al. 2007). Patient presentations to a cardiologist, cardiac surgeon, vascular surgeon or stroke neurologist with clinically manifest atherosclerosis are typically preceded by decades of endothelial dysfunction and depressed vascular repair throughout the entire arterial bed (Ross 1993). The systemic

nature of atherosclerosis is highlighted by the fact that >50% of patients with stroke or peripheral vascular disease have co-morbid atherosclerotic coronary disease (Hirsch, Haskal et al. 2006; Brott, Halperin et al. 2011) and patients with manifest disease in multiple arterial beds are at an increased risk of cardiovascular death and recurrent events (Steg, Bhatt et al. 2007). Since the description of circulating marrow cells that repair the endogenous arterial bed, “endothelial progenitor cells” (EPCs), an increasing research interest has been focused on how risk factors impact on the numbers of these cells and their ability to repair the vasculature and maintain endothelial function.

3. Endothelial progenitor cells and atherosclerosis

The modern concept that circulating marrow cells, EPCs, circulate in adult animals and repair the vasculature originates stems from the observation in the late 90s that marrow-derived mononuclear cells circulate in adult animals and directly contribute to neovascularization in animal models of hindlimb ischemia, myocardial infarct remodeling and post-stroke neovascularization (Asahara, Murohara et al. 1997; Asahara, Masuda et al. 1999; Zhang, Zhang et al. 2002; Metharom and Caplice 2007). The clinical relevance of EPC numbers was brought to the forefront cardiovascular risk prognostication when EPC numbers were shown to correlate positively with flow mediated brachial artery reactivity (a measure of endothelial function) and inversely with the Framingham risk score (Hill, Zalos et al. 2003; Ghani, Shuaib et al. 2005; Chironi, Walch et al. 2007). Endothelial dysfunction observed in patients with cardiovascular disease or its risk factors may reflect a depressed ability to “renew” the endothelium from the circulating pool of EPCs which act to restore endothelial function. Indeed, patients with coronary artery disease (CAD) and stroke were shown to have EPC numbers that are reduced when compared to *age-matched* healthy volunteers (Vasa, Fichtlscherer et al. 2001; Lambiase, Edwards et al. 2004; Ghani, Shuaib et al. 2005). EPC numbers, which are usually assessed by flow cytometry for CD34+KDR+ cells, carry prognostic significance in patients with and without cardiovascular disease. EPC numbers predict clinical events in patients with established CAD. Amongst patients with CAD, lower EPC numbers were associated with increased severity of CAD and higher risks of death from cardiovascular causes, major cardiovascular events, revascularization or hospitalization (Schmidt-Lucke, Rossig et al. 2005; Werner, Kosiol et al. 2005; Kunz, Liang et al. 2006; Wang, Gao et al. 2007). In asymptomatic individuals, EPC numbers correlate with the number of vascular beds with subclinical disease. In a study using ultrasound to characterize disease in the carotid artery, abdominal aorta and femoral artery, the number of EPCs cells was shown to be decreased stepwise in patients with plaque in 0, 1, 2 and 3 of the sites (Chironi, Walch et al. 2007). Further, EPC numbers correlate with cardiovascular disease surrogates such as carotid intima-media thickness even after correction for the Framingham risk score and C-reactive protein (Fadini, Coracina et al. 2006).

In addition to absolute EPC numbers, the functional capacity of EPCs in repairing the vasculature is impaired by cardiac risk factors. EPCs harvested from the marrow of human patients with ischemic cardiomyopathy show an impaired capacity to effect neovascularization and incorporate into the vasculature in a mouse hindlimb ischemia model (Heeschen, Lehmann et al. 2004). In a human trial testing the efficacy of EPCs in repairing the coronary vasculature after a re-perfused myocardial infarction, the migratory capacity of EPCs to chemotaxins was the strongest multivariate predictor of reduction in

infarct size (Britten, Abolmaali et al. 2003). Reduced EPC migration to chemotaxins and reduced ability of human EPCs to effect neovascularization in animal hindlimbs has also been related to individual cardiovascular risk factors such as increasing age, hypertension, hypercholesterolemia, family history of CAD, smoking and high Framingham risk scores (Vasa, Fichtlscherer et al. 2001; Hill, Zalos et al. 2003; Heeschen, Lehmann et al. 2004; Schmidt-Lucke, Rossig et al. 2005; Wang, Gao et al. 2007). While EPCs can be harvested from bone marrow to treat myocardial ischemia (Britten, Abolmaali et al. 2003) or threatened limb ischemia (Comerota, Link et al. 2010) on an investigational basis, herein we focus on the impact of cardiovascular risk factors on EPCs and the potential utility of measuring EPC numbers for risk assessment in primary and secondary prevention. We discuss the impact of individual risk factors on EPC number with a focus on studies undertaken in human subjects and describe how risk factor control boosts EPC numbers. Each of the discussed risk factors individually suppresses EPC mobilization from the marrow and decreases peripheral survival making EPC number a universal risk factor (Hoenig, Bianchi et al. 2008).

4. Insulin resistance, the metabolic syndrome and diabetes

Diabetes is a risk factor associated with heightened cardiovascular risk and endothelial dysfunction (De Vriese, Verbeuren et al. 2000; III 2002). In some series, diabetes has been associated with the same coronary risk as established coronary disease thereby making it a “coronary artery disease risk-equivalent” (Haffner, Lehto et al. 1998). Diabetics without manifest cardiovascular disease have decreased EPC numbers compared to age-matched controls (Tepper, Galiano et al. 2002) and diabetics with manifest macrovascular disease such as CAD, peripheral vascular disease or stroke have further reduced EPC numbers (Fadini, Miorin et al. 2005; Brunner, Hoellerl et al. 2011). Further, EPCs in diabetics are dysfunctional when compared to EPCs from non-diabetic subjects. The depressed EPC numbers in diabetes are thought to contribute to impaired collateralization of vascular ischemic beds (Waltenberger 2001) and may predispose this group to developing non-healing diabetic ulcers which may be ameliorated by injecting EPCs into ischemic lower limb muscles (Huang, Li et al. 2005). Indeed, among diabetic patients with peripheral vascular disease, EPC numbers correlated negatively with the ankle brachial index and patients with ischemic ulcers had the lowest EPC numbers (Fadini, Miorin et al. 2005). Blood sugar levels are inversely correlated with EPC numbers implying a direct relationship between hyperglycemia and depressed EPC numbers (Fadini, Miorin et al. 2005). In the laboratory, hyperglycemia directly impairs EPC function by impairing the ability of these cells to migrate (Krankel, Adams et al. 2005). Diabetics with good glucose control have higher EPC numbers and more functional EPCs when compared to diabetics with poorly controlled glucose (Churdchomjan, Kheolamai et al. 2010) and treating newly-diagnosed diabetics with secretagogues increases EPC numbers and is associated with a concordant improvement in endothelial function (Kusuyama, Omura et al. 2006; Liao, Chen et al. 2010). Likewise, insulin-sensitizing agents such as pioglitazone or rosiglitazone boost EPC numbers and the increase in EPCs is correlated with the reduction in C-reactive protein and increase in adiponectin (Kusuyama, Omura et al. 2006; Makino, Okada et al. 2008). The inverse relationship between EPC numbers and HbA1c and insulin resistance indices implies that EPC numbers decline in pre-diabetic states such as the metabolic syndrome and insulin resistance (Tepper, Galiano et al. 2002; Penno, Pucci et al. 2011). Indeed, EPC

numbers decrease as more metabolic syndrome criteria are met (Fadini, de Kreutzenberg et al. 2006; Jialal, Devaraj et al. 2010) and are also decreased in other pre-diabetic states such as gestational diabetes (Penno, Pucci et al. 2011) or the polycystic ovarian syndrome (Dessapt-Baradez, Reza et al. 2011). Given that EPC numbers repair the vasculature and maintain endothelial dysfunction, this decreased capacity for repair of the vasculature may provide a mechanism for the increased risk of cardiovascular events observed in patients with the metabolic syndrome (Mottillo, Filion et al. 2010).

5. Gender and age

Age and male gender are irreversible cardiovascular risk factors. Healthy middle-aged women have higher EPC numbers than men (Hoetzer, MacEneaney et al. 2007). Young men have similar EPC numbers as post-menopausal women and this may explain why men are prone to cardiovascular disease at a younger age. Women, on average tend to develop cardiovascular disease after menopause with an incidence that equals that of age-matched men 10 years after the menopause. This time in a woman's life, 10 years after the menopause, is associated with a decrease in EPC numbers and EPC function (Bulut, Albrecht et al. 2007; Rousseau, Ayoubi et al. 2010). This decline in EPC numbers may be due to the lack of estrogen since hyper-estrogenic states (e.g. during ovarian stimulation) have been shown to be associated with an increase in EPC numbers and there is a normal variation with the ovarian cycle (Rousseau, Ayoubi et al. 2010). Hormone replacement therapy can boost EPC numbers in post-menopausal females by 25% (Bulut, Albrecht et al. 2007) and enhance endothelial function (Sanada, Higashi et al. 2003; Kalantaridou, Naka et al. 2006).

Ageing is associated with endothelial dysfunction and dysfunctional EPCs that are more prone to apoptosis and have reduced proliferative capacity (Heiss, Keymel et al. 2005; Kushner, Maceneaney et al. 2011). Further, the elderly are less able to mobilize EPCs in response to ischemic stimuli (Scheubel, Zorn et al. 2003). With ageing, the endothelial progenitor cells have shortened telomeres, which are the repetitive DNA at the ends of chromosomes that protect DNA integrity (Kushner, Van Guilder et al. 2009). Telomere shortening has been described in patients with CAD compared to healthy controls (Ogami, Ikura et al. 2004). Hence, this may provide a mechanism whereby EPCs from elderly individuals are more likely to undergo proliferative senescence and an increased susceptibility to apoptosis which can contribute to decreased EPC numbers. This generally occurs around the age of 55 which is temporally associated with the increased period of cardiovascular risk within a human's lifetime (Kushner, Van Guilder et al. 2009). Hence, the ability to generate functional EPCs, to rejuvenate the endothelium lining the arteries and maintain endothelial function may be key in the pathogenesis of cardiovascular disease with aging.

6. Hypertension

Hypertension is associated with a doubling in the risk for cardiovascular disease with every 20/10 mmHg increment (Chobanian, Bakris et al. 2003). Hypertension is associated with endothelial dysfunction and decreased EPC numbers and reduced EPC function (Vasa, Fichtlscherer et al. 2001; Umemura, Soga et al. 2008; Schulz, Gori et al. 2011). The treatment of hypertension, specifically with drugs inhibiting the renin-angiotensin system, is associated with increased EPCs whereas the use of other classes of drugs such as calcium antagonists, diuretics, and beta-blockers has not been associated with such effects

(Umemura, Soga et al. 2008). Similarly, treatment of diabetics with angiotensin receptor blockers boosts EPC numbers (Bahlmann, de Groot et al. 2005). Treating patients with an angiotensin-converting enzyme (ACE) inhibitor such as ramipril has similar effects (Bahlmann, de Groot et al. 2005). Angiotensin II reduces the proliferative capacity of cultured EPCs and induces cell death (Imanishi, Hano et al. 2005). Such observations may explain why drugs such as ACE inhibitors may have beneficial effects that are greater than the observed reduction in blood pressure (Yusuf, Sleight et al. 2000).

7. Dyslipidemia

Hypercholesterolemia is a pivotal cardiovascular risk factor and much there is much focus on treating this risk factor (ATP III 2002). Low density lipoprotein cholesterol (LDL-C) is the primary treatment target in both primary and secondary prevention of cardiovascular disease and there is a log-linear relationship between LDL-C level and CAD risk (ATP III 2002). LDL-C is inversely correlated with EPC number and function in human patients (Chen, Zhang et al. 2004). Statin therapy has been shown to increase EPC numbers and function (Fadini, Albiero et al. 2010; Jaumdally, Goon et al. 2010) and to enhance EPC numbers in response to ischemic stimuli (Spadaccio, Pollari et al. 2010; Hibbert, Ma et al. 2011). The improvement of endothelial function associated with statin use is directly correlated with the increase in EPC numbers and measures of EPC function (Higashi, Matsuoka et al. 2010). Similarly, lipid apheresis for resistant hypercholesterolemia improves EPC function and mobilization (Patschan, Patschan et al. 2009; Ramunni, Brescia et al. 2010). Low high density lipoprotein cholesterol (HDL-C) has been identified as secondary therapeutic target and reconstituted HDL-C infusion improves endothelial function and raises EPC numbers (Nieuwdorp, Vergeer et al. 2008).

8. Inflammatory conditions

Inflammatory conditions such as rheumatoid arthritis (RA) have, relative to traditional risk factors, been only recently associated with an increased cardiovascular risk. Like other cardiovascular risk factors, RA is associated with endothelial dysfunction (Herbrig, Haensel et al. 2006). Patients with RA have a life expectancy that is reduced by 5-10 years and the excess mortality is from cardiovascular disease which is increased roughly 4-fold (Wrigley, Lip et al. 2010). RA is particularly associated with a virulent form of coronary atherosclerosis characterized by high coronary artery calcium scores. However, the patients with RA that are at particular cardiovascular risk are those with active disease and high disease activity scores (Grisar, Aletaha et al. 2005). EPC numbers and EPC proliferative capacity show an inverse correlation with disease activity scores (Grisar, Aletaha et al. 2005; Herbrig, Haensel et al. 2006; Egan, Caporali et al. 2008). The increased risk of cardiovascular events is not limited to RA and has been described in other inflammatory states such as systemic lupus erythematosus (SLE) (Urowitz, Bookman et al. 1976; Roman, Shanker et al. 2003), human immunodeficiency virus (HIV) infection (van Leuven, Sankatsing et al. 2007), inflammatory bowel disease (Danese and Fiocchi 2003) or periodontitis (Mattila, Nieminen et al. 1989). Pre-menopausal women with SLE have a risk of myocardial infarction that is increased a staggering 50-fold compared to healthy controls (Manzi, Meilahn et al. 1997). SLE is associated with impaired EPC function and hence a decreased capacity to repair the endothelium (Deng, Li et al. 2010; Ablin, Boguslavski et al. 2011). Inflammatory conditions

are almost universally associated with increased inflammatory markers such as C-reactive protein (CRP) and cytokines such as tumor necrosis factor alpha (TNF- α) which is primarily made by macrophages and inhibits proliferation of repair cells in the body. CRP and TNF- α are directly toxic to EPCs; reducing survival and impairing function (Verma, Kuliszewski et al. 2004; Chen, Zhong et al. 2011). The number of EPCs in patients with inflammatory diseases such as Kawasaki's disease is inversely correlated with plasma CRP and TNF- α (Xu, Men et al. 2010). Treating inflammatory disease such as RA with steroids or anti-TNF- α therapies boosts EPC numbers and may thus have salutary effects on cardiovascular health (Ablin, Boguslavski et al. 2006; Grisar, Aletaha et al. 2007).

9. Physical activity

A recent meta-analysis has shown that individuals exercising ~150 minutes at moderate intensity have a 14% lower risk of CAD compared to sedentary individuals (Sattelmair, Pertman et al. 2011). There was a dose-response relationship with higher grades of physical activity associated with proportional reductions in incident CAD. In patients with CAD, exercise-based rehabilitation is associated with a 20% reduction in mortality and a 26% reduction in cardiac mortality (Taylor, Brown et al. 2004). Exercise enhances endothelial function and increases NO bioavailability (Hambrecht, Adams et al. 2003; Green, Maiorana et al. 2004; Higashi and Yoshizumi 2004). Since EPC number is a fundamental determinant of endothelial function, it would be expected that exercise mobilizes EPCs. Indeed, a three month exercise prescription in humans increases EPC numbers and this independent of the effects of exercise on body mass, adiposity, blood pressure or lipids (Hoetzer, Van Guilder et al. 2007). Importantly, the improvement in endothelial function correlated with the increase in the number of circulating EPCs ($r=0.81$, $p<0.001$) and the increase in NO synthesis (Steiner, Niessner et al. 2005). This suggests that exercise-induced EPC mobilization enhances vascular repair. Exercise may also halt atherosclerotic disease progression as ascertained in both the coronary and carotid beds (Belardinelli, Paolini et al. 2001; Hambrecht, Walther et al. 2004; Rauramaa, Halonen et al. 2004). While multiple studies have shown exercise to mobilize EPCs, the total amount of physical activity has been associated directly with EPC numbers which is consistent with a dose-response (Adams, Lenk et al. 2004; Sandri, Adams et al. 2005; Luk, Dai et al. 2009). Of great interest is the intensity of exercise required to mobilize EPCs. Most protocols have described symptom-limited exercise testing that is of a vigorous nature (Adams, Lenk et al. 2004; Rehman, Li et al. 2004; Sandri, Adams et al. 2005). While 10 minutes of moderate (~70% of VO₂ max) exercise did not increase circulating EPC numbers, 30 minutes of moderate or intense (~80% VO₂ max) exercise increased EPC numbers (Laufs, Urhausen et al. 2005). This level of intensity is approximately consistent with guideline recommendations for the secondary prevention of CAD (Smith, Allen et al. 2006).

10. Conclusion: A paradigm for cardiovascular risk assessment

From the above discussion, it is clear that cardiovascular risk factors individually and collectively decrease EPC number and function. This includes traditional risk factors such as age, gender, lipids, hypertension and smoking as well as emerging risk factors such as inflammatory diseases and risk factors that are difficult to quantify such as a family history of vascular disease. Moreover, EPC numbers respond to risk factor modification and thus

may provide a dynamic assessment of cardiovascular risk. EPC numbers correlate directly with endothelial function and inversely with Framingham risk score in asymptomatic individuals (Hill, Zalos et al. 2003; Ghani, Shuaib et al. 2005; Chironi, Walch et al. 2007). EPC numbers correlate inversely with the number of vascular beds with subclinical disease in asymptomatic patients (Chironi, Walch et al. 2007) and with cardiovascular disease surrogates such as carotid intima-media thickness after correction for the Framingham risk score and CRP (Fadini, Coracina et al. 2006). We believe that the measurement of EPCs represents a unique opportunity for cardiovascular risk assessment in the primary prevention setting. While patients in the low risk category by traditional risk factors are unlikely to have their risk category altered by EPC measurement, EPC measurement could be of great utility in the asymptomatic patient at intermediate risk of cardiovascular disease. Such a patient could be re-categorized into a low risk category if their EPC count is high or could be deemed suitable for the commencement of medications for risk factor control if the EPC count is low and categorizes the patient at higher risk. Patients who are at high risk by traditional risk-assessment tools or who have established cardiovascular disease would need treatment and would be unlikely to have high EPC counts. This proposed paradigm is illustrated in Figure 1.

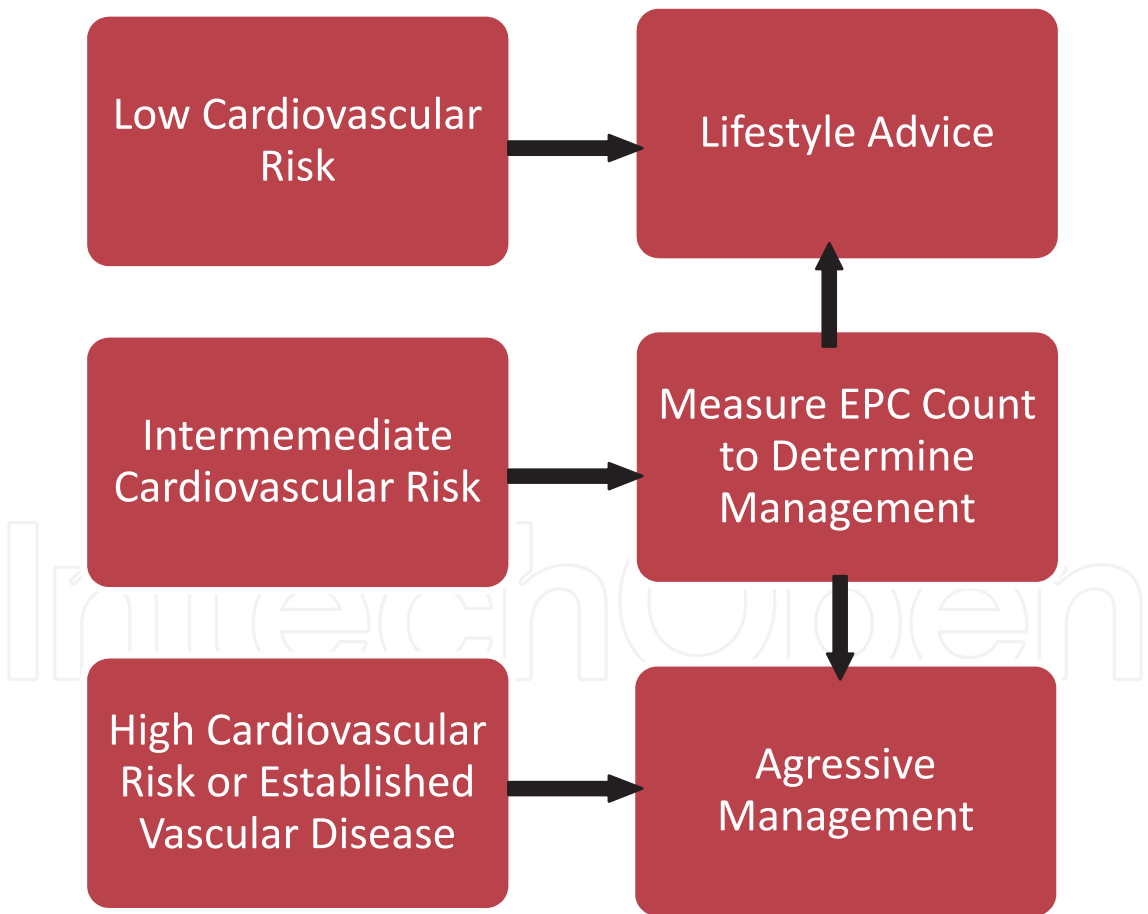


Fig. 1. A Proposed Paradigm for the Prevention of Cardiovascular Disease Utilizing EPCs

The measurement of EPC utilizes flow cytometry which is available in many metropolitan hospitals. The cost of a single EPC count is relatively low costing ~35AUD (30€ or \$40USD)

if EPCs are defined as CD34+KDR+ cells. However, there are several barriers to the implementation of EPC number as a cardiovascular risk prognosticator. Firstly, there is lack of universal agreement on the surface markers that define EPCs. While most studies define EPCs as CD34+KDR+ cells, others also utilize the AC133 surface marker. We propose that the CD34+KDR+ definition should be utilized since EPC number measured in this way have predicted cardiovascular events (Schmidt-Lucke, Rossig et al. 2005; Werner, Kosiol et al. 2005; Kunz, Liang et al. 2006; Wang, Gao et al. 2007). The second major barrier to the implementation of EPC number in routine cardiovascular risk assessment is the lack of established "normal" and "at risk" levels. These need to be established from primary prevention cohorts and can be measured retrospectively in one cohort and then validated in another. Thirdly, a set of standards for the measurement of EPC numbers will be required. This would include studies on the normal biological variability of EPC numbers and accepted standards for acceptable intra-measurement and inter-measurement coefficients of variation. However, this marker of cardiovascular risk has many advantages which include integrating cardiovascular risk in a single measurement and followed serially to assess the impact of risk factor modification on cardiovascular risk.

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Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

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