Curr Atheroscler Rep (2013) 15:321
DOI 10.1007/s11883-013-0321-0

VASCULAR BIOLOGY (RS ROSENSON, SECTION EDITOR)

Biomarkers and Sustainable Innovation in Cardiovascular Drug Development: Lessons from Near and Far Afield

Russell M. Medford · T. Forcht Dagi · Robert S. Rosenson · Margaret K. Offermann

Published online: 20 March 2013

Abstract Future innovative therapies targeting cardiovascular disease (CVD) have the potential to improve health outcomes and to contain rising healthcare costs. Unsustainable increases in the size, cost and duration of clinical trial programs necessary for regulatory approval, however, threaten the entire innovation enterprise. Rising costs for clinical trials are due in large part to increasing demands for hard cardiovascular clinical endpoints as measures of therapeutic efficacy. The development and validation of predictive and surrogate biomarkers, as laboratory or other objective measures predictive or reflective of clinical endpoints, are an important part of the solution to this challenge. This review will discuss insights applicable to CVD derived from the use of predictive biomarkers in oncologic drug development, the evolving role of high density lipoprotein (HDL) in CVD drug development and the impact biomarkers and surrogates have on the continued investment from multiple societal sources critical for innovative CVD drug discovery and development.

Keywords High density lipoprotein · HDL functionality · Macrophage cholesterol efflux · Biomarker · Atherosclerosis · Cardiovascular disease · Clinical trials · Low density lipoproteins · Statins · Predictive · Cost-benefit · Investment · Healthcare costs · Risk · Validation · Adaptive clinical trial · Regulatory pathways · Archived clinical sample · Genetics · Surrogate · Drug development · Oncology

This article is part of the Topical Collection on *Vascular Biology*

R. M. Medford (✉) · T. F. Dagi · M. K. Offermann
The Salutramed Group, Inc., Atlanta, GA, USA
e-mail: rmedford@salutramed.com

M. K. Offermann
e-mail: mkoffermann@salutramed.com

T. F. Dagi
The Division of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA
e-mail: TFD7@hms.harvard.edu

T. F. Dagi
The School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, Northern Ireland, UK

T. F. Dagi
HLM Venture Partners, Boston, MA, USA

R. S. Rosenson
Cardiometabolic Disorders, Mount Sinai Heart, New York, NY, USA
e-mail: robert.rosenson@mssm.edu

R. S. Rosenson
Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Introduction

Notwithstanding a number of important advances in our understanding of molecular and biochemical mechanisms underlying atherosclerosis and its associated risk factors, and despite the success of certain clinically effective therapeutics such as the HMG-CoA reductase inhibitors (statins), cardiovascular disease (CVD) and its associated metabolic disorders remain the leading cause of death and disability in the United States. CVD accounts for over one-third of all US deaths in 2012 [1]. CVD and stroke are also the most costly diseases in the US. They account for almost $300 billion in annual costs, or 16 % of total US health expenditures [1]. By 2030, 40.5 % of the US population is projected to have some form of CVD with a projected total annual cost burden exceeding $800 billion [2].

The translation of basic scientific discoveries into clinically effective therapeutics over the last 20 years has had a significant, but still only a limited impact upon the prevention and treatment of CVD. Large prospective clinical trials have established that pharmacologic therapy can reduce the risk of major cardiovascular (CV) events by 25–30 % when

patients achieve LDL-C-lowering goals using various statins [3]. The mechanisms underlying this residual cardiovascular risk of 65–70 % in statin-treated patients include lipid and non-lipid related factors [4]. While multifaceted risk reduction approaches addressing known risk factors have been proposed [5], the need for new and innovative approaches for the prevention and treatment of CVD extending beyond statins, and specifically the metabolic and vascular processes underlying atherosclerosis, remains in place.

The development of the next generation of cardiovascular therapeutics to address unmet clinical needs is neither straightforward nor assured. The process that creates and brings to the market new therapies to treat disease is complex, long-term, fraught with risk (scientific, clinical, regulatory and commercial) and very capital intensive. The process involves multiple interdependent stakeholders with distinct roles and agendas, including scientists, clinicians, patients, investors, industry, insurers, the government and academia. Given the large annual investment in overall US medical research and development from the pharmaceutical and biotechnology industries ($44 billion in 2008) [6] and the National Institutes of Health ($31 billion in 2012) [7], a working understanding of this stakeholder interdependence by the stakeholders themselves is critical if cardiovascular drug discovery and development is to be valued and funded by society.

A major threat to the enterprise of innovative cardiovascular drug development is the progressive increase in time and expense of conducting clinical trials for regulatory approval. The costs are now estimated to exceed $1 billion for each approved drug, with over 15 years required, on average, to move from laboratory discovery to market approval [8–10]. This cost burden derives in part from formal regulatory hurdles and in part from societal and regulatory demands for near certainty around the safety and clinical efficacy of new drugs prior to approval, as well as their comparative effectiveness. To meet these important standards, huge trials involving thousands of patient-years are required. The costs of clinical trials of this magnitude are unlikely to be sustainable in the face of reduced government support for biomedical research [11] and reductions in funding for research and development by the biopharmaceutical industry and the public and private financial markets [12]. The consequences threaten to affect both the development and clinical availability of new and innovative CV therapeutics and the resources needed to fund the basic and clinical sciences in academia.

One solution that begins to address this threat to innovative CV research and development involves the use of biomarkers [13]. A biomarker is an objectively measured indicator, such as a laboratory or imaging test, of a normal biological, physiological or pathogenic process, or a pharmacologic response to an intervention. A "surrogate marker" is a special type of biomarker that, after validation arrived upon through additional scientific and clinical testing, can be stipulated as a substitute for and predictor of specific clinical endpoints. A clinical endpoint as used in clinical trials is a characteristic or variable that reflects how a patient feels, functions, or survives [13].

New types of biomarkers can serve as predictors of both therapeutic and adverse clinical effects in selected patient populations. A validated surrogate marker for CV disease indications can reduce development time and clinical trial duration and cost. At the same time, the surrogate marker can build confidence in its correlation with and predictive strengths against hard clinical endpoints such as myocardial infarction, stroke and cardiovascular death. A validated surrogate marker pathway to drug approval that offers less expensive but reasonable and compelling, clinically equivalent predictive [surrogate] endpoints may also serve to mitigate risks for investors and may encourage investment.

This review will discuss two important examples of the application of biomarkers to drug development and their influence on both public and private funding of scientific and translational research. The first example is drawn from oncology, which has utilized an integrated and more efficient basic science-clinical trial approach over the last 10 years to great success. The second describes the evolution of HDL in our understanding of basic mechanisms underlying atherosclerosis to illustrate the opportunities and challenges surrounding the creation of validated biomarkers and surrogates in CV drug development. Finally, this review will discuss the role of surrogate markers in modulating investment risk.

Biomarkers and the Development of Novel Cancer Therapeutics: Lessons for Cardiovascular Drug Development

Effective biomarkers and surrogate endpoints have accelerated the development of novel therapeutics in oncology over the last 10 years in ways that reflect the influence of improved understanding of molecular biology and mechanisms of disease on clinical trials design. A number of insights from this dynamic are applicable to the current challenges facing cardiovascular drug development.

Types of cancer that were once categorized and treated as a single disease are now segmented from the perspective of molecular events in their pathogenesis. Predictive biomarkers have been identified and validated and are used to direct therapy in a growing number of tumors, including lung, breast, colorectal, kidney, head and neck cancer, and melanoma [14–18]. Clinical trials that select patients based on predictive biomarkers give rise to enriched populations that reduce the number of patients needed to assess clinical efficacy. As a consequence, the cost and time needed for clinical testing are reduced. In a similar manner, improved understanding of the heterogeneous processes that contribute to atherosclerosis

might lead to distinct targets or biomarkers that could aid in drug development.

Adaptive clinical trials represent another approach to improving the efficiency of clinical development. Adaptive trials test the predictive value of new biomarkers and help determine whether improved outcomes are caused by specific interventions or by intrinsic differences in the rate of progression of the different subtypes of disease. An example of this approach is the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial, in which an initial equal randomization period was followed by an adaptive randomization scheme based on relevant molecular biomarkers [19•, 20, 21]. Four different treatments were evaluated for efficacy in patient groups that differed in their molecular biomarker profiles, and specific treatments were prospectively demonstrated to work with specific subgroups selectively based on the molecular biomarker profiles. The time needed to obtain important clinical information was shortened, and a smaller percentage of patients was subjected to ineffectual treatment because of this innovative clinical design.

While improved survival is often a gold standard for US Food and Drug Administration (FDA) approval of new therapies, several studies with survival as the endpoint have been criticized on ethical grounds. In some cases, in order to maintain clear distinctions between treatment arms, control groups cannot cross over to the new treatment. This impediment presents potential difficulties when one arm trends clearly towards significant benefit. One instance that came to public attention involved a comparison of B-Raf inhibitors to standard chemotherapy in patients with metastatic melanoma whose tumors had activating B-Raf mutations [22•, 23, 24]. Rapid tumor regression and improvement in quality of life was seen in approximately half of patients with B-Raf mutations, in comparison to fewer than 10 % of patients on standard chemotherapy [22•]. The trial achieved its goal of showing a survival benefit, and B-Raf inhibitors are now routinely used [22•, 25].

Regulatory pathways that depend upon hard endpoints such as survival can be onerous. They often take many years to prove and can be criticized if they deny patients quality of life improvements that become evident more rapidly. Thus, it is important to move towards clinical trial designs and approval mechanisms that adapt to patient needs in a safe and ethical manner.

Validation of surrogates and predictive biomarkers requires access to outcome data from multiple clinical trials. Prospective randomized trial design remains the gold standard. The burdens of cost, duration and availability have limited both the number of trials available to validate biomarkers and the tools available for patient management. One expedient that has proven successful in oncology is to use archived serum and tissue samples from blinded randomized studies. This method could also accelerate the validation of new biomarkers for cardiovascular disease.

The validation of Oncotype Dx for estrogen receptor (ER) positive breast cancer relied on archived samples and clinical data from completed randomized clinical trials for much of its validation [26, 27]. ER positive tumors evince a spectrum of possible clinical behavior. One cannot be certain that estrogen blockade alone will suffice to prevent recurrence in any given case, even though it is statistically effective in the ER positive population overall. The consequence of recurrence can be death due to metastatic disease. Clinical guidelines thus recommended cytotoxic chemotherapy for most ER positive patients with tumors greater than 1 cm in size, even though the vast majority of patients on estrogen blockade alone were *not* likely to recur.

Laboratory studies suggested that gene profiles could help identify patients with low risk of recurrence compared to those at high risk who might benefit from chemotherapy. Oncotype Dx utilized gene expression from a panel of 21genes to develop a predictive recurrence score (RS). It focused initially on ER positive breast cancers.

Withholding cytotoxic chemotherapy from a group of patients in order to determine the predictive value of the test would have violated the standard of care and increased the risk of metastatic disease in some patients, raising important ethical concerns. Instead, initial testing was accomplished without putting patients at risk by obtaining and blindly analyzing tissue samples collected from 1982 through 1988 from the randomized National Surgical Adjuvant Breast Cancer Project B-14 trial, where clinical outcomes were tracked over time. The data demonstrated that the recurrence score accurately classified patients into low and high risk, with the low-risk group showing no benefit from cytotoxic chemotherapy and the high-risk group showing reduced rates of recurrence when cytotoxic chemotherapy was used. The use of archived samples not only saved time and money, but also decreased risk to patients with breast cancer.

Recent additional data also derived from archived samples from a distinct randomized clinical trial suggest that Oncotype DX is equally prognostic for hormone receptor–positive, postmenopausal, tamoxifen-treated patients with positive nodes. Chemotherapy provides little, if any, benefit for patients with low RS, despite the presence of positive nodes [28]. The National Comprehensive Cancer Network guidelines include Oncotype Dx for decision-making for early-stage ER positive breast cancer patients, and additional prospective trials are underway to determine whether Oncotype Dx can guide management of additional subgroups of breast cancer [29, 30]. Cost-benefit analyses have shown that Oncotype Dx decreases overall cost of treating breast cancer and improves quality of life in patients who are at low risk for recurrence, and who otherwise would have received cytotoxic chemotherapy [31•, 32].

These studies illustrate the effectiveness of using archived samples linked to randomized clinical trials. Their outcomes can accelerate the development of tools that are useful in drug development and patient management. In oncology, the federal government supported the clinical trials whose samples and data were used for the validation of these tools through clinical cooperative groups. In the cardiovascular arena, in contrast, most trials are funded through the private sector. New policies and protections are needed to provide incentives for the owners of pertinent samples and datasets to make them available for biomarker development and validation.

HDL – Structure vs. Function in the Development of a New CV Biomarker

The history of the evolving role of high density lipoprotein (HDL) as a biomarker for the development of new therapeutic approaches in cardiovascular disease illustrates the challenges and opportunities inherent in the interplay between fundamental discovery science and clinical science. There is considerable evidence for HDL cholesterol (HDL-C) as a biomarker for cardiovascular risk. In multiple, prospective population studies, the first dating back more than 45 years [33], low levels of HDL-C have been consistently and strongly associated with increased risk of coronary heart disease (CHD) events [34]. The associations between low levels of HDL-C and cardiovascular disease (CVD) risk remain statistically significant in multivariate models that adjust for age, sex, non-lipid risk factors and certain lipid risk markers (LDL-C and non-HDL-C). HDL-C contains a heterogenic population of molecules [35]. Epidemiological studies and clinical trials that have measured HDL subclasses have shown that the larger, cholesterol-enriched HDL subclasses [36–38] are more predictive of cardiovascular risk than smaller, cholesterol-depleted HDL subclasses. Based on these studies, the cholesterol carrying capacity of HDL has evolved into a well-established marker of CV risk [39–41].

It remains unclear whether HDL-C plays an active and direct role in human atherosclerosis disease progression and whether it can qualify as a valid target for therapeutic intervention. Molecular genetic studies of HDL metabolism in preclinical animal models have confirmed the key role of HDL as a modulator of atherosclerotic vascular disease [42]. Nevertheless, clinical trials utilizing therapies that increase HDL-C as the surrogate measure of efficacy have failed repeatedly to demonstrate a reduction in the major cardiovascular endpoints (MACE) that include myocardial infarction, cardiovascular death and stroke. Recent examples of negative results include large, well-powered randomized, prospective CV outcome trials with niacin [43–45] and CETP inhibitors [46, 47]. Similar results were obtained in a recent well-powered, human genetic meta-analysis that failed to demonstrate a causal relationship between genetic mechanisms that increase the cholesterol carrying capacity of HDL and the risk of myocardial infarction [48•]. These findings raise serious questions regarding a simple, causal relationship between HDL-C levels per se and atherosclerosis disease progression.

Several lines of evidence, however, suggest that HDL-C acts as an indirect biomarker of disease. Although HDL-C is statistically independent of LDL-C as a CV risk factor, low levels of HDL-C are inversely correlated with the concentration of apolipoprotein B-containing lipoproteins (VLDL and LDL particles) [49, 50]. In analyses of prospective population and clinical trials of lipid modifying therapies that included either LDL particle concentration (LDL-P) or apolipoprotein B, the conventional associations between HDL-C and CVD risk were either diminished or negated [51–53]. These data strongly suggest that HDL-C is simply a biomarker for excess apolipoprotein B-containing lipoproteins. In the aggregate, these findings raise the prospect that HDL-C as conventionally measured is only an indirect biomarker of cardiovascular risk with either no or only a limited role in disease progression, and either limited or no utility as a surrogate marker for predicting CV endpoints in response to therapeutic intervention.

While HDL-C as conventionally measured appears to have failed as a therapeutic surrogate predictive of clinical outcomes so far, an evolving body of work focused on HDL *functionality* raises the possibility of developing a new generation of robust HDL biomarkers for enhanced risk assessment, patient stratification and targeted drug development. Nuclear magnetic resonance (NMR) spectroscopy as a measure of HDL particle concentration (HDL-P) has provided interesting insights into cardiovascular risk. In prospective population studies and clinical trials of lipid modifying therapy, HDL-P provides added incremental information on risk prediction compared to HDL-C, even in models that include LDL-P [51–53]. These more statistically robust studies have also challenged previously held beliefs that large cholesterol-enriched HDL particles were the most cardioprotective. In the VA-HIT trial, small HDL-P was more strongly related to reduced risk than either medium or large HDL-P [52]. The importance of HDL-P as a measure of HDL risk was further supported in a genome wide association study (GWAS) that reported on polymorphisms in phospholipid transfer protein (PLTP). Polymorphisms in PLTP were associated higher total HDL-P and small HDL-P rather than changes in HDL-C [54]. In individuals showing PLTP polymorphisms, small HDL-P proved to be a significant marker of reduced CHD risk.

Our developing understanding of HDL from a functional perspective raises new challenges. For example, we now know that HDL particles undergo constant remodeling and therefore cannot be considered discrete, static, or unvarying entities from a physiological perspective. Static measures have proven

inadequate in characterizing HDL and defining the properties of these anti-atherogenic lipoprotein [55]. The incomplete understanding of macrophage cholesterol efflux has led to a focus on the cholesterol carrying capacity of HDL particles or the terminal measure of macrophage cholesterol efflux. This focus has distracted the cardiovascular field from crucial physiological mechanisms associated with small HDL particles. It is the cholesterol-absent and phospholipid-depleted apo A-I complex that interacts with the macrophage ABCA1 transporter. This is the essential transporter necessary for macrophage cholesterol efflux [56]. Moreover, only 5 % of the cholesterol content in HDL is derived from the macrophage. Thus, an emphasis on HDL-C levels results in a misguided signal regarding the efficiency of the most important step in reverse cholesterol transport.

Although small HDL particles contain less cholesterol than large particles, they have more surface proteins contributing to the anti-oxidant, anti-inflammatory and anti-infective properties of HDL [35, 57–59]. In contrast to failed studies that attempted to increase the cholesterol load of mature, cholesterol-rich particles, the administration or creation of nascent apo A-I complexes (pre-beta HDL or HDL-VS), in order to exploit their interaction with ABCA1 transporter and maturation into small spherical HDL particles, is a pathway that has succeeded in reducing coronary atherosclerosis progression [44, 60, 61]. Clinical studies with an apo A-I inducer have also been initiated [61]. This illustrates the critical role clinical testing can play on the validation and utility of surrogate markers in general, and HDL-functional assays in particular.

In the future, the use of HDL functionality assays can be expected to help optimize targets for HDL modifying therapies. The integration of structure-function relationships can be expected as part of any future effort to characterize the proteome of discrete subpopulations of HDL particles. However, this transition will require high throughput, cost-effective, validated measures of the major HDL functions as well as coordination with and access to prospective cardiovascular endpoint trials and stored serum and biological samples. A new generation of validated, HDL function-based biomarker(s) offers the potential to dramatically reduce the cost and time of bringing innovative CV therapeutics to the clinic through enhanced drug development decision making, smaller and faster prospective clinical trials and ultimately, regulatory approval based on these predictive and surrogate biomarkers.

Surrogates and Their Impact on Investment: A Primer

The commercial success of a drug is determined by its market size, market share and price, and by the cost factors associated with its manufacture and distribution. These variables also characterize a drug's profitability. When deciding whether to undertake an investment, financial investors are driven by the financial returns an investment is projected to return. The minimum required return, sometimes called the hurdle rate, reflects the level of risk assigned to the investment. The higher the risk profile, the higher the hurdle rate.

Risk profiles incorporate both real risks, whose probabilities can be estimated objectively and with fair precision, and perceived or imputed risks, whose contributions are assigned subjectively and often arbitrarily, but which carry no less influence. The risk profile is used not only to establish a hurdle rate, but also to compare the relative attractiveness of investment opportunities. Investors have differing appetites for risk. Risk is never eliminated, nor is the lower risk opportunity invariably the one chosen. Irrespective of what constitutes "acceptable" risk to any given investor, what matters ultimately is whether, once an acceptable risk profile has been achieved, the risks can be managed, and the hurdle rate achieved.

A major barrier to investment in drug development is that a large part of the investment risk is systematic and cannot be mitigated by diversification. Classical risks characterized as systematic include toxicity, effectiveness as measured against endpoints in phased clinical trials, regulatory approval, pricing, reimbursement, adoption, the term, or time before the investor will see a return on investment, and overall capital efficiency. In the current environment, comparative effectiveness considerations must be added to the list.

The size and dynamics of the cardiovascular market space make this an inherently attractive area for investment, despite the systematic investment risks. The deployment of appropriately validated surrogate markers in the cardiovascular arena may mitigate these risks by shortening the duration and shrinking the size of trials, particularly those in which treatment effects would otherwise require huge numbers of patients studied over many years.

Many investors, for example, for reasons both logical and arbitrary, are reluctant to invest before Phase II data are available. Validated surrogate markers are able to accelerate Phase II trials, provide useful insights into mechanisms of action and enhance strategic assessments of trials data [13]. The impact of shorter and smaller trials can be calculated [62]. Improvement in any of these areas could reduce phased clinical trials risks and improve the investment risk profile. Nevertheless, it is fundamentally important to determine the fidelity of the marker to the clinical outcome in question; the ease with which the surrogate can be measured; the extent of cost saving; and whether the data that emerge will suffice to drive regulatory approval, adoption and reimbursement [63].

Summary

Predictive and surrogate biomarkers are often used to accelerate phased clinical trials and reduce the costs of therapeutic drug

development. They have an important role in decision making through Phase II clinical trials, yet highly validated biomarkers utilized for Phase III trials or for market approval decisions by regulatory authorities in the field of cardiovascular drug development are becoming increasingly rare. A new generation of biomarkers are needed to delineate enriched populations in CV disease and to reduce the duration, size and cost of a clinical trial program leading to regulatory approval for a specific CV disease indication. Validated biomarkers can reduce the exposure of patients to clinical trials from which they are unlikely to benefit and serve as putative companion diagnostics to identify patients most likely to benefit.

New predictive and surrogate biomarkers may come from many sources, including advances in our scientific understanding of HDL lipoprotein function [64], inflammation and inflammatory markers such as VCAM-1 [65, 66], vascular molecular imaging platforms [67•] or through systems biology [68•]. Irrespective of their derivation, candidate biomarkers can and should be accelerated in their development and validation in blinded studies using archived samples from randomized clinical outcome trials, similar to the approach that has been used for some oncologic biomarkers.

Through the Accelerated Approval Pathway, the FDA can approve new drugs targeting serious and life-threatening conditions using biomarkers that are "reasonably likely based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity" [69]. While not originally intended for chronic cardiovascular and metabolic disease indications, Accelerated Approval potentially provides a rational, staged pathway to cardiovascular surrogate biomarker development when used in conjunction with a rigorous evaluation methodology [13].

Validated biomarkers have a major impact on assessing the proof of concept of a new therapeutic product, thereby affecting the willingness of financial stakeholders—non-for-profit, governmental, philanthropic, for-profit or institutional—to invest. Without validated biomarkers and a staged approach to regulatory approval to increase confidence and mitigate risk [70•], the current model for commercial drug development, relying on huge and expensive cardiovascular endpoint trials, is not likely to be sustainable from a financial stakeholder standpoint. This has already had a chilling effect on scientific innovation and its translation into clinical trials in the fields of atherosclerosis and associated metabolic diseases such as diabetes.

Conclusion

In conclusion, the use of surrogates in phased clinical drug development through Phase II is based on the calculus that the value of surrogate endpoints on the whole outweighs the risks that the surrogate may not reflect ultimate hard clinical outcomes. The challenge in the cardiovascular arena is to improve and validate the library of available biomarkers such that the same risk/benefit calculus can be applied across the entire drug development process through to regulatory approval. The lack of adequate surrogates and predictive biomarkers, and with them, the lack of new, clinically available and innovative therapeutic approaches to cardiovascular disease, is the social cost to be paid for a reluctance to integrate emerging scientific information into the methodology and standards for drug development.

Conflict of Interest Russell M. Medford declares that he has no conflicts of interest.

T. Forcht Dagi is a board member and has stock options with Axela Biosciences, consultancy for and has stock/stock options with Syngile, Inc, and is a paid consultant and has travel/accommodations covered or reimbursed by Broadview, and by Masimo, Inc.

Robert S. Rosenson is a consult to Abbott, Daiichi Sankyo, Kowa, LipoScience, and Sanofi-Aventis, has grants/grants pending with Sanofi-Aventis, received honoraria from Kowa, received royalties from UpToDate Medicine and has stock/stock options with LipoScience.

Margaret K. Offerman declares that she has no conflicts of interest.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation. 2012;125:e2–e220.
2. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011;123:933–44.
3. Alsheikh-Ali AA, Lin JL, Abourjaily P, et al. Prevalence of low high-density lipoprotein cholesterol in patients with documented coronary heart disease or risk equivalent and controlled low-density lipoprotein cholesterol. Am J Cardiol. 2007;100:1499–501.
4. Mora S, Wenger NK, Demicco DA, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. Circulation. 2012;125:1979–87.
5. Lonn E, Bosch J, Teo K, et al. The polypill in the prevention of caridovascular disease. Key concepts, current status, challenges and future directions. Circulation. 2010;122:2078–88.
6. Shackleford B. Health and defense applications account for 40 % of business R&D in the United States. In: InfoBrief: National Center for Science and Engineering Statistics: National Science Foundation. 2012. http://www.nsf.gov/statistics/infbrief/nsf12329/.
7. NIH. The NIH Almanac - Appropriations. In: National Institutes of Health. 2013. http://www.nih.gov/about/almanac/appropriations/part2.htm.
8. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ. 2003;22:151–85.

9. Morgan S, Grootendorst P, Lexchin J, et al. The cost of drug development: a systematic review. Health Policy. 2011;100:4–17.
10. Vernon JA, Golec JH, Dimasi JA. Drug development costs when financial risk is measured using the Fama-French three-factor model. Health Econ. 2010;19:1002–5.
11. Couzin J, Miller G. NIH budget. Boom and bust. Science. 2007;316:356–61.
12. Burrill GS. Biotech 2012: innovating in the New Austerit. San Francisco: Burrill and Company, LLC; 2012. p. 2012.
13. Institute of Medicine of the National Academies Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease, Board on Health Care Services, Board on Health Sciences Policy, and Food and Nutrition Board. Evaluation of biomarkers and surrogate endpoints in chronic disease. In: Micheel CM, Ball JR, editors. Washington: The National Academies Press; 2010. p. 1–234.
14. Mehta R, Jain RK, Badve S. Personalized medicine: the road ahead. Clin Breast Cancer. 2011;11:20–6.
15. Oakman C, Santarpia L, Di Leo A. Breast cancer assessment tools and optimizing adjuvant therapy. Nat Rev Clin Oncol. 2010;7:725–32.
16. Escudier B, Szczylik C, Porta C, et al. Treatment selection in metastatic renal cell carcinoma: expert consensus. Nat Rev Clin Oncol. 2012;9:327–37.
17. Custodio A, Feliu J. Prognostic and predictive biomarkers for epidermal growth factor receptor-targeted therapy in colorectal cancer: beyond KRAS mutations. Crit Rev Oncol Hematol. 2013;85:45–81.
18. Rao SD, Fury MG, Pfister DG. Molecular-targeted therapies in head and neck cancer. Semin Radiat Oncol. 2012;22:207–13.
19. • Kim ES, Herbst RS, Wistuba II, et al. The BATTLE trial: personalizing therapy for lung cancer. Cancer Discov. 2011;1:44–53. *This describes a new prospective trial design in which equal randomization is combined with adaptive randomization utilizing biomarker data. Patients were progressively assigned to the treatment with greatest potential benefit based on cumulative data.*
20. Gold KA, Kim ES, Lee JJ, et al. The BATTLE to personalize lung cancer prevention through reverse migration. Cancer Prev Res (Phila). 2011;4:962–72.
21. Rubin EH, Anderson KM, Gause CK. The BATTLE trial: a bold step toward improving the efficiency of biomarker-based drug development. Cancer Discov. 2011;1:17–20.
22. • Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507–16. *This describes a prospective randomized trial in which the difference between the two arms was profound and evident early in the trial. While the original trial design did not allow for crossover, the data and safety monitoring board determined midway through the trial that both the overall survival and progression-free survival end points had met prespecified criteria for statistical significance in favor of the new treatment, and thus recommended that crossover be allowed.*
23. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010;363:809–19.
24. Harmon A. New drugs stir debate on rules of clinical trials. New York Times. 2010. http://www.nytimes.com/2010/09/19/health/research/19trial.html?pagewanted=all.
25. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380:358–65.
26. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006;24:3726–34.
27. Kirk R. Risk factors. Oncotype DX assay predicts local recurrence in breast cancer. Nat Rev Clin Oncol. 2010;7:300.
28. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol. 2010;11:55–65.
29. Ramsey SD, Barlow WE, Gonzalez-Angulo AM, et al. Integrating comparative effectiveness design elements and endpoints into a phase III, randomized clinical trial (SWOG S1007) evaluating oncotypeDX-guided management for women with breast cancer involving lymph nodes. Contemp Clin Trials. 2013;34:1–9.
30. Zujewski JA, Kamin L. Trial assessing individualized options for treatment for breast cancer: the TAILORx trial. Future Oncol. 2008;4:603–10.
31. • Kim C, Paik S. Gene-expression-based prognostic assays for breast cancer. Nat Rev Clin Oncol. 2010;7:340–7. *This reviews the progress that has occurred in validating predicitive biomarkers using archived samples from completed randomized clinical studies.*
32. Joh JE, Esposito NN, Kiluk JV, et al. The effect of Oncotype DX recurrence score on treatment recommendations for patients with estrogen receptor-positive early stage breast cancer and correlation with estimation of recurrence risk by breast cancer specialists. Oncologist. 2011;16:1520–6.
33. Gofman JW, Young W, Tandy R. Ischemic heart disease, atherosclerosis, and longevity. Circulation. 1966;34:679–97.
34. Di Angelantonio E, Sarwar N, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302:1993–2000.
35. Rosenson RS, Brewer Jr HB, Chapman MJ, et al. HDL measures, particle heterogeneity, proposed nomenclature, and relation to atherosclerotic cardiovascular events. Clin Chem. 2011;57:392–410.
36. Asztalos BF, Collins D, Cupples LA, et al. Value of high-density lipoprotein (HDL) subpopulations in predicting recurrent cardiovascular events in the Veterans Affairs HDL Intervention Trial. Arterioscler Thromb Vasc Biol. 2005;25:2185–91.
37. Asztalos BF, Cupples LA, Demissie S, et al. High-density lipoprotein subpopulation profile and coronary heart disease prevalence in male participants of the Framingham Offspring Study. Arterioscler Thromb Vasc Biol. 2004;24:2181–7.
38. Musunuru K, Orho-Melander M, Caulfield MP, et al. Ion mobility analysis of lipoprotein subfractions identifies three independent axes of cardiovascular risk. Arterioscler Thromb Vasc Biol. 2009;29:1975–80.
39. Expert panel on detection, evaluation and treatment of high blood cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285:2486–97.
40. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Atherosclerosis. 2007;194:1–45.
41. Gotto Jr AM, Brinton EA. Assessing low levels of high-density lipoprotein cholesterol as a risk factor in coronary heart disease: a working group report and update. J Am Coll Cardiol. 2004;43:717–24.
42. Reardon CA, Getz GS. Mouse models of atherosclerosis. Curr Opin Lipidol. 2001;12:167–73.
43. AIM-HIGH Investigators, Boden WE, Probstfield JL, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365:2255–67.
44. Tardif JC, Gregoire J, L'Allier PL, et al. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. JAMA. 2007;297:1675–82.
45. Merck Announces HPS2-THRIVE Study of TREDAPTIVE™ (Extended-Release Niacin/Laropiprant) Did Not Achieve Primary Endpoint. 2012. http://www.mercknewsroom.com/press-release/prescription-medicine-news/merck-announces-hps2-thrive-study-tredaptive-extended-relea.

46. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007;357:2109–22.
47. Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med. 2012;367:2089–99.
48. • Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet. 2012;380:572–80. *A Mendelian randomization design was used to test causality between HDL levels and myocardial infarction that utilized a data set of 19,139 cases of myocardial infarction and 50,812 myocardial-infarction-free controls. This paper demonstrated that genetically increased levels of plasma HDL cholesterol were not causally associated with risk of ischaemic heart disease. This approach might prove useful in building evidence for causality between next generation CV predictive and surrogate biomarkers and CV clinical endpoints*.
49. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. Am J Cardiol. 2002;90:22i–9.
50. Gotto Jr AM, Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Circulation. 2000;101:477–84.
51. Mackey RH, Greenland P, Goff Jr DC, et al. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: MESA (multi-ethnic study of atherosclerosis). J Am Coll Cardiol. 2012;60:508–16.
52. Otvos JD, Collins D, Freedman DS, et al. Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. Circulation. 2006;113:1556–63.
53. Parish S, Offer A, Clarke R, et al. Lipids and lipoproteins and risk of different vascular events in the MRC/BHF Heart Protection Study. Circulation. 2012;125:2469–78.
54. Vergeer M, Boekholdt SM, Sandhu MS, et al. Genetic variation at the phospholipid transfer protein locus affects its activity and high-density lipoprotein size and is a novel marker of cardiovascular disease susceptibility. Circulation. 2010;122:470–7.
55. Rosenson RS, Brewer Jr HB, Ansell B, et al. Translation of HDL function into clinical practice: current prospects and future challenges. Submitted.
56. Rosenson RS, Brewer Jr HB, Davidson WS, et al. Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. Circulation. 2012;125:1905–19.
57. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499–502.
58. Camont L, Chapman MJ, Kontush A. Biological activities of HDL subpopulations and their relevance to cardiovascular disease. Trends Mol Med. 2011;17:594–603.
59. Kontush A, Chantepie S, Chapman MJ. Small, dense HDL particles exert potent protection of atherogenic LDL against oxidative stress. Arterioscler Thromb Vasc Biol. 2003;23:1881–8.
60. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA. 2003;290:2292–300.
61. Waksman R, Torguson R, Kent KM, et al. A first-in-man, randomized, placebo-controlled study to evaluate the safety and feasibility of autologous delipidated high-density lipoprotein plasma infusions in patients with acute coronary syndrome. J Am Coll Cardiol. 2010;55:2727–35.
62. Fox NC, Cousens S, Scahill R, et al. Using serial registered brain magnetic resonance imaging to measure disease progression in Alzheimer disease: power calculations and estimates of sample size to detect treatment effects. Arch Neurol. 2000;57:339–44.
63. Katz R. Biomarkers and surrogate markers: an FDA perspective. NeuroRx. 2004;1:189–95.
64. Rosenson RS, Brewer Jr HB, Ansell B, et al. Concept of dysfunctional HDL in clinical practice. Submitted.
65. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol. 2012;32:2045–51.
66. Tardif JC, McMurray JJ, Klug E, et al. Effects of succinobucol (AGI-1067) after an acute coronary syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2008;371:1761–8.
67. • Quillard T, Libby P. Molecular imaging of atherosclerosis for improving diagnostic and therapeutic development. Circ Res. 2012;111:231–44. *An excellent review of next generation CV imaging approaches that measure the dynamic biology and function of the atherosclerotic plaque as potential next generation CV biomarkers for CV drug discovery, development and approval*.
68. • Califf RM, Shah SH, Newby LK. Biomarker bonanza? J Am Coll Cardiol. 2010;55:1197–9. *A short, well-argued but cautionary counterpoint to this review's positive assessment of biomarkers and their potential to impact CV drug discovery and development*.
69. FDA. 21CFR314 - Subpart H–Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. In: 21. Edited by Government U. Code of Federal Regulations; 2012. CFR - Code of Federal Regulations Title 21, Volume 5, Subpart H–Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314&showFR=1&subpartNode=21:5.0.1.1.4.8.
70. • Eichler HG, Oye K, Baird LG, et al. Adaptive licensing: taking the next step in the evolution of drug approval. Clin Pharmacol Ther. 2012;91:426–37. *A comprehensive review of recent proposals for adaptive licensing (AL), which proposes a fundamental change in the current, binary decision paradigm for drug development and approval. AL incorporates a phased, progressive and flexible regulatory decision-making process that recognizes the changing uncertainties of drug safety and efficacy during clinical development and after approval*.