Use of Multiple Biomarkers to Estimate Cardiovascular Drug Efficacy: Advantage of a PRE Score

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Abstract

In cardiovascular disease, drugs are targeted toward normalizing a single risk factor, the on-target effect. The ultimate goal of drug treatment is to provide long-term cardiovascular organ protection. In recent years, several trials have shown that drugs with promising effects on the on-target risk factor failed to improve long-term cardiovascular protection. One explanation for these failures is that a drug does not only affect the risk factor to which it is targeted but also other

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parameters, off-target effects, which may also affect long-term cardiovascular outcomes. The drug effect on these off-target effects may be as large or even larger than the on-target effect. The off-target drug effects may consequently have an important impact on the drug effect on cardiovascular outcomes.

This chapter provides an overview of on-target and off-target effects of drugs used in cardiovascular risk management. Keynote in this chapter is that ignoring off-target effects of a drug may lead to severe misinterpretations about the long-term cardiovascular protective effect, with major consequences for society and individual patients. To solve this problem, all effects of a drug should be incorporated into a risk algorithm to obtain a more accurate estimation of the drug effect on long-term cardiovascular outcome.

Keywords

Biomarkers • Drug effects • Cardiovascular complications • Clinical trials • Drug development

Abbreviations

ACEi	Angiotensin-converting-enzyme inhibitor
ADVANCE	Action in diabetes and vascular disease: preterax and diamicron MR-controlled evaluation
ALTITUDE	Aliskiren trial in type 2 diabetes using cardiorenal end points
ARB	Angiotensin receptor blocker
DRI	Direct renin inhibitor
HDL-C	High-density lipoprotein cholesterol
hs-CRP	High-sensitivity C-reactive protein
IDNT	Irbesartan diabetic nephropathy trial
LDL-C	Low-density lipoprotein cholesterol
NT-proBNP	N-terminal pro-braintype natriuretic peptide
PRE score	Parameter response efficacy score
RAAS	Renin-angiotensin-aldosterone system
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study
UKPDS	UK Prospective Diabetes Study

Key Facts

- Cardiovascular disease is a major global health concern, accounting for four million deaths in Europe each year.
- Cardiovascular disease is usually characterized by systemic atherosclerosis, which is a process that involves endothelial plaque formation eventually in micro- and macro-vascular disease.
- In order to slow down this progress and to prevent occurrence of fatal or nonfatal cardiovascular complications, many patients require multiple drug treatments.

- In the past 20 years, several treatments have been proven effective in reducing cardiovascular events, and this has resulted in a steady decrease in the incidence of cardiovascular disease.
- However, with an increasing prevalence of obesity in both developed and developing countries, combined with high salt intake, consumption of fatty foods, a sedentary lifestyle, and ongoing smoking habits, it is questionable whether the achievements in reducing cardiovascular morbidity and mortality can be sustained on the long term.
- New innovative treatment strategies are recommended to mitigate the burden of cardiovascular disease.

Definitions

Biomarker A laboratory measurement that serves as an indicator of a physiological or pathophysiological process or as a response to treatment which affects such a process.

Cardiovascular risk factor A biomarker which has a direct causal relationship with cardiovascular disease.

Dose finding The process to find the dose of the drug with optimal efficacy and safety.

Hard outcome clinical trial Drug study in which the actual long-term effect of a drug (e.g., preventing myocardial infarction or stroke) is established on clinically meaningful outcomes.

On-target effect Drug effect on the cardiovascular risk factor to which the drug is targeted to.

Off-target effect Drug effects on parameters beyond the on-target effect.

PRE score Algorithm which involves short-term drug-induced changes in on-target and many off-target cardiovascular risk markers and integrates these short-term changes into a score which denotes the chances of long-term cardiovascular risk change (reduction or increase).

Renin-angiotensin-aldosterone system (RAAS) Hormonal system which regulates sodium and water excretion and blood pressure.

Risk engine Algorithms such as Framingham, UKPDS, and ADVANCE which are developed to provide individual long-term (i.e., 5 or 10 years) risk estimations to develop cardiovascular complications based on the individual presence of cardiovascular risk factors including age, gender, smoking habits, and diabetes.

Introduction

Cardiovascular protective drugs are targeted toward an effect on a single cardiovascular risk marker. For example, a cardiovascular protective drug is targeted toward lowering blood pressure (for antihypertensive drugs), toward changing lipid profiles (with either low-density lipoprotein (LDL)-lowering or high-density lipoprotein (HDL)-increasing drugs), or toward lowering HbA1c (for oral glucose-lowering drugs). However, targeting a drug toward a single cardiovascular risk factor is not a goal at itself but a mean to determine whether a drug is organ protective. In current drug development processes, a drug is considered to be organ protective if the drug has a substantial effect on the cardiovascular risk factor which it is targeted to within a short time period (e.g., 3 or 6 months), the on-target effect. The assumption made is that the on-target effect will translate into long-term cardiovascular protection and that the drug does not have any other effect on risk factors, off-target effects, that may influence long-term outcome as well. This implies that the on-target drug effect serves as a surrogate/proxy to estimate the long-term cardiovascular efficacy. If positive, this estimation justifies the conduct of a large hard outcome clinical trial in which the actual long-term protective effect (e.g., preventing myocardial infarction or stroke) is established in a time period of about 4 years. Safety of a drug is typically ascertained by monitoring the drug effect on a regular set of "safety" parameters, which are usually less rigorously determined compared to the drug effect on the on-target parameter. This approach of estimating long-term cardiovascular protection has resulted in registration and authorization of several drugs which are currently used in clinical practice (Cohen 2010, 856–865; Zhao et al. 2009, 315–325).

Off-Target Effects

The fact that a drug has a substantial effect on the cardiovascular risk factor which it is targeted to does not necessarily imply that the drug delivers the expected long-term cardiovascular protection. Recent cases have illustrated this notion. Sibutramine was launched in 1999 as a weight-lowering drug which should improve cardiovascular outcome. However, a few years after registration, excessive cases of hypertension and tachycardia were reported leading to cardiovascular events among sibutramine users. Therefore, in 2010, European authorities decided to suspend marketing authorization (James et al. 2010, 905–917). Rosiglitazone received marketing authorization in 2000 as an HbA1c-lowering drug, which was supposed to improve prognosis in patients with type 2 diabetes. However, after its introduction to the market, meta-analyses revealed that rosiglitazone increased risk of myocardial infarction and heart failure, despite its consistent HbA1c-lowering effect. The increased heart failure incidence could be attributed to renal tubular sodium retention leading to excessive extracellular fluid retention and weight gain, which fueled discussions about the safety of rosiglitazone. Eventually, marketing authorization of rosiglitazone was suspended in 2010 (Blind et al. 2011, 213–218; Nissen and Wolski 2010, 1191–1201). The development program of torcetrapib, a cholesteryl

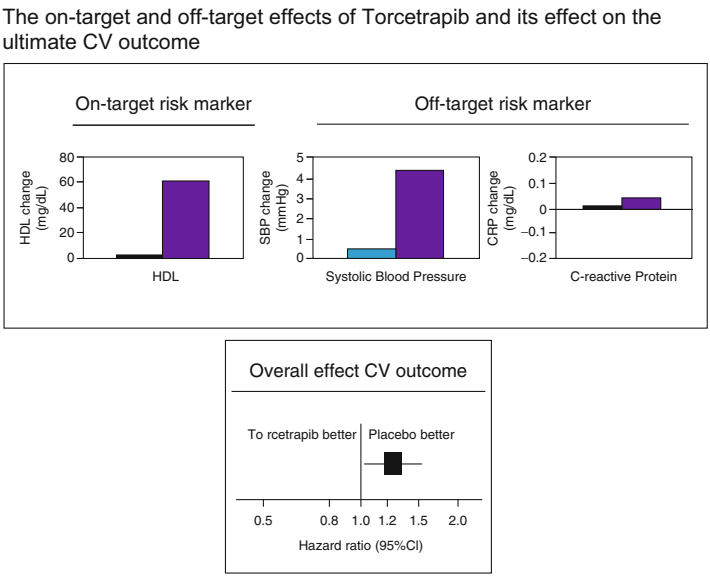

Fig. 1 Effect of the cholesteryl esterase protein inhibitor torcetrapib on on-target (HDL-C) and off-target risk markers and cardiovascular outcome (Data derived from (Barter et al. 2007, 2109–2122). *CI* confidence interval, *HDL-C* high-density lipoprotein cholesterol)

ester transfer protein-inhibiting and high-density lipoprotein cholesterol (HDL-C)-raising drug, was prematurely terminated, because a hard outcome trial showed no improvement in cardiovascular outcome despite increases in HDL cholesterol (Barter et al. 2007, 2109–2122). Additional investigations revealed that this unexpected finding was attributable to a rise in blood pressure as a consequence of increased mineralocorticoid activity, which possibly counteracted the beneficial effect of the drug on HDL-C (Fig. 1; Hu et al. 2009, 2211–2219; Sofat et al. 2010, 52–62). A more recent example of a drug in this drug class is dalcetrapib. In a large outcome trial, the drug indeed increased HDL cholesterol, but it did not lead to significant reductions in cardiovascular risk compared to placebo. Dalcetrapib increased systolic blood pressure and C-reactive protein. These effects may have increased cardiovascular risk and may have blunted the degree of cardiovascular protection with dalcetrapib (Schwartz et al. 2012).

These cases of drug failure in late-stage drug development teach us that targeting a drug to a single biomarker may lead to serious misinterpretations of the actual long-term drug effect, with major consequences for society and individual patients. In all these cases, the drug had effects on other parameters than the target risk parameter alone. Currently, these so-called off-target effects are considered as side effects, which implies less rigorous measurement and reporting. Estimating the drug effect on cardiovascular morbidity or mortality by only taking the on-target drug effect into account may be problematic. Firstly, the off-target effects may also influence long-term cardiovascular protection as shown in Fig. 2.

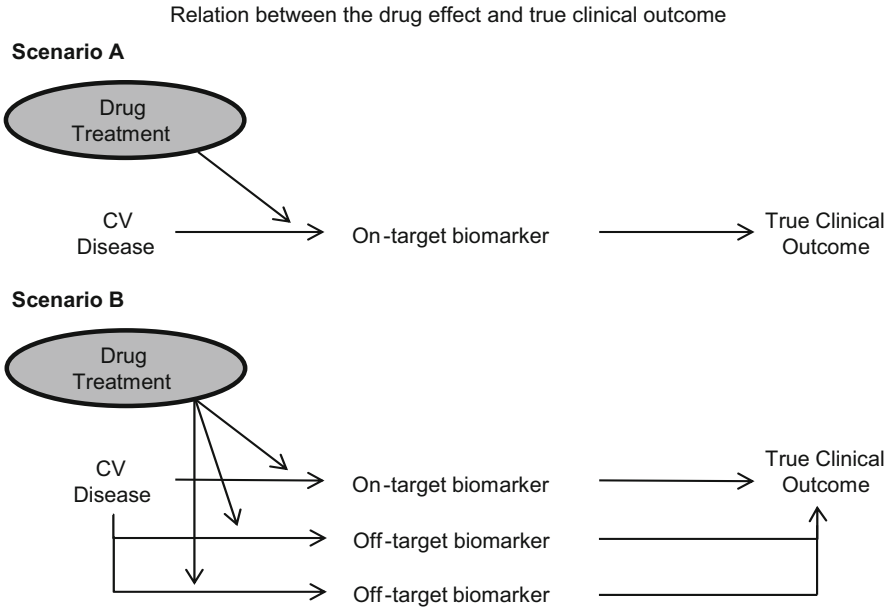

Fig. 2 Representation of on-target and off-target biomarkers determining true clinical outcome. In scenario A, the drug is assumed to affect the on-target biomarker alone, which completely explains the drug effect on true clinical outcome. In scenario B, the drug is assumed to affect off-target biomarkers as well, which also contribute to the ultimate drug effect on the true clinical outcome. *CV* Cardiovascular

Secondly, the response in the on-target and off-target parameters may be different between individuals. For example, angiotensin receptor blockers are registered for blood pressure lowering. However, these drugs also decrease albuminuria and hemoglobin and increase serum potassium. It appears that individual patients show a wide variability in responses in these multiple parameters, indicating that the response in the off-target parameters cannot be estimated from the response in blood pressure. As drug-induced changes in blood pressure, albuminuria, hemoglobin, and serum potassium are all associated with cardiovascular risk, combining the drug effect on multiple parameters may be a more rational approach to estimate drug effects on hard cardiovascular outcomes instead of using the drug effect on a single parameter.

A New Proposal: The PRE Score

How can a drug effect on multiple biomarkers be integrated into a composite drug response which acquires a more accurate estimation of the long-term drug effect? First, insights must be obtained what cardiovascular risk factors are affected during

drug treatment on short term and to what extent these changes in risk factors influence long-term cardiovascular outcome. Then, these on-target and off-target effects should be integrated into a composite response score which relates the change in multiple parameters to the long-term cardiovascular outcome. Such composite risk scores consisting of multiple risk markers already exist for predicting cardiovascular risk of individual patients. A well-known example is the Framingham risk score. Similar multiple parameter scores should be developed for predicting a drug effect on cardiovascular outcomes as well. One such score, the multiple risk parameter response efficacy (PRE) score has been developed. This score involves short-term drug-induced changes in on-target and many off-target cardiovascular risk markers and integrates these short-term changes into a score which denotes the chances of long-term cardiovascular risk change (reduction or increase) (Fig. 3).

The PRE score was tested and validated in already completedrandomized controlled trials in patients with type 2 diabetes and nephropathy either assigned to losartan or placebo (RENAAL trial) or irbesartan or placebo (IDNT trial). Both losartan and irbesartan are registered as antihypertensive drugs. As shown in Fig. 4, both losartan and irbesartan appeared to have *nine* short-term off-target effects beyond blood pressure lowering. Changes in any single risk marker failed to predict the ultimate drug effect on renal/CV outcome in the trials. However, the PRE score, integrating all available risk markers, accurately predicted the ultimate drug effect on long-term cardiovascular outcome (Fig. 5; Smink et al. 2014b, 208–215). Subsequently, the PRE score was validated by predicting the long-term effect of a direct renin inhibitor (DRI) aliskiren on top of conventional RAAS-blocking agents (ACEi or ARB). It was shown that aliskiren, in contrast to what was expected based on estimations of the on-target drug effect, would only moderately improve renal and cardiovascular outcomes (Smink et al. 2014a, 434–441). The early termination of the ALTITUDE trial confirmed the lack of effect of aliskiren on top of conventional RAAS blockade (Parving et al. 2012, 2204–2213).

The PRE Score and Dose Finding

Another aspect to consider is that off-target and on-target effects of a drug may be dose dependent. Proper dose selection is required to provide information on the dose beyond which no additional cardiovascular protection will be established or even harm as a result of off-target effects setting off the on-target effect. Choosing the right dose for the hard outcome trial is a crucial decision in the design of trials, and a wrong dose selection may result into failure of the trial. An example of the wrong dose selection is the avosentan drug development. In a phase 2b study with the endothelin antagonist avosentan, dose-dependent reductions in albuminuria were shown with an apparent maximum albuminuria-lowering effect of avosentan at doses of 10 mg/day. Higher doses up to 50 mg/day were tested but they had no additional effect on albuminuria, but higher avosentan doses dose-dependently increased body weight as a consequence of fluid retention. For the phase 3 trial

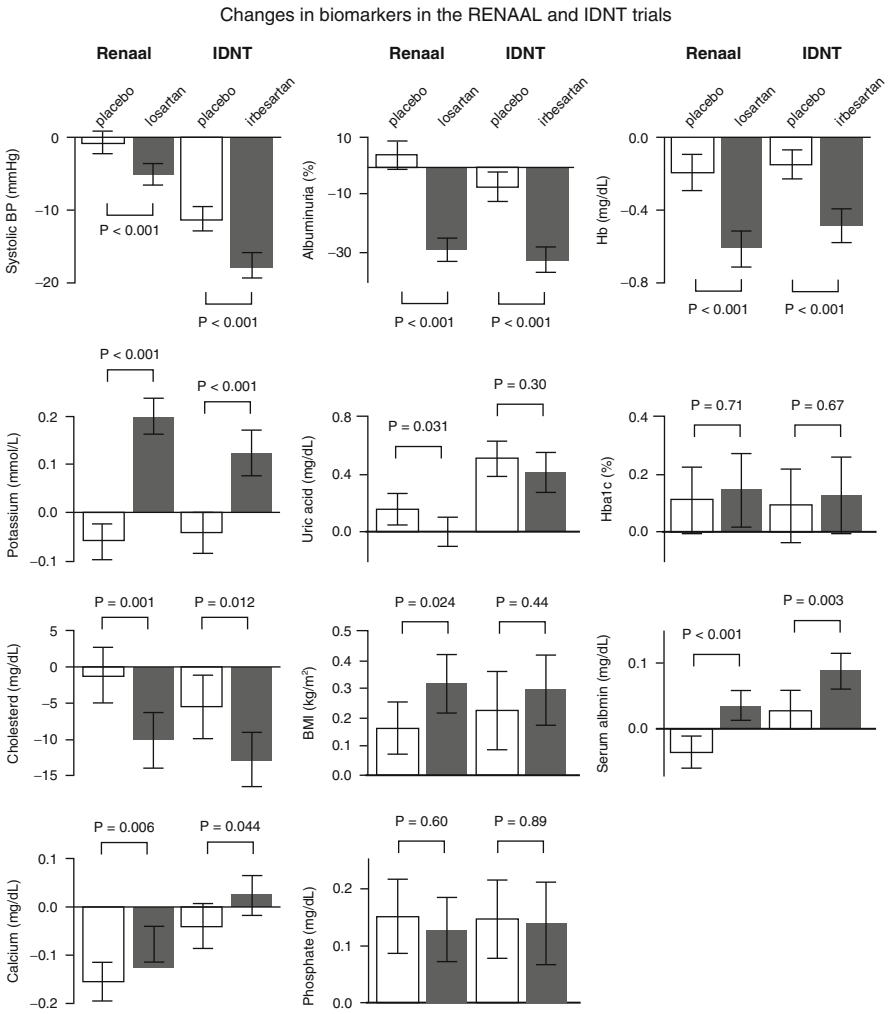

Fig. 3 Change in biomarkers after 6 months placebo or ARB treatment in the RENAAL and IDNT trials. *ARB* angiotensin receptor blocker, *IDNT* Irbesartan Diabetic Nephropathy Trial, *RENAAL* Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan trial (With permission from *Clinical Pharmacology and Therapeutics*)

with avosentan in patients with diabetic nephropathy, it was decided to use a 25 mg/day and 50 m/g dose (Wenzel et al. 2009, 655–664). Unfortunately, the phase 3 trial was early terminated due to excesses of heart failure and mortality due to fluid retention in the avosentan groups (Mann et al. 2010, 527–535). Of course, it is always easy to judge dose selection in hindsight, but this example illustrates the importance of involving off-target drug effects in the dose selection during drug development. Currently, dose selection is based on changes in a single on-target risk

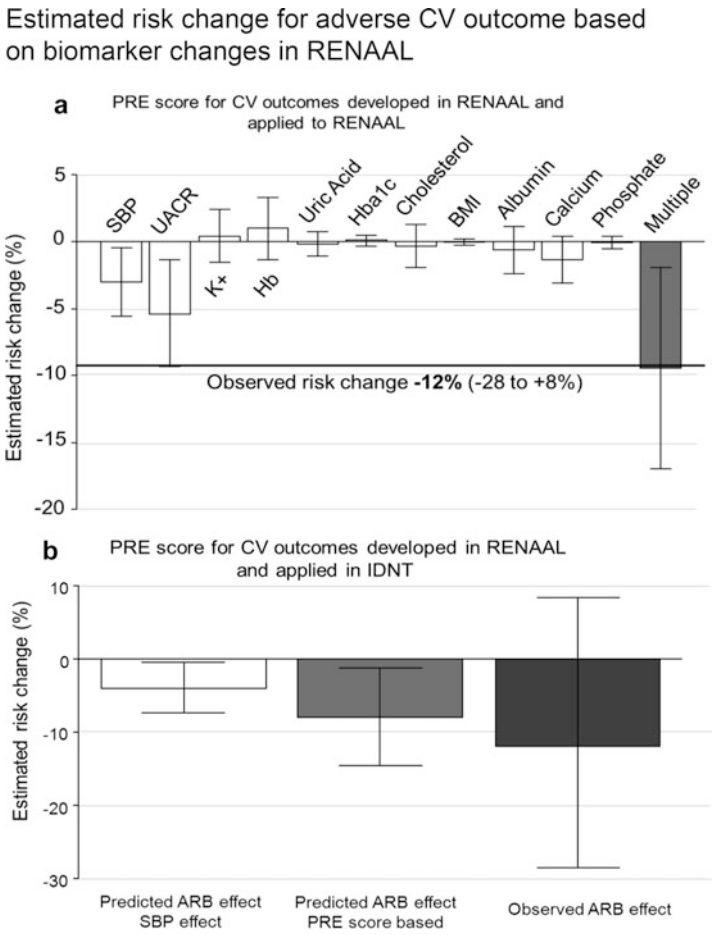

Fig. 4 Observed and predicted long-term relative renal and cardiovascular risk change (%) based on single and multiple PRE scores. The actual observed treatment effect is indicated by the solid line. The predicted treatment effect based on single and multiple PRE scores are shown by the vertical bars. The PRE score was developed in the RENAAL trial and applied to the baseline and month 6 values of the placebo and losartan treatment arm of the RENAAL trial. (**a**) Validation of the PRE score in the IDNT trial. The PRE score is developed in the RENAAL trial and applied to the baseline and month 6 measurements of the irbesartan and placebo arm of the IDNT trial. (**b**) *IDNT* Irbesartan Diabetic Nephropathy Trial, *PRE* parameter response efficacy, *RENAAL* Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan trial (With permission from *Clinical Pharmacology and Therapeutics*)

factor. However, given that drugs have multiple effects on cardiovascular risk factors, it appears more appropriate to select the optimal dose based on changes in multiple cardiovascular risk factors. Application of the PRE score is one strategy to select optimal drug doses during drug development based on multiple cardiovascular risk factors.

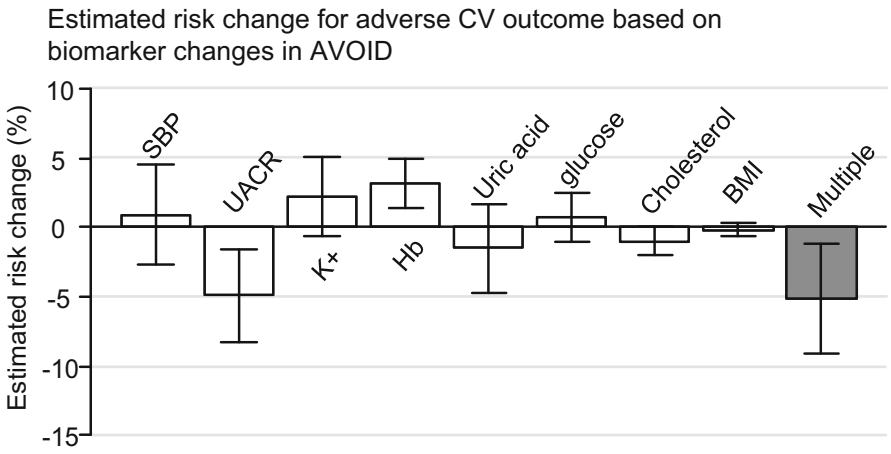

Fig. 5 Estimated relative risk change for the cardiovascular end point based on single and multiple PRE scores. *CV* cardiovascular, *PRE* parameter response efficacy (With permission from *European Journal of Preventive Cardiology*)

Potential Applications to Prognosis, Other Disease, and Conditions

What is the novelty of the PRE score? As described above, the PRE score may provide an accurate estimation about (lack of) long-term organ protection that follows from treatment. This estimation is based on a score in which multiple treatment-induced biomarker effects are incorporated. This is not a novel concept and already in use by current cardiovascular risk engines such as Framingham, UKPDS, and ADVANCE. However, estimations provided by these risk engines are based entirely on traditional cardiovascular risk factors including blood pressure, cholesterol, hba1c, etc. (Stevens et al. 2001, 671–679; Kengne et al. 2011; Wilson et al. 1998, 1837–1847). Studies have shown that individual cardiovascular risk profiles cannot be determined by traditional cardiovascular risk factors alone but should also include novel biomarkers as albuminuria, hs-CRP, NT-proBNP, etc. (Folsom et al. 2006, 1368–1373). PRE score-based estimations incorporate drug-induced changes in novel biomarkers. This has the potential to lead to more accurate drug efficacy estimations.

What are the implications of the PRE score? PRE score-based predictions of long-term organ protection are based on the short-term effect on multiple biomarkers, and therefore fewer patients will be unnecessarily exposed to ineffective or even harmful drugs. Furthermore, the PRE score can be used to perform dose selection, which may be beneficial for clinical trial conduction. Finally, the PRE score may contribute in optimizing drug treatment in daily clinical practice. An integrated score including the on-target and off-target effects may offer the physician and the patient a more

reliable tool to estimate and evaluate the overall prescribed drug effect on long-term outcomes. Changes in off-target effects may preclude adjusting or stopping treatment, despite absence of a substantial effect on the on-target parameter. This could be relevant for the patient-clinician dialogue.

Conclusion

Currently, drugs in cardiovascular disease are targeted toward a single biomarker. The ultimate goal is to reduce cardiovascular morbidity and mortality. Several cases have taught us that the single biomarker approach may lead to serious misinterpretations about the long-term cardiovascular protective effect of the drug. The PRE score, which incorporates multiple short-term biomarker effects of a drug, provides a more accurate insight of the long-term cardiovascular protective effect.

Summary Points

- Drugs in cardiovascular disease are targeted toward normalizing a single cardiovascular risk factor, the on-target effect, whereas the ultimate goal is to provide long-term cardiovascular protection.
- Several cases have shown that cardiovascular drugs were effective in normalizing cardiovascular risk factors but fail to provide long-term protection.
- These unexpected findings could be attributable to the drug effect on other parameters, the off-target effects.
- Ignoring the off-target effects of a drug may lead to severe misinterpretations of the drug effect on long-term cardiovascular outcome with major consequences for society and individual patients.
- To obtain a more accurate estimation of the drug effect on long-term cardiovascular outcome, all effects of a drug should be incorporated into a risk algorithm, the PRE score.

References

Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007;357 (21):2109–22.

Blind E, Dunder K, de Graeff PA, Abadie E. Rosiglitazone: a European regulatory perspective. Diabetologia. 2011;54(2):213–8.

Cohen AF. Developing drug prototypes: pharmacology replaces safety and tolerability? Nat Rev Drug Discov. 2010;9(11):856–65.

Folsom AR, Chambless LE, Ballantyne CM, Coresh J, Heiss G, Wu KK, Boerwinkle E, et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. Arch Intern Med. 2006;166 (13):1368–73.

Hu X, Dietz JD, Xia C, Knight DR, Loging WT, Smith AH, Yuan H, Perry DA, Keiser J. Torcetrapib induces aldosterone and cortisol production by an intracellular calcium-mediated mechanism independently of cholesteryl ester transfer protein inhibition. Endocrinology. 2009;150(5):2211–9.

James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, Torp-Pedersen C, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med. 2010;363(10):905–17.

Kengne AP, Patel A, Marre M, Travert F, Lievre M, Zoungas S, Chalmers J, et al. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. Eur J Cardiovasc Prev Rehab. 2011;18:393–8.

Mann JF, Green D, Jamerson K, Ruilope LM, Kuranoff SJ, Littke T, Viberti G, ASCEND Study Group. Avosentan for overt diabetic nephropathy. J Am Soc Nephrol: JASN. 2010;21 (3):527–35.

Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med. 2010;170(14):1191–201.

Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, Chaturvedi N, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012;367 (23):2204–13.

Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med. 2012;367:2089–99.

Smink PA, Hoekman J, Grobbee DE, Eijkemans MJ, Parving HH, Persson F, Ibsen H, et al. A prediction of the renal and cardiovascular efficacy of aliskiren in ALTITUDE using short-term changes in multiple risk markers. Eur J Prev Cardiol. 2014a;21(4):434–41.

Smink PA, Miao Y, Eijkemans MJ, Bakker SJ, Raz I, Parving HH, Hoekman J, Grobbee DE, de Zeeuw D, Lambers Heerspink HJ. The importance of short-term off-target effects in estimating the long-term renal and cardiovascular protection of angiotensin receptor blockers. Clin Pharmacol Ther. 2014b;95(2):208–15.

Sofat R, Hingorani AD, Smeeth L, Humphries SE, Talmud PJ, Cooper J, Shah T, et al. Separating the mechanism-based and off-target actions of cholesteryl ester transfer protein inhibitors with CETP gene polymorphisms. Circulation. 2010;121(1):52–62.

Stevens RJ, Kothari V, Adler AI, Stratton IM, United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci (London, England: 1979). 2001;101(6):671–9.

Wenzel RR, Littke T, Kuranoff S, Jurgens C, Bruck H, Ritz E, Philipp T, Mitchell A, SPP301 (Avosentan) Endothelin Antagonist Evaluation in Diabetic Nephropathy Study Investigators. Avosentan reduces albumin excretion in diabetics with macroalbuminuria. J Am Soc Nephrol: JASN. 2009;20(3):655–64.

Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837–47.

Zhao L, Jin W, Rader D, Packard C, Feuerstein G. A translational medicine perspective of the development of torcetrapib: does the failure of torcetrapib development cast a shadow on future development of lipid modifying agents, HDL elevation strategies or CETP as a viable molecular target for atherosclerosis? A case study of the use of biomarkers and translational medicine in atherosclerosis drug discovery and development. Biochem Pharmacol. 2009;78(4):315–25.