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Cardiovascular pharmacotherapy: Innovation stuck in translation

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ABSTRACT

Systematic reviews of animal studies have revealed serious limitations in internal and external validity strongly affecting the reliability of this research. In addition inter-species differences are likely to further limit the predictive value of animal research for the efficacy and tolerability of new drugs in humans. Important changes in the research process are needed to allow efficient translation of preclinical discoveries to the clinic, including improvements in the laboratory and publication practices involving animal research and early incorporation of human proof-of-concept studies to optimize the interpretation of animal data for its predictive value for humans and the design of clinical trials.

1. Introduction

The last 75 years, prevention and treatment of atherosclerosis and its devastating consequences on organ function have changed dramatically. As a result of this global effort, cardiovascular disease has been surpassed by cancer as the major cause of death in Western society. Major milestones in this development are well reviewed by Nabel and Braunwald (2012) and summarized in Table 1. The main developments in cardiovascular pharmacotherapy include pharmacotherapy of risk factors of atherosclerosis (hyperlipidemia, hypertension, diabetes) and drugs targeting coagulation and platelet aggregation.

However, there are still challenges to conquer: the prevalence of vascular driven end-organ damage, mainly heart failure, renal failure and cognitive impairment, is still increasing and has a major impact on quality of life and national economies.

New targets for cardiovascular pharmacotherapy have been identified by geneticists and molecular biologists and validated in animal models. These targets include stem cells and vascular growth factors (in the field of regenerative medicine), new targets in lipid and glucose metabolism, mediators of vascular inflammation and pharmacological strategies to improve resistance of cells to ischemia-reperfusion injury. However, attempts to translate these preclinical findings to humans *in vivo* have been frustrated by disappointing efficacy in clinical trials and/or the association with serious adverse events (see Table 2 for some examples).

In spite of ethical concerns, animal research remains an important tool to translate preclinical findings to humans. To justify major investments in cardiovascular animal research (from an ethical as well as economic points of view), animal studies should result in new, clinically effective and safe therapies. Therefore, successful translation of preclinical findings to patients is paramount. Unfortunately, recent studies have revealed serious limitations in the predictive value of animal research for outcome of clinical trials (Howells et al., 2012; Pound et al., 2004). As can be concluded from Table 1, the number of publications in PubMed on cardiovascular topics involving animals is increasing dramatically. However, this pace is not followed by a similar increase in the number of clinical milestones. In this short review, we discuss causes and potential solutions for the apparent obstruction in the pipeline of translational cardiovascular research.

2. Internal validity of animal research

The internal validity of a study determines the extent to which the study findings represent a cause-effect of the variable(s) under investigation. The internal validity is threatened by systematic errors (bias) and may be severely compromised when confounding factors are present in the experimental design.

In a recent systematic review and meta-analysis of animal research on renal local and remote ischemic preconditioning, we screened all published animal research on this topic for documentation of key study quality indicators associated with bias (Wever et al., 2012). In none of the 58 identified studies allocation of experimental groups was reported to be blinded. In 26% of the studies, histology was

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Table 1
Clinical milestones in pharmacotherapeutic prevention and treatment of atherosclerosis and its consequences in relation to number of published cardiovascular studies with animals in that year.

Year	Milestone	Impact	Number of animal studies (reviews excluded)[a]
1948	Start of Framingham Heart study	Recognition of risk factors for atherosclerosis (1961)	99 (98)
1954	Introduction of warfarin in medicine	Improved survival of patients with venous and arterial thrombosis	250 (250)
1962	First beta-blocker developed (black)	Start of modern antihypertensive pharmacotherapy	741 (733)
1972	National High Blood Pressure Education Program	Large randomized trials start to appear that prove health benefit from pharmacological treatment of hypertension	16,946 (15,936)
1976	First HMG-CoA-reductase inhibitor described (endo)	HMG-CoA inhibitors have changed the feasibility and efficacy of treatment of hyperlipidemia dramatically, and are still the only drug class in this area with proven benefit on hard clinical endpoints	21,407 (20,415)
1985	TIMI 1 trial	Early myocardial reperfusion saves lifes. Start of thrombolytic therapy	34,092 (31,747)
1985	National Cholesterol Educational Program	Start of modern lipid lowering pharmacotherapy; start of major randomized trials that helath benefit from pharmacological treatment of hypercholesterolemia.	
1985	Aspirin in acute myocardial infarction prevents reinfarction	Start of antiplatelet therapy	
1992	SAVE trial	Paradigm shift in pharmacotherapy of heart failure: inhibition of neurohumoral activation improves survival	46,767 (39,215)
1996	Beta blockade improves survival in heart failure		52,398 (43,019)
1998	UKPDS trial	Intensive regulation of blood pressure, and glucose (with metformin) in patients with type 2 diabetes prevents macrovascular complications	57,862 (47,304)
1999	RALES trial	Aldosterone receptor antagonists reduce mortality on top of ACE inhibition and Beta-blockade in patients with systolic LV heart failure	62,282 (50,514)
2001	Introduction of new antiplatelet drugs (P2y12 antagonists, glycoprotein IIb/IIIa inhibitors)	Facilitation of stent therapy in acute coronary syndromes.	71,184 (57,441)
2002	ALLHAT trial	Prove of synergistic health benefit of blood pressure and lipid lowering therapy in primary prevention. Revival of thiazide diuretics.	76,614 (61,338)
2013	Introduction of direct oral anticoagulants	Good oral alternatives for coumarine derivatives	94,972 (80,483)

[a] Pubmed search restricted to the year and the year after the particular milestone with the following search strategy: ((((Atherosclerosis OR heart failure OR myocardial infarction OR stroke OR hypertension OR diabetes OR hypercholesterolemia OR hyperlipidemia)) AND (Animal OR rat OR mouse OR mice OR rabbit OR dog OR monkey))) AND ("year of milestone"[Date–Publication]: "year after milestone"[Date–Publication]). Between brackets, the number of articles is depicted with the term 'NOT "review"[Publication Type]' added to the search strategy. This search was performed on November 11 2014.

Table 2
Examples of recent failures in translation.

Drug	Proposed indication	Preclinical support for indication and cause of clinical failure
Rimonabant (CB1 receptor antagonist)	Obesity and metabolic syndrome	Central CB1 receptors stimulate food intake in animals (Kyrou et al., 2006). Post-registration withdrawal because of increased depression and suicide (Topol et al., 2010)
Rosiglitazone and pioglitazone (PPAR-gamma agonists)	Type 2 diabetes	PPAR-gamma agonists improve glucose metabolism (Finegood et al., 2001; Kramer et al., 2001; Smith et al., 2000), reduce myocardial infarct size (Wayman et al., 2002; Yue et al., 2005; Yue Tl et al., 2001) and prevent atherosclerosis in animals (Li et al., 2000). In humans, PPAR-gamma agonists improve glucose metabolism (Mudaliar and Henry, 2001) but has been associated with an increased risk for myocardial infarction (Nissen and Wolski, 2007). Pioglitazone and rosiglitazone are associated with increased incidence of (bladder) cancer in humans (Hsiao et al., 2013).
Dalcetrapib, Torcetrapib (CETP inhibitors)	Low HDL-cholesterol	Torcetrapib and Dalcetrapib increase HDL cholesterol and torcetrapib reduce atherosclerosis in rabbits (Morehouse et al., 2007). Torcetrapib increases (cardiovascular) mortality in humans because of an off-target effect on aldosterone release and subsequent increase in blood pressure (Barter et al., 2007; Forrest et al., 2008). Dalcetrapib modestly improves HDL but has no effect on cardiovascular events (for review: Rader and deGoma (2014)). Two other CETP inhibitors (Anacetrapib and Evacetrapib) are currently in phase 3.
Darapladib (Lp-PLA_2 inhibitor)	Atherosclerosis	In animals, darapladib inhibits vascular inflammation and atherosclerosis and reduces plaque rupture (Wilensky et al., 2008). In humans, darapladib alters plaque composition suggesting plaque stabilization (Serruys et al., 2008). In phase 3, it did not reduce cardiovascular events in patients with stable coronary artery disease (Stability-Investigators et al., 2014).

performed without blinding the observer for the allocated intervention. Less than 50% of the studies reported randomization of the animals across intervention groups. In less than 10% of the studies baseline characteristics of the various treatment groups were described as equal. Only 35% of the studies clearly documented the number of animals that were excluded from the analysis and/or mentioned prespecified exclusion criteria, while in 25% of the studies not even the number of included animals was specified. Nine studies did not report the gender of the animals. We contacted the authors of 30 papers to clarify important missing information. Only 8 responded, of which 6 were able to provide additional data. Based on these observations and experience, we conclude that at least in this area of animal research (renal ischemic preconditioning), internal validity is poor to put it mildly: in fact this analysis proved the naivety of all involved scientists (both reviewers and authors) to provide and accept such a poor documentation of key elements to support the validity of the experiments.

What about other areas of animal research in the cardiovascular field? A systematic review of over 500 animal studies on ischemic preconditioning of the heart showed very similar results to our findings for renal preconditioning, which further emphasizes the major flaws in reporting and potentially high risk of bias in the majority of animal studies in this field (Wever et al. unpublished data). MacDougall and Muir (2011) performed a meta-analysis on the effect of hyperglycemia on cerebral infarct size after middle cerebral artery occlusion (). Similar to our observations, they reported random