Developing therapies for the metabolic syndrome: challenges, opportunities, and... the unknown

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Abstract: Metabolic syndrome refers to a clustering of established and emerging cardiovascular disease risk factors within a single individual. The established risk factors, such as obesity, diabetes, dyslipidaemia and hypertension, and other emerging risk factors are closely related to central obesity (especially intra-abdominal adiposity) and insulin resistance. However, debate continues about the very existence of the metabolic syndrome. Despite the controversies, many existing and new therapies are targeting the metabolic syndrome and component risk factors. To date, no therapies have been approved specifically for treating the metabolic syndrome. In this article some of the challenges and opportunities in developing therapies for the metabolic syndrome are discussed.

Keywords: cardiovascular disease, metabolic syndrome, obesity, type 2 diabetes

Introduction

Metabolic syndrome refers to a clustering of established and emerging cardiovascular disease (CVD) risk factors within a single individual. These risk factors are closely related to the presence of central obesity (especially intra-abdominal adiposity) and insulin resistance. The resulting metabolic consequences include atherogenic dyslipidaemia (i.e. increased levels of triglycerides, decreased high-density lipoprotein [HDL] cholesterol and increased small, dense low-density lipoprotein [LDL] cholesterol), hypertension, pro-inflammatory and pro-thrombotic states and abnormalities of glucose tolerance (i.e. prediabetes and type 2 diabetes mellitus [T2DM]). The diagnosis of the metabolic syndrome in an individual imparts a twofold to threefold increased risk of CVD and a fivefold risk of T2DM [Gami *et al.* 2007; Grundy, 2006].

In view of the incredible numbers of people affected by these chronic risk states and associated complications, biotech and pharmaceutical companies are exploring the role of existing therapies and are developing many new drugs targeting the metabolic syndrome. Indeed, one review on new therapies for the metabolic syndrome listed the number of potential ‘drug targets’ at

nearly 10,000 (i.e. targets in the genome, proteome, transcriptome, etc.) [Flordellis *et al.* 2005]. However, no drugs are currently approved for the indication of metabolic syndrome [Heal *et al.* 2009; Food and Drug Administration, 2008a, 2007].

Some of the challenges and opportunities in developing therapies for the metabolic syndrome will now be explored.

Drug discovery

Although potentially helpful for clinical practice, current definitions of the metabolic syndrome are largely inadequate for effective drug discovery and development [Matfin 2010; Grundy, 2006]. As there is a lack of a single aetiological factor or central pathophysiological abnormality identified as mediating the constellation of features of the metabolic syndrome, targeting of specific pathways to impact on the multiple abnormalities of the syndrome is not currently possible for a drug discovery purpose. Some of the targets under investigation, so-called master metabolic regulators, include pathways activated by the insulin receptors, adenosine monophosphate (AMP) kinase, inflammatory cascades, endocannabinoid receptors, nuclear receptors,

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glucocorticoids and mitochondrial oxidative pathways [Grundy, 2006].

In order to better understand the genetic architecture of the metabolic syndrome and its associations, a number of large-scale genome-wide association studies (GWASs) have been performed [Monda *et al.* 2010; Edwards *et al.* 2008]. It is hoped that loci harbouring susceptibility or protective genes for the metabolic syndrome will enable specific drug discovery targets to be identified and developed.

Drug development

From a drug development perspective, many challenges exist. For drug development to be ultimately successful, diagnosis of the metabolic syndrome needs to be commonly accepted by clinicians, investigators, sponsors of clinical trials (e.g. biotech and pharmaceutical companies, government bodies, academic institutes, professional organizations), regulators and payers of healthcare. This latter group is particularly important as billions of people globally are affected by this condition (it is estimated by the International Diabetes Federation [IDF] that one quarter of the world's adults are affected by the metabolic syndrome) and the expense associated with the prevention and treatment of the metabolic syndrome and its associations would be astronomical [Alberti *et al.* 2005]. This would require a very robust pharmacoeconomic package as part of the clinical development program for new therapies to be proven 'cost effective' and acceptable to healthcare payers (and surrogates such as the UK National Institute of Health and Clinical Excellence [NICE]).

Clinical trial issues

Definition of the metabolic syndrome

With no adequately validated or universal definition of this diagnosis, the problem of inclusion in clinical trials and interpretation of outcome results could be problematic [Matfin, 2010]. It is foreseeable that varying definitions could be implemented as varying inclusion criteria for different studies, and also heterogeneity in terms of number of parameters and emphasis. This variation in emphasis could have a definite impact on the outcome of studies (i.e. CVD, T2DM, or other endpoints). This is also a problem for paediatric metabolic syndrome clinical trials (the metabolic syndrome affecting children and adolescents is a growing and concerning issue),

where varying definitions are used [Steinberger *et al.* 2009]. Heterogeneity within and between studies can also result from ethnicity-specific criteria, i.e. differences in definition of abnormal waist circumference for different ethnic groups in metabolic syndrome diagnostic criteria [Misra and Khurana, 2008].

One potential benefit of having a simple definition of metabolic syndrome for drug development would be in assessing how an investigational drug (e.g. erectile dysfunction [ED] or antihypertensive drug) behaves in clinical trial subjects with or without the metabolic syndrome as per the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [Grundy *et al.* 2005] and IDF definitions [Alberti *et al.* 2005].

Comparator

Other clinical trial issues include the choice of comparator, especially the use of placebo control (possible ethical considerations) or the choice of an active comparator when several classes (and even many agents within a class) exist for each therapeutic category (i.e. antidiabetic, antihypertensive, lipid lowering, antiplatelet, etc.). In addition, several therapies that are currently used in cardiac and metabolic conditions (e.g. diet and exercise, statins, angiotensin converting enzyme-inhibitor [ACE-I], angiotensin II receptor blocker [ARB] and thiazolidinedione [TZD]) could potentially confound results of a new agent under investigation for the metabolic syndrome. These treatments can have pleiotropic effects on several different pathways associated with the metabolic syndrome. For example, ACE-Is have been demonstrated in numerous studies to decrease the conversion of prediabetes to T2DM [Matfin and Pratley, 2010]. In contrast, statin therapy has recently been shown to slightly increase the risk (~9%) of T2DM in patients treated with these agents [Sattar *et al.* 2010]. It is possible, therefore, that if a clinical trial is designed to test whether a new therapy will decrease conversion to T2DM in metabolic syndrome patients, that these and other therapies could have an impact on the end result. It would be unethical to stop or exclude patients on these therapies in clinical trials (as many as 60% of diabetes patients in clinical trials can be on ACE-I for example), but the effects on the study interpretation should be negated by appropriate randomization (including consideration of stratified randomization).

However, the use of multiple-therapies addressing various components of CVD risk (e.g. blood pressure [BP], lipid, glucose, antiplatelet) as part of the standard-of-care in both the investigational and control arms, can definitely have an impact on outcome event rates potentially resulting in the need for larger sample sizes and/or duration of study. In addition, if a CVD risk factor is relatively weak in isolation, this can also have an impact on the clinical trial sample size and duration. Indeed, the importance of good glycaemic control in isolation for reducing macrovascular disease has been difficult to establish until the publication of the 10-year follow up of the United Kingdom Prospective Diabetes Study (UKPDS) [Holman *et al.* 2008] and a recent meta-analysis involving a total follow up of 163,000 patient years showed that intensive glycaemic control reduced nonfatal myocardial infarction (MI) by 17% and coronary heart disease (CHD) by 15% [Ray *et al.* 2009]. This gives some idea of the size and duration of a CVD outcome study potentially needed to demonstrate a 'positive' result for new therapies for the metabolic syndrome.

The duration of studies for trials investigating new drugs for the metabolic syndrome also depend on the stage of development (i.e. proof of concept [POC] studies are obviously much shorter than a CVD outcome study).

Clinical endpoints

Many features of the metabolic syndrome could be potential targets for new treatments: prevention of diabetes and its complications; atherogenic dyslipidaemia; nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH); polycystic ovarian syndrome (PCOS)-related abnormalities; human immunodeficiency virus (HIV)-related dysmetabolic problems; prevention of CVD; or even prevention of cancer [Matfin, 2010]. The proposed drug indication will clearly have an impact on the appropriate study design and choice of endpoints (i.e. is the treatment targeting prevention of diabetes, or CVD morbidity and mortality, etc.). Endpoints chosen must be able to be proven as medically valuable (i.e. based on clinical significance and pharmacoeconomic considerations) as well as scientifically valid. In lieu of proper outcome studies, appropriate biomarkers and surrogate endpoints should be monitored [Matfin, 2007].

For CVD-related endpoints, Framingham Risk Score or other global CVD risk engines (e.g. UKPDS risk score, QRISK2 algorithm) could also be utilized [Matfin, 2007]. However, small changes in many CVD risk factors (i.e. quantitative changes in parameters such as glucose, LDL, BP, body weight, which would not normally lead to approval by regulatory authorities based on regulatory guidance and/or precedent) are unlikely to be accepted by regulatory authorities unless these changes can be demonstrated to ultimately have an impact on CVD hard outcomes in a clinical trial. In view of the current drug regulatory environment as typified by the ongoing rosiglitazone debacle [Kaul *et al.* 2010; Nissen, 2010; Goldfine, 2008; Nissen and Wolsky, 2007] and recent withdrawal of the antiobesity drug sibutramine in Europe [Williams, 2010], it is anticipated that CVD hard-outcome studies will be needed earlier in clinical development for the demonstration of benefit and (perhaps even more importantly) safety (especially if a CVD safety signal occurs in earlier studies). This has been borne out with the new Food and Drug Administration (FDA) CV guidance for anti-diabetes drugs published in September 2008 [Parks and Rosebraugh, 2010; Food and Drug Administration, 2008b; Goldfine, 2008].

The simple use of counting of metabolic syndrome parameters should not be acceptable as an endpoint (e.g. three parameters out of the five at baseline, decreasing to two parameters at study end, does not necessarily mean 'reversal' or improvement in metabolic syndrome resulting from the therapy under investigation). Such dichotomous ('Yes' or 'No') scoring is too simplistic for many purposes. This relates to the fact that the parameters are interrelated and are not equal in risk, especially as they have different emphasis with respect to CVD and diabetes. In addition, the stability of the metabolic syndrome over time is ill defined [Ferranini, 2007]. It may display a relatively high rate of spontaneous regression (as is the case with the prediabetes category, impaired glucose tolerance [IGT]). Despite these considerations, several studies including one study using rimonabant (a novel agent initially indicated for the management of obesity in several countries prior to being withdrawn worldwide due to safety reasons) reported reversal of the diagnosis of metabolic syndrome in a proportion of subjects (64.8% reduction) who had metabolic syndrome as defined by NCEP ATP III at baseline, using such a simple counting system [Van Gaal *et al.* 2005].

Regulatory

One of the most important considerations in drug development for the metabolic syndrome is the question: is the metabolic syndrome a new entity or simply a new name for existing risk factors? We already have a growing arsenal of treatments for hypertension, dyslipidaemia and diabetes. Are these conditions distinct in their genesis and, more importantly, do they differ in their response to available drugs as part of the metabolic syndrome as opposed to their response in the absence of the metabolic syndrome? Does reversing metabolic syndrome, per se, alter risk? These and many other important questions are the subject of intense debate and investigation.

From a regulatory standpoint, the lack of a universal definition, the lack of a single aetiological factor or central pathophysiological abnormality identified as mediating the constellation of features, uncertainty regarding study endpoints, heterogeneous study population, existing treatments and regulatory precedent for established risk factors, etc., all suggest that some challenges will have to be solved before there will be approval of any new or existing drug for the indication of metabolic syndrome [Heal *et al.* 2009]. In February 2007, the FDA stated in a draft-guidance document for obesity drug development that 'it does not necessarily consider the metabolic syndrome to represent a distinct disease entity' [Food and Drug Administration, 2007]. However, the FDA concluded that 'a therapeutic product intended to treat metabolic syndrome should *normalize* or improve *all* components of the syndrome, independent of weight loss, and ultimately be shown to prevent the development of diabetes and reduce CVD morbidity and mortality' [Food and Drug Administration, 2007]. This stance was again reiterated by the FDA in the antidiabetes drug development guidance in March 2008 [Food and Drug Administration, 2008a]. This is a very high aspiration for any one drug, hence, increased interest in formulations that contain several drugs addressing various components of the metabolic syndrome simultaneously (i.e. 'polypill' and fixed-dose combination [FDC] therapies) [Grundy, 2006].

The 'polypill' for the metabolic syndrome?

The concept of a 'polypill', which contains more than one agent and would simultaneously address more than one cardiometabolic risk factor, appears attractive. Several studies have shown

the value of multifactorial CV risk targeting in high-risk patients. For example, the STENO-2 study showed that simultaneously addressing glycaemic control, renin blockade, and using antilipid and antiplatelet agents in T2DM patients, reduced death from CVD [Gaede *et al.* 2008].

The original proposal of the 'polypill' by Wald and Law suggested combining aspirin, a β -blocker, an ACE-I, a statin, a diuretic, and folic acid, all in one tablet [Wald and Law, 2003]. This tablet was to be taken once daily and was nontitratable. This example and other proposed 'polypills' may result in improved compliance (due to reduction in the polypharmacy pattern which is the norm for these complex patients), decreased costs for the patient and society (due to the use of generic drugs), and greater impact on complications (decreasing human and societal costs). Arguments against the use of such a 'polypill' relate to size of the tablet and, critically, the exposure of patients to drugs they may not need. If a patient should experience an adverse event, it could prove difficult to determine which component (if any) had caused this adverse event.

Nonetheless, several 'polypills' are currently in development (for example, combining aspirin, β -blocker, ACE-I and statin), and may have specific value in the developing world [Reddy, 2007]. The Indian Polycap Study (TIPS) included 2053 patients aged 45–80 years without CVD but with one risk factor (T2DM, high BP, smoker within the past 5 years, increased waist-hip ratio [WHR] or abnormal lipids) [Yusuf, 2009]. They were randomized to receive the Polycap, which included hydrochlorothiazide 12.5 mg, atenolol 50 mg, ramipril 5 mg, simvastatin 20 mg and aspirin 100 mg, or to eight other groups who received various components of the polypill either alone or in combination. Results showed that the polypill lowered BP similarly to the added effects of the three antihypertensive components. Adverse effects with the polypill were not increased compared with the other eight groups, and there appeared to be no drug-drug interactions. There was slightly less cholesterol lowering with the polypill than in patients who received simvastatin alone and the reduction in BP was lower than projected from the antihypertensives included. The estimated risk reductions seen in this study would translate into a 62% reduction in CHD and 48%

reduction stroke. Clearly other large outcome studies are needed to more fully assess the true feasibility of the polypill strategy. These investigations are being driven by numerous individual groups, as well as a collaborative effort called Single Pill to Avert Cardiovascular Events (SPACE) being run by the George Institute in Sydney, Australia.

Many pharmaceutical companies are also developing or have launched FDC tablets addressing various components of the metabolic syndrome (e.g. antihypertensive agent combined with a statin). These FDCs could contain generic and/or nongeneric drugs. A FDC of a new agent and an established agent should be studied in a manner that demonstrates that each of the individual components makes a contribution to the claimed effects of the FDC, and that the combination is acceptably safe. If the FDC consists of two currently approved and marketed drugs, and will be labelled for the same indications and patient populations as the separately approved therapies, and the safety and efficacy of these drugs have been established in co-administration, a full factorial efficacy trial may not be necessary to demonstrate the contribution of each FDC component to the claimed effects. In this setting, pharmacokinetic (PK) data defining any drug–drug interactions between the components generally should be sufficient. There are exceptions to this approach, such as situations where there are potential safety concerns with the co-administration of the two components.

Conclusions

Currently, despite the thousands of publications related to all aspects of the metabolic syndrome, it seems that developing therapies for the metabolic syndrome is likely to be based on therapeutic lifestyle changes. However, the use of ‘polypills’ and FDC drug therapy for the metabolic syndrome (especially using generic agents) is attractive from a public-health and pharmaceutical company perspective. Bariatric surgery can also have a profound beneficial impact on the metabolic syndrome and its associations in individuals [O’Brien, 2006]. However, this option is largely restricted to the developed world and its availability is limited even in these countries.

From a regulatory standpoint, it is unlikely in the foreseeable future that any one agent can meet the high hurdle required for approval for the treatment of the metabolic syndrome. In addition, because of the billions of people affected by the metabolic syndrome and its associations, a critical

component of any new therapy for this problem would include the pharmacoeconomic aspects, i.e. who ultimately pays for treatment?

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