

Importance of achieving the composite endpoints in diabetes

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ABSTRACT

Well-conducted randomized controlled trials are instrumental in providing vital data on safety and efficacy of new molecules under consideration for approval. However acquiring such data involves huge cost and focused scientific endeavor. Selection and reporting of endpoints of a therapy is essential to assess the effect(s) of an intervention on overall disease control and guidelines have suggested the use of composite endpoint (CEP) in clinical trial design over individual endpoints to demonstrate the compound effect. Composite endpoints have been preferred for their ability to assess the net clinical benefit of an intervention, avoid misinterpretation associated with competing risks, avoid the challenge of using a single outcome to validate the study objectives and reduce the sample size requirements in trials on patients treated for diabetes. Concerns for misinterpretation or difficulty in interpretation of trial results involving CEPs arise when differences in the components with respect to either clinical importance or event rates, or magnitude of treatment effect exist and when there's a possibility of biases due to competing risk. Suggestions for construction of composite endpoints and reporting the results of trials involving CEPs have been presented to improve the interpretations of overall effect of new interventions.

Key words: Diabetes mellitus type 2, randomized controlled trials as topic, research design, treatment outcome

INTRODUCTION

Composite endpoints (CEP) have been used since three decades for the assessment of trial outcomes.^[1] It consists of two or more individual endpoints which are cumulatively used to demonstrate an overall and clinically relevant treatment effect of an intervention.^[2] Patients experiencing any of these individual endpoints are considered to have experienced the CEP of interest.^[3]

Advanced medical care in recent times has reduced the frequency of adverse events in patients during follow-up

of trials. This has challenged the clinical investigators for large sample sizes and long follow-ups to test the incremental benefits and draw strong conclusions on individual endpoints (efficacy and/or safety) for new drugs.^[4] The use of CEPs in clinical trials enabled the investigators to identify the number of patients with one or more adverse events in a single trial^[4] with smaller sample size and limited time frame.

CEPs are increasingly being used in chronic and complex conditions like cardiovascular disease (CVD), asthma, diabetes and rheumatoid arthritis to assess the overall disease control. Major adverse cardiac events (MACE; consisting of myocardial infarction, stroke, and cardiac death) is a widely accepted CEP used in drug approvals for CV trials.^[5] For acute coronary syndromes, individual endpoints such as nonfatal myocardial infarction, hospitalization for unstable angina and death from cardiovascular causes are used in the design of CEP.^[6,7] Similarly, asthma exacerbations, asthma-control days and forced expiratory volume in 1 second (FEV1) constitute

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the individual endpoints of a CEP in an asthma trial and are used to determine the best step-up therapy in children with uncontrolled asthma, receiving low-dose inhaled corticosteroids.^[8] The individual endpoints used to construct a CEP for a trial must be associated with the primary objective of the trial, be biologically achievable, and possess clinical importance for both clinicians and patients. The main advantage of using CEPs in clinical trials has been to improve the statistical efficiency of the trial. Using CEPs in clinical trials increases the number of event rates (for more than one endpoint) during short follow-up time, thus reducing the resources and the length of study with smaller sample size. In view of the trial investigators, CEPs can best be used to assess the net clinical benefit of an intervention. However, investigators and readers should be cautious on the selection, use and interpretation of individual endpoints of the CEP used in a clinical trial especially when treatment effects vary across the individual endpoints and/or CEPs are not presented and discussed clearly. A systematic review of parallel group randomized clinical trials (mostly CV) published in 2008 using composite of primary end points found that components are often inconsistently defined, unreasonably combined and inadequately reported and suggest to report every single combination of events in a table to avoid flaws in reporting individual endpoints.^[9] Given the wide applicability of using CEPs, it is not surprising that clinical trials on patients with diabetes have reported combination of efficacy and safety outcomes for new interventions.^[10-12] Current anti-hyperglycemic therapies are usually associated with risks such as hypoglycemia and weight gain^[13] which in turn affects the quality of life, patient's compliance to therapeutic recommendation,^[14] morbidity^[15] and increases the risk of CV complications especially for overweight patients and cause substantial psychological distress.^[16] Therefore, treatment guidelines now include recommendations on achieving weight reduction, avoiding hypoglycemia and targets for systolic and diastolic blood pressure (SBP and DBP, respectively) and circulating lipids in addition to glycemic targets.

The American Diabetes Association (ADA) and Canadian Diabetes Association (CDA), suggest multiple goals of therapy, including reduction of glycated hemoglobin (HbA1c) <7%, no incidence of hypoglycemia and less or no weight gain (or weight loss if obese) in patients with diabetes.^[17,18] American Association of Clinical Endocrinologists recommend a stringent glycemic target of HbA1c <6.5% with low risk of hypoglycemia,^[19] further endorsed by National Institute for Health and Clinical Excellence (NICE)^[20] in patients treated for diabetes. Although achieving multiple (metabolic) goals is essential in the treatment of diabetes, only a handful of clinical trials

conducted in patients with diabetes have reported the use of CEP. In line with this, the current review focuses on the importance of using and achieving CEPs and issues in reporting the outcomes of clinical trials for the treatment of patients with diabetes. Recommendations on defining CEP and reporting results of clinical trials involving CEPs are also suggested.

COMPOSITE ENDPOINTS IN DIABETES: ADVANTAGES

HbA1c is an important measure of glycemic control and routinely used as primary endpoint for diabetes clinical trials. However, due to the association of diabetes with vascular complications, it is equally important to measure and achieve control on multiple metabolic targets (such as hypoglycemic episodes, weight gain, SBP and LDL-cholesterol) for desired outcomes in diabetes. Investigators have evaluated these individual endpoints, in addition to glycemic targets to demonstrate multiple effects of new interventions under investigation for both patient and physician.^[11,13] As more and more clinical trials continue to evaluate the efficacy of candidate drugs and existing interventions, importance of achieving CEPs in diabetes therapies is gradually becoming a standard practice. The clinical correlation from studies using CEPs in patients with diabetes is summarized in Table 1.^[11,12,14,21-25] The use of CEPs in clinical trials on diabetes helps in the following:

- Assess the net clinical benefit of an intervention
- Avoid bias in outcome of an intervention due to competing risks
- Avoid the challenge to choose a single endpoint
- Provide improved statistical efficiency.

Assess the net clinical benefit of intervention

A wide-range of oral and injectable interventions is available which help achieve glycemic targets in patients with diabetes. However, achieving glycemic targets is not sufficient to assess the overall clinical benefit of an intervention in patients receiving treatment for diabetes, as therapies often need to address more than one therapeutic goal. Most interventions aimed at improving glycemic control are associated with the risk of hypoglycemia and weight gain.^[13] Including the individual endpoints related to both efficacy and safety to construct the CEP of a trial can serve as a means of differentiating multiple options for treating diabetes and thus provide a comprehensive picture of overall clinical benefit of an intervention.

In a recent clinical trial, addition of liraglutide to metformin followed by intensification with basal insulin (detemir) was

Table 1: Clinical correlation from studies using composite endpoints, in patients with diabetes

| Study | CEP used | Result | Clinical correlation |
|---|---|---|---|
| Clinical trials | | | |
| Insulin detemir to patients with T2DM on metformin and sequential intensification with liraglutide ^[21] | HbA1c <7% with no weight gain, no hypoglycemia | 21% patients in insulin detemir group, 9% from control group ($P=0.0016$) achieved CEP | Net clinical benefit of intervention assessed: Mixed outcomes of individual endpoints was overcome by addressing more than one therapeutic goal |
| FIELD study: Effect of fenofibrate on CVD events in patients with T2DM ^[22] | Death due to coronary disease or nonfatal infarction | CEP did not show a statistically significant benefit between treatment and control groups (10.4/1000 vs. 11.7/1000 events, $P=0.16$) | Bias due to competing risk avoided: Outcome of individual endpoint might be misleading on overall treatment effect |
| HEELA study-Exenatide vs. insulin glargine in obese patients with diabetes inadequately controlled ≥ 2 OADs ^[11] | HbA1c $\leq 7.4\%$, weight gain ≤ 1 Kg | 53.4% of patients in exenatide group and 19.8% of patients from insulin glargine group achieved CEP ($P<0.001$) | Challenge to choose single endpoint is avoided: Effect of intervention might not be visible due to similarity in outcome of individual endpoints in both groups |
| Pramlintide vs. basal insulin ^[12] | HbA1c $\leq 7.0\%$ or reduction $\geq 0.5\%$, daily PPG increments ≤ 40 mg/dl, no increase in body weight, no severe hypoglycemia | 25% of patients in pramlintide group and 7% of patients from placebo group achieved CEP ($P<0.001$) | Improved statistical efficiency of the trial: Overall effect of intervention on multiple metabolic targets achieved with limited sample size and time frame |
| DREAM trial Effect of rosiglitazone on decreasing the incidence of T2DM in high risk patients ^[23] | Incidence of diabetes and death | Rosiglitazone reduced the risk of diabetes or death by 60% | Misleading interpretation: Individual endpoints of unequal clinical importance combined to minimize harmful effects due to intervention |
| Longitudinal study on RDNS cohort to assess the efficacy of ARIs in preventing diabetic peripheral neuropathy ^[24] | Nerve conduction, cardiac autonomic function, neurologic examination and patient symptoms | None of the drugs achieved CEP | Large number of components: Increase work and resources, difficulty in accurate ascertainment of components |
| Post-hoc analysis | | | |
| Meta-analysis of LEAD trials | HbA1c <7.0%, no weight gain and no hypoglycemic events | 40% of liraglutide 1.8 mg group, 32% of liraglutide 1.2 mg group achieved CEP | Net clinical benefit and superiority of an existing drug on multiple metabolic targets assessed from analysis of trial data |
| Post-hoc analysis of sitagliptin vs. glipizide in patients with inadequate glycemic control (HbA1c 6.5%-10%) on metformin therapy ^[14] | HbA1c reduction >0.5%, no hypoglycemia, no increase in body weight | 38.1% of patients in sitagliptin group and 11.8% in glipizide group achieved CEP | Net clinical benefit and superiority of an existing drug on multiple metabolic targets assessed from analysis of trial data |
| Database of patients undergone RYGB surgery vs. RMM for T2DM with 2 years of follow-up data ^[25] | HbA1c <7%, LDL cholesterol <100 mg/dl, and SBP <130 mmHg | Patients in the RYGB group had 5.2 times greater odds of achieving CEP than RMM group | Superiority of an existing therapeutic approach assessed from analysis of patient data |

CEP: Composite endpoint, T2DM: Type 2 diabetes mellitus, HbA1c: Glycated hemoglobin, FIELD: Fenofibrate Intervention and event lowering in diabetes, CVD: Cardiovascular disease, HEELA: The helping evaluate exenatide in patients with diabetes compared with long-acting insulin, PPG: Postprandial glucose, OADs: Oral anti-diabetes drugs, DREAM: Diabetes reduction Assessment with ramipril and rosiglitazone medication, RDNS: Rochester diabetic neuropathy study, ARIs: Aldose reductase inhibitors, LEAD: Liraglutide effect and action in diabetes, RYGB: Roux-en-Y gastric bypass, RMM: Routine medical management, LDL: Low-density lipoprotein, SBP: Systolic blood pressure

evaluated in patients with type 2 diabetes mellitus (T2DM) having HbA1c $\geq 7\%$.^[21] The primary endpoint of the study was 'change in HbA1c% from 0-26 weeks' to determine whether adding insulin detemir to metformin plus liraglutide was superior to continuing with metformin plus liraglutide. Additionally, the CEP of participants reaching 'HbA1c <7% with no weight gain or hypoglycemia (during period)' was assessed. The study reported, the proportion of participants achieving the CEP was significantly greater in the insulin detemir group (21%) than the control group (9%; $P = 0.0016$). Interestingly, a conflicting picture evolves when one considers the individual endpoints of the same study. For example, while weight reduction was less (0.16 kg vs. 0.95 kg), the rate of minor hypoglycemia was higher (0.286 vs. 0.029 events per participant year) in the detemir group compared to control.^[21] Thus; this case

demonstrates the importance of CEP in assessing the net clinical benefit of an intervention. In a contemporary database study, Leslie *et al.*, used ADA defined composite endpoints of HbA1c (<7%), LDL cholesterol (<100 mg/dl) and SBP (<130 mmHg) for CVD risk factor control, to compare databases of patients ($BMI \geq 35$ kg/m²) using Roux-en-Y Gastric Bypass (RYGB) surgery and routine medical management for T2DM and at least 2 years of follow-up data.^[25] The study demonstrated that patients in RYGB group had significant improvement in achieving the CEP over two years compared to the routine medical management group.^[25] Thus, the use of CEP gives a new dimension in assessing the net clinical benefit of an approach rather than an individual endpoint in the management of diabetes.

Avoid bias in outcome of an intervention due to competing risks

CEPs are not only used to capture the net clinical benefit of an intervention or reduce the sample size requirement but also to avoid bias in the assessment of an intervention effect in the presence of competing risks. In situations where the occurrence of one outcome decreases the probability of another outcome of clinical importance, the possibility of bias due to competing risks arises.^[2]

In a randomized clinical trial (RCT), the efficacy of fibrates in the prevention of primary CV events was analyzed in patients with diabetes;^[22] the CEP of ‘death due to coronary disease or nonfatal infarction’ was used. The incidence of one of the outcome, nonfatal infarction was significantly lower in the treatment group (6.4/1000 patient-years at risk) than placebo group (8.4/1000 patient years at risk) ($P = 0.01$) whereas the incidence of competing risk, ‘death due to coronary disease’ was higher in the treatment group (4.4/1000 patient-years) than control group (3.7/1000 patient-years) ($P = 0.22$). However, analyzing the CEP, ‘death due to coronary disease or nonfatal infarction’ did not show a significant benefit: 10.4/1000 in the treatment group versus 11.7/1000 in the control group ($P = 0.16$).^[22] Here, the overall risk of nonfatal infarction was reduced in the treatment group as there were fewer patient-years of follow-up. If the individual endpoint of ‘rate of nonfatal infarction’ was to be compared for the effect of intervention, the treatment might have appeared more effective than it actually was in reducing the number of myocardial infarctions. Hence, instead of using individual endpoints, the CEP of ‘death or nonfatal infarction’ was used and the possible bias due to competing risks was abolished as both outcomes were equivalent for analysis of treatment effect.

Avoid the challenge to choose single endpoint

If a single primary endpoint cannot be selected from multiple measurements associated with the study objective or if selection of a single endpoint from many options becomes controversial, CEPs could be used as an alternative to validate the objective of the study. Use of CEP in such situations was described by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.^[26] In Helping Evaluate Exenatide in patients with diabetes compared with Long-Acting insulin study (HEELA), patients with T2DM (having BMI >27 kg/m²) with increased CV risk and inadequately controlled on two or three oral antidiabetic drugs (OADs) were randomized (1:1 ratio) to treatment by exenatide or insulin glargine for 26 weeks.^[11] A CEP of ‘HbA1c $\leq 7.4\%$ with minimal weight gain (≤ 1 kg)’ was used to evaluate the treatment outcome. CEP was

achieved by more than half (53.4%) of the patients in exenatide group compared to 19.8% of patients from the insulin glargine group. In this specific example, had the individual endpoint HbA1c was selected as primary endpoint, the effect of intervention would not have been visible or detectable as both the groups showed similar improvements in HbA1c ($P = 0.924$).^[11] Inclusion of ‘weight gain ≤ 1 kg’, which is of clinical importance for this patient group (BMI >27 kg/m²) as an individual outcome improved the overall treatment effect and helped in understanding the benefit of using more than one endpoint.

In clinical trials on patients with diabetes it is always important to use CEP to demonstrate the compound effect that best reflects the overall efficacy of an intervention under investigation rather than use a single outcome.

Provide improved statistical efficiency

Statistical efficiency is one of the major advantages of using CEPs in clinical trials. Use of CEP in a trial would ensure higher number of endpoint events observed in a given timeframe among the study population that can be attributed to the intervention, thus decreasing the sample size and increasing the statistical precision and efficiency of treatment. There’s an inverse relationship between achieving HbA1c targets and avoiding hypoglycemia in diabetes treatments, particularly insulin therapies.^[27] Hence, use of CEP that looks at HbA1c outcomes (absolute or % population reaching a specific target) among the efficacy evaluable population who did not experience “unacceptable” hypoglycemia and/or weight gain would improve the statistical efficiency and characterization of the overall treatment effects of a drug^[12,14] in a single trial. A recent placebo-controlled study evaluated the efficacy and safety of pramlintide, an analogue of amylin hormone in patients with T2DM sub optimally controlled with basal insulin.^[12] A CEP of ‘HbA1c $\leq 7\%$ or reduction $\geq 0.5\%$, mean daily postprandial glucose increments ≤ 40 mg/dl, no increase in body weight and no severe hypoglycemia’ was used. An overall power for reaching the CEP was expected to be $\sim 85\%$ with no adjustment to the significance level ($\alpha=0.05$). Significantly more number of patients in the treatment group achieved the CEP over placebo (25 vs. 7%; $P < 0.001$) at week 16.^[12] In this specific example, the use of CEP with multiple outcomes was observed with a small sample size of only 90 patients per treatment arm. The study certainly saved resources, time and subjects had the drug been tested with individual endpoints. The results might possess clinical importance to patients, providers and drug developers without the need to adjust for multiple comparisons or

validate complex modeling approaches to analyze data.^[28] The underlying advantage of such an approach is the reduction in logistics and cost of drug development in conducting trials for individual endpoints.

COMPOSITE ENDPOINTS IN DIABETES: DISADVANTAGES

The use of CEPs in clinical trials may provide a net clinical benefit of an intervention and avoid the possible bias due to competing risks or overcome the challenge of low event rates, but it has certain drawbacks and challenges. Several investigators caution on possibility of misinterpretation of results when heterogeneity exists in clinical importance among individual endpoints. The clinical correlation from studies using composite endpoints, in patients with diabetes has been summarized in [Table 1]. The disadvantages of using CEPs in clinical trials on patients treated for diabetes include:

- Combining components of unequal importance
- Interpretation of outcomes while using CEPs in clinical trials
- Excessive influence of clinician-driven endpoints influences the outcomes
- Larger resource requirement with increase in the number of components.

Combining components of unequal importance

The individual endpoints in a trial are combined to form a CEP under the assumption that all the components are equivalent in the analysis of treatment outcome. In trials where components of unequal clinical importance (patient related) are combined to form a CEP, the interpretation of the effects of intervention becomes difficult. For example in a composite endpoint of ‘death due to coronary disease and nonfatal infarction’ for patients with diabetes, the two outcomes whether a patient dies or experiences nonfatal infarction are considered equivalent in the analysis.^[22] Accurate reporting of individual endpoints in such trials is important for interpretation of results of clinical importance.

Similarly, in clinical trials on patients with T2DM if ‘incident diabetes or death’ is used to define the CEP, applying the effect of intervention on both the components of CEP will be misleading. Death is an outcome of greater importance to these patients with impaired fasting glucose or impaired glucose tolerance than the incidence of diabetes. Combining components of unequal importance to patients appears to mislead the real outcome of a trial or make a therapy look far better than it is. In an RCT that investigated the effects of rosiglitazone in patients at high risk for developing diabetes,^[23] the authors reported that 8 mg of rosiglitazone

daily, together with lifestyle recommendations, substantially reduced the risk of diabetes or death by 60% in individuals at high risk for diabetes. It appears that rosiglitazone had a significant and important effect on the risk of death in patients. However, the primary outcome in the trial was driven entirely by ‘development of diabetes’ and found no effect of rosiglitazone on mortality. The outcome ‘development of diabetes’ assessed in patients taking rosiglitazone, was almost certain that patients taking this medication would have a lower rate of ‘diabetes and death’. This is because ‘development of diabetes’ is based on HbA1c and plasma glucose measurements which could be delayed in patients taking the drug. The harmful cardiac effects of rosiglitazone were minimized in reporting the outcome of this trial by focusing on reduction of one of the individual endpoints of the CEP that included the word ‘death’. Reporting the overall outcomes that rosiglitazone decreased ‘diabetes and death’ in this trial is a misrepresentation to the readers. By including ‘diabetes and death’ as part of CEP, the trial can claim that it is the only statistically fair way to report the results.

Similarly, if the important component of CEP is not considerably modified by the effects of the treatment or have unequal magnitude, the results of CEP can be misleading. In the CAPRICORN trial, patients with left-ventricular dysfunction after acute myocardial infarction were treated with a beta-blocker, carvedilol. The important outcome, ‘all-cause mortality’ was lower in the treatment group but the overall CEP (all-cause mortality or hospital admission for CV problems) showed no difference between the groups.^[29]

Interpretation of outcomes while using CEPs in clinical trials

The use of a CEP could be disadvantageous when the effect of the intervention has opposite effects on individual endpoints. In this situation, interpretation of outcome results while using CEP to measure the overall treatment effect might be uninformative. For instance, a recent RCT compared the efficacy of glucagon-like peptide-1 (GLP-1) receptor agonist, exenatide, against insulin glargine, in a population of overweight patients with T2DM who were at high risk of CV disease and not adequately controlled by ≥ 2 OADs. A CEP of ‘HbA1c ($\leq 7.4\%$) with minimal weight gain (≤ 1 kg)’ was used to compare treatment with exenatide *vs.* insulin glargine.^[11]

The proportions of patients achieving the CEP were 53.4% for the exenatide group and 19.8% for the insulin glargine group ($P < 0.001$). The interpretation of this result could be misleading since exenatide and insulin

glargine did not demonstrate a significant difference in HbA1c improvements, an important outcome of the trial. The two groups had an opposite effect on body weight, the outcome of less clinical importance, (-2.73 Kg *vs.* $+2.98$ Kg respectively, $P < 0.001$) after 26 weeks.^[11] Here, the overall treatment effect is masked by an individual endpoint of less clinical importance. It is up to the reader to evaluate the risk of spurious interpretation of the outcome of intervention measured using a CEP. The greatest risk of using a CEP occurs when a clear positive effect observed in a trial is due to the individual endpoint of little clinical significance, whereas the effect of a clinically significant endpoint does not exist or lack persuasiveness. In trials where individual components (health outcomes) of a CEP have equal clinical importance, assuming similar effects of the intervention on each component would not be misleading in both relative and absolute terms. For example, in a study, if the individual endpoints myocardial infarction, death and stroke were considered of equal patient importance, the distribution of a 5% absolute risk reduction in CEP among them will not matter much. The overall outcome will be the same, even though the effect of intervention differs substantially. But patients assign varying (clinical) importance to individual components and hence, possible differences in treatment effects between them cannot be ignored. In such cases, the extent of gradient of importance between the individual components of a CEP becomes debatable.^[4]

Excessive influence of clinician-driven endpoints influences outcomes while using CEPs

Individual endpoints of a trial (used in a CEP) that are determined by judgment of a clinician rather than describing directly the disease can influence the overall effect of treatment towards a favorable outcome. Inclusion of clinician-driven endpoints (such as blood pressure, percutaneous revascularization, mechanical ventilation, hospitalization, transplantation, use of rescue therapy, shunt, initiation of new antibiotics, amputation, dialysis etc.) in clinical trials was found to be predictive of a statistically significant result for composite outcomes.^[30] The interpretation of outcomes while using CEPs should be treated extremely carefully with full awareness of rationale behind the use of components and the uncertainties that some trials fail to clarify. In few instances, the sponsor of a trial may prefer to focus on a positive result based on a CEP rather than reporting the precaution needed in the interpretation of treatment effect with a particular drug. These clinician-driven endpoints might not be of clinical importance than disease outcomes and might be vulnerable to bias due to subjectivity. In such scenario CEPs can be less sensitive than single endpoint for detecting clinically important effects.

Larger resource requirement with increase in the number of components

Theoretically, any number of component endpoints can be included in the design of a CEP for a trial. Inclusion of each component requires an accurate ascertainment of the individual components. A large number of these components increase the work of investigators and resources invested in the trial to ensure accurate account of the number of events.^[3,31]

A longitudinal study^[24] was conducted on Rochester diabetic neuropathy study (RDNS) cohort to access the efficacy of therapies aimed at preventing the progression of diabetic peripheral neuropathy.^[5] A CEP, accepted by the FDA as primary efficacy endpoint was designed using different aspects of the disorder: Nerve conduction, neurologic examination, cardiac autonomic function, and patient symptoms. However, none of the dozen or more aldose reductase inhibitors has shown a robust effect using the CEP and approved for this or any other indication by FDA.^[24] The study might have included too many individual outcomes in CEP for drug approval increasing the resources for accurate ascertainment. Instead using only median nerve conduction (with significant positive effects for many of these compounds) could have been an appropriate component outcome and choice for drug approval.^[5] If at least one of these drugs would have been approved, it could have proved beneficial to patients in long-term. In this case, it is important to realize that inappropriate use of CEPs can be less sensitive than component endpoint for detecting clinically important effects.

SUGGESTIONS FOR USE OF COMPOSITE ENDPOINTS IN CLINICAL TRIALS

Due to the underlying advantages and disadvantages that exist in the use of CEPs in clinical trials, uniformity in the selection and reporting of components of CEP is essential in order to improve the interpretation of clinical trial data for new interventions. Satisfactory methods should be established for the development and validation of CEPs, similar to the well-recognized psychometric methods used in the development and validation of measures of subjective health states.^[32,33]

Suggested recommendations for design of composite endpoints of a trial

Special consideration should be given in the selection of individual endpoints of a CEP in a clinical trial design. The primary endpoint of a trial can be a clear and simple-to-measure endpoint or a more complicated endpoint. The suggestions listed for constructing the CEP

will help to avoid the frequent occurrence of individual components of less clinical significance. A good number of authors acknowledge the emphasis of pre-specifying the CEP and defining all the components before the commencement of the clinical trial.^[30,31] The CONSORT guidelines should be followed to clearly define the individual components of CEP and the secondary outcomes used in the study.^[34] The selection and use of individual outcomes in CEP should be based on different manifestations of the same underlying pathophysiologic process of the disease under study. Components that are least influenced by the intervention should be avoided to address the overall disease control conditions and prevent unanticipated or harmful interpretations of trial outcomes. Selection of individual endpoints with a clinical significance that can be observed in all the patients participating in the trial will project the real outcomes of the trial. Investigators should be careful not to incorporate clinically insignificant components.

CEPs should be chosen in order to prevent any heterogeneity across individual outcomes, in terms of clinical relevance to patient, their frequency of occurrence, and the expected effect of the intervention. This can be achieved by weighting the importance of individual endpoints and avoid components of dissimilar patient importance. The greater the difference in the frequency of events of individual components of a CEP, the greater will be the uncertainty about the applicability and interpretation of the intervention effect on individual components.^[2]

RECOMMENDATIONS

- Prespecify the CEP of the trial and the corresponding individual endpoints before beginning of the clinical trial^[30]
- All components of the CEP should be consistently defined as secondary endpoints and reported with primary analysis results^[30]
- The number of components of a CEP in a trial should be limited to 3 or 4^[35]
- The individual components of a CEP should have accomplished experimental and clinical evidence^[35]
- Authors should strictly follow the CONSORT standards for reporting the individual endpoints in RCTs^[34]
- Individual endpoints that have limited or no effect due to intervention of interest should be avoided^[31,36]
- Individual endpoints with equivalent clinical importance and sensitivity to intervention should be integrated^[2]
- Subjective and objective endpoints in terms of clinical relevance and effect of intervention should not be combined.^[30,37]

SUGGESTED RECOMMENDATIONS ON REPORTING RESULTS OF CLINICAL TRIALS INVOLVING CEPS

A careful review of relative importance, frequency and consistency of intervention effect across the components of a composite endpoint are the crucial steps in the interpretation of clinical trial results. Readers should essentially recognize the benefits and drawbacks of choosing to combine clinical outcomes.

All individual endpoints of a CEP should be reported separately in the study to prevent the misinterpretation and determine whether any component dominates the effect of treatment on the composite endpoint.^[30] In their classification of hierarchical levels of outcome information, Lubsen and Kirwan (2002) indicated 4 levels.^[38] Level 1: All-cause mortality, Level 2: Cause-specific mortality, Level 3: Non-fatal clinical events, Level 4: Symptoms, signs and para-clinical measures. All possible outcomes from level 1 to level 4 should be considered and displayed in mutually exclusive categories. Misinterpretation of the effect can occur when the analysis for an endpoint other than all-cause mortality (level 1) ignores information from higher levels. In such cases an effect can be assessed by using endpoints that combine information from several levels which facilitate a better understanding of treatment effects.

Authors and journal editors should ensure that the reporting of the results of the clinical trial is unambiguous and avoids the suggestion that individual components of the composite have been demonstrated to be effective.^[37] Poor reporting of the results may lead to difficulty in interpretation of trial outcome where a composite endpoint is in use.^[32] The individual components of a CEP should be reported separately according to the importance of the result within the CEP. All components should be stated separately; even when some components of a CEP are statistically insignificant.

RECOMMENDATIONS

- All components of CEP should be reported independently to avoid misinterpretation and assess the effect of individual components on overall effect of treatment^[30,37,38]
- It should be ensured by authors and journal editors that description of trial results are unambiguous and avoid hypothesizing that individual components (of less clinical importance) have been effective^[9,30]
- Individual endpoints of a CEP should be reported according to hierarchical levels and in mutually

exclusive categories; Level 1: All-cause mortality, Level 2: Cause-specific mortality, Level 3: Non-fatal clinical events, Level 4: Symptoms, signs and para-clinical measures^[37,38]

SUMMARY

The present review focuses on the importance of using CEPs in clinical trials on patients with T2DM and disadvantages of inappropriate usage of CEPs. The review also focuses on suggestions for the design and reporting of appropriate CEPs for clinical trials. Use of CEPs in addition to individual treatment targets, helps assess the overall disease control using the intervention of interest. Use of a combination of clinical outcomes related to efficacy (reduction in HbA1c or SBP or LDL-cholesterol levels) and safety (hypoglycemia or weight gain) would address more than one therapeutic goal to address the net clinical utility of an intervention and avoid possible spurious effect of using one component in the analysis due to competing risk factor bias. This is important since most drugs used in diabetes can lower blood glucose levels but the concurrent impact on safety outcomes is not clinically proven and an assessment of this outcome can serve to differentiate and evaluate current and future glucose-targeted interventions. Among the different therapies for diabetes, incretin-based interventions have an advantage of achieving the glycemic efficacy and demonstrating safety over other commonly used therapies for patients with diabetes. They have the potential to lower HbA1c, decrease weight, have low risk of hypoglycemia as well as improve the beta-cell function in patients with diabetes.^[14] A recent meta-analysis of 26-week patient-level data from seven trials for a composite outcome of HbA1c <7%, no weight gain and no hypoglycemic events showed liraglutide (a GLP-1 receptor agonist) was clearly superior to the other drug classes. Similarly, a post-hoc analysis of data from a clinical trial in patients with inadequate glycemic control at baseline (HbA1c >6.5% and <10%) on metformin monotherapy demonstrated that sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor achieved a CEP of 'HbA1c reduction of >0.5% without hypoglycemia and weight gain^[39] over glipizide.

Use of CEP in trials can increase the statistical efficiency of the effect of an intervention by reducing the sample size and decreases the human and cost-related resources. This would not only help the people conducting trial to support registration of new drugs that have become arduous, lengthy, and expensive but also to redirect the diverting resources (by trial sponsors) just when they are most needed. However, interpretation of the results of CEPs should be read carefully both by the authors and

readers when considerable heterogeneity exists between the components pertaining to either the importance, or magnitude of treatment effect. There is a requirement for the rigorous development of guidelines for the use of CEPs in clinical practice that would help in overcoming the problem of limited available resources for clinical trials. Though only few diabetes trials have been conducted demonstrating the benefits of using CEPs as primary endpoint, investigators should be cautious in identifying components and reporting the results of CEPs in future. Long-term outcome studies are required to determine if improvements in CEPs observed in diabetes clinical trials will have significant long-term effects on clinical outcomes.

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