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Review

Cardiovascular outcome trials in type 2 diabetes: A critical analysis

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1. Introduction

Diabetes is associated with two-fold excess risk of vascular diseases, which is independent of other traditional risk factors [1]. Patients with type 2 diabetes without any history of preceding cardiovascular disease have similar risk of myocardial infarction as patients with history of previous myocardial infarction without type 2 diabetes [2]. There is 50% increased risk of cardiovascular death and this is one of the main causes of mortality in patients with diabetes [3]. Controversies about the drugs used to control blood sugar and enhanced cardiovascular risk are there in literature since decades. The University Group Diabetes Program (UGDP) raised questions about the enhanced cardiovascular mortality associated with the use of tolbutamide [4]. Subsequent meta-analysis had revealed that second and third generation sulfonylureas are not associated with increased cardiovascular mortality [5]. In 2007 it was reported that rosiglitazone is associated with increased cardiovascular mortality. The report was a meta-analysis of more than forty studies, many studies were of very short duration (24 weeks), and few studies without any cardiovascular mortality were not included in the analysis [6]. Despite all the flaws of the study, it generated extensive discussion in the public and press, which culminated into the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance for the approval of glucose-lowering medications in 2008 and 2012, respectively [7,8]. FDA and EMA made it compulsory to have cardiovascular (CV) safety assessment, if the pre-marketing data revealed a hazard ratio (HR) between 1.3 and 1.8 with a 95% confidence interval (CI). If the premarketing clinical data had already established a H.R < 1.3, then post-marketing trial is not mandatory.

Licensing of any new drug requires multi phased preclinical and clinical studies. Phase 3 clinical trials are most expensive as they account for more than 90% of the total cost involved in the development of the drug [9]. CVOT imposes a great burden in terms of the cost of the development of new antihyperglycemic drugs. This may be unfavorable for innovation and investment. Because of huge financial burden, it leaves the field open only for the bigger pharmaceutical companies. The cost of the development is then transferred to the patients. 79% of 425 million people with diabetes are living in low and middle income countries. The average annual expenditure per person with diabetes is lower than 250 US dollar in this part of world, so they may not be able to afford the newer medication despite pressing need for the same [10].

2. Outcome summary of CVOT

After the advisory by FDA and EMA, several major CV outcome trials (CVOTs) had been conducted till now. Nine trials of different class of drugs have been completed till 2017 (Table 1) which includes three dipeptidyl peptidase–4 inhibitors (DPP-4i), two sodium-glucose co-transporter 2 inhibitor (SGLT-2i) and four glucagon-like peptide-1 analogues (GLP-1a) classes [11]. CV safety has also been established for insulin glargine and degludec [12–14]. Mostly patients with established CVD or high CVD risk were included in the study to ensure statistically significant number of events within a short time span. Recruited participants have long standing diabetes (mean 7.1–16.4 years) with baseline average A1C between 7.2 and 8.7% [11]. The ongoing CVOT has been summarized in Table 2.

3. DPP-4 inhibitors

Five CVOT involving almost 50,000 patients have been intended

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Table 1
Brief overview of completed CVOT till date.

Study	TECOS	SAVOR-TIMI 53	EXAMINE	ELIXA	SUSTAIN-6	EXSCEL	LEADER	EMPA-REG OUTCOME	CANVAS Program
Class of drug	DPP-4 Inhibitor			GLP-1 Analogue				SGLT-2 Inhibitor	
Drug	Sitagliptin	Saxagliptin	Alogliptin	Lixisenatide	Semaglutide	Exenatide QW	Liraglutide	Empagliflozin	Canagliflozin
Drug class	DPP-4 I	DPP-4 I	DPP-4 I	GLP-1 A	GLP-1 A	GLP-1 A	GLP-1 A	SGLT-2 I	SGLT-2 I
Intervention	Sitagliptin/ placebo	Saxagliptin/ placebo	Alogliptin/ placebo	Lixisenatide/ placebo	Semaglutid/ placebo	Exenatide QW/ placebo	Liraglutide/ placebo	Empagliflozin/ placebo	Canagliflozi/ placebo
N	14,671	16,492	5380	6068	3297	14,752	9340	7020	10,142
Follow-up (years)	3.0	2.1	1.5	2.1	2.1	3.2	3.8	3.1	2.4
Established CVD (%)	100	78	100	100	58.8	73.1	81	99	65.6
Diabetes duration (years)	11.6	10.3	7.1	9.3	13.9	12	12.8	.> 10 (57%)	13.5
Mean age (year)	65.5	65	61	60.3	64.6	62	64.3	63.1	63.3
Number of events accrued	1690	1222	621	805	254	1744	1302	772	1011
CHF(%)	18	13	28	22.4	23.6	16.2	17.9	10	14.4
Primary outcome	4-point MACE	3-point MACE	3-point MACE	4-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE
HR for Primary outcome	0.98	1.00	0.96	1.02	0.74	0.91	0.87	0.86	0.86
Key secondary outcome	3-point MACE	Expanded MACE	4-point MACE	Expanded MACE	Expanded MACE	Individual components of MACE	Expanded MACE	4-point MACE	All-cause and CV mortality
CV death	1.03	1.03	0.85	0.98	0.98	0.88	0.78	0.62	0.96
MI	0.95	0.95	1.08	1.03	0.74	0.97	0.86	0.87	0.89
Stroke	0.97	1.11	0.91	1.12	0.61	0.85	0.86	1.18	0.87
HF hospitalization	1.00	1.27	1.19	0.96	1.11	0.94	0.87	0.65	0.67
All-cause mortality	1.01	1.11	1.11	0.94	1.05	0.86	0.85	0.68	0.87
Progressive nephropathy		1.08			0.64		0.78	0.61	0.60

Table 2
Ongoing CVOT.

Study	CAROLINA	CARMELINA	REWIND	ITCA650	PIONEER 6	HARMONY Outcomes	DECLARE-TIMI	VERTIS CV
Drug class	DPP-4 Inhibitor		GLP-1 Analogues				SGLT-2 Inhibitor	
Drug	Linagliptin	Linagliptin	Dulaglutide	Exenatide in DUROS	Oral Semaglutide	Albiglutide	Dapagliflozin	Ertugliflozin
Intervention	Sitagliptin/ glimipride	Linagliptin/ placebo	Dulaglutide/ placebo	ITCA650/placebo	Oral Semaglutide/placebo	Albiglutide/ placebo	Dapagliflozin/ placebo	Ertugliflozin/ placebo
N	6000	7003	9901	4156	3176	9400	17,276	8000
CV status	CVD or age ≥ 70 years or ≥ 2 CV risk factors	High risk for CV events	CVD or ≥ 2 CV risk factors	Preexisting CAD,CVA,PAD	Preexisting CAD or > 60y with one CV risk factor	Preexisting CAD,CVA,PAD	High risk for CV events	Preexisting CAD
HbA1c levels (%)	7.5–8.5	6.5–10	≤9.5	≥6.5	–	>7.0	–	7.0–10.5
Age (years)	˃ 45 ˂ 85	≥18	≥50	≥40	≥50	≥40	≥40	≥40
Primary outcome	3-P MACE	3-point MACE	4-point MACE	4-P MACE	3-point MACE	3-point MACE	3-P MACE + HF hospitalization	3-point MACE

to evaluate the CV safety of DPP-4 inhibitors. Three of them has been completed, SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in myocardial infarction), EXAMINE (Examination of CV Outcomes with Alogliptin versus Standard of Care) and TECOS (Trial Evaluating CV Outcomes with Sitagliptin). Majority of patients had established CVD (78% in SAVOR-TIMI, 100% in EXAMINE, and TECOS). Patient included in EXAMINE had acute coronary syndrome during last 3 months. All the three completed trials achieved the primary endpoint of CV safety but none of them were associated with any evidence of CV benefit [15–17]. Saxagliptin in the SAVOR-TIMI-53 was found to be associated with 27% increased risk of hospitalization for heart failure (HR 1.27 [95% CI 1.07–1.51], P = 0.007), similar but statistically non-significant trend was noted with Alogliptin in the EXAMINE (HR 1.19 [95% CI 0.90–1.58], P = 0.220). This lead to a warning by the FDA particularly in patients who are having established heart and kidney disease [18]. CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) including 7003 patient and CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) including 6072 patients are ongoing trials to compare the non-inferiority of Linagliptin relative to glimepiride and to assess the CV safety of Linagliptin respectively [19,20]. CARMELINA trial met its primary endpoint of 3 point major adverse cardiovascular events (MACE) with no additional safety concern coming out, demonstrating long term CV safety with linagliptin. The full data including renal outcome would be read out on 4th October 2018 during European Association for the Study of Diabetes [21].

4. .SGLT-2 inhibitors

Nine CVOT including almost 62,000 patients have been intended to evaluate the CV and renal safety of SGLT-2i. Of these, two trials EMPA-REGOUTCOME and the CANVAS Program have been concluded, and each reported not only CV safety but also superiority for major adverse cardiovascular events and composite renal outcomes independent of glycemic control [22,23]. The results of ongoing seven CVOT will be available within the next 2–3 years [24–30]. EMPA-REG study included all patients with established CVD while in CANVAS one third patients had only CV risk factors with no prior CV events.

Emplagliflozin was associated with an increased rate of genital mycotic infection specially in women but no increase in additional adverse events, including ketoacidosis, fractures, hypoglycemia, lower extremity amputations, venous thromboembolism and acute kidney injury. CV protection appeared to be independent of empagliflozin's glycemic effect indicating that other mechanisms activated by SGLT-2i may be responsible for the favorable CV outcome [31–33]. Because of this empagliflozin received FDA approval for reduction of CV in adult patients with type 2 diabetes mellitus and cardiovascular disease, which was later endorsed by American Diabetic Association [34,35]. The fresh analysis of EMPA-REG OUTCOME study presented at the recent ADA 2018 conference suggested the CV benefits of empagliflozin to extend across TIMI risk categories for secondary prevention [36].

In preclinical studies in rodent model SGLT-2i has been found to decrease liver fat content. In a recent study from India use of empagliflozin was associated with significant decline in the liver fat content in patients with non alcohalic fatty liver disease [37].

Similar to empagliflozin, canagliflozin was associated with increased risk of genital mycotic infection but no increase in venous thromboembolism or hypoglycemic events. But there was increased risk of ketoacidosis though the number was small but it was significant. Along with this it was also associated with almost twofold increase in risk for lower extremity amputation (6.3 vs 3.4 events/1000 patient-years for canagliflozin vs placebo) and a 26% increased relative risk of fracture incidence in the canagliflozin group [23].

5. GLP-1 analogues

Eight CVOT including almost 60,000 patients have been intended to evaluate the CV safety of GLP1a. Out of these, four trials have been completed, the results of ongoing CVOT will be available within the next 1–2 years [11].

Lixisenatide was found to be CV neutral and it was not associated with any superiority in CV outcomes [38]. Once daily liraglutide was associated with significant reduction in 3 point MACE [39]. Similar to empagliflozin, liraglutide also received FDA approval for reduction of CV in adult patients with type 2 diabetes mellitus and cardiovascular disease [40], which was later endorsed by American Diabetic Association [35]. Semaglutide once weekly was also achieved superiority in terms of 3-P MACE, and currently it is under FDA review [41]. It was associated with significant decline in nonfatal stroke (HR 0.61, $P = 0.04$) and a nonsignificant decrease in nonfatal MI (HR 0.74, $P = 0.12$), with neutral trend for CV death or all-cause mortality. Once-weekly treatment with 2 mg of the long-acting extended-release exenatide was associated with neutral CV outcome. One of the factors for the results could be high proportion of patients discontinuing the drug (43%) [42].

6. Discussion

The FDA recommendation had changed the attention of diabetes research towards the cardiovascular safety of the drugs. According to FDA recommendation, a pooled analysis of independently adjudicated major adverse cardiovascular events, including cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke is required to rule out any significant increase in the cardiovascular risk [7]. In comparison to the FDA advisory, the European Medicines Agency (EMA) requirements are less stringent. EMA mandates a controlled outcome study with at least 1.5–2 years of follow-up when an adverse cardiovascular effect is suspected [8]. Each medicine used in the management of diabetes whether from the same or different class has the potential for additional properties that can influence the adverse events. Specific regulatory requirements need to be formulated for individual new drugs depending upon the preliminary data. As heart failure is not included as a specific outcome measure in the FDA advisory, only some of the CVOT have included heart failure as a secondary endpoint [43–45]. Incidence of heart failure is almost comparable to other cardiovascular disease in CVOT [46]. Inclusion of only cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke for accessing the cardiovascular safety may be inadequate. The thiazolidinedione are associated with fluid retention while DDP-4 inhibitors have been found to influence the B type natriuretic peptide. This may be the reason for their association with heart failure [47–49].

In presence of these evidences there is a need to individualized goals for the safety assessment of a particular drug. So while planning a CVOT depending upon the preliminary data of initial phases of drug development, heart failure can be included as the primary or secondary endpoint [45].

One of the gratifying results of the CVOT to date, no new serious cardiovascular adverse effect has come out from these analyses, instead now there are evidence of cardiovascular benefit from the study with SGLT-2i and GLP-1a.

Because of the evidence which have now, we need to answer that what quantity and quality of evidence is required to have approval from the regulatory authorities regarding cardiovascular safety. Is it justified to expend such a huge amount of resources just to rule out adverse effect instead of assessing the efficacy?

Having tight supervisory policies may be reasonable if there is good quality evidence for the same, but putting unselective guidelines may lead to unnecessary overregulation. As unintended and harmful effect can occur with the use of any medicine, it is important to decide that what is the level of acceptable risk and what level of confidence is required by the patients and health care providers to achieve the benefits associated with better glycaemic control, if no evidence of CV protection is found in the CVOT.

Major source of mortality in patients with diabetes is cardiovascular disease, so there should be more stress and resources for establishing the effectiveness rather than ruling out harm. These trials have mandate to rule out any excessive CV mortality so it need to be seen whether they can optimally detect any CV benefit if it is present. As per requirement from FDA they included patients with high risk for CV events or they already have established cardiovascular disease [11]. This approach is useful because of high risk population, enough number of CV events can be achieved in a short duration and with less number of patients so that statistical significance can be achieved. From the CV safety point this subgroup of patients are more prone to adverse CV outcome with the drug if they exist and they are least likely to have any benefit in terms of CV outcome [11].

The findings from the follow-up of the UKPDS have demonstrated significant CV benefit after long duration of follow-up in intensively treated arm. While ADVANCE, ACCORD, VADT trials failed to show any CV benefit in the intensively treated arm. But there was an important difference between the UKPDS and other

studies in terms of the recruited patients [50–53]. In UKPDS only the newly diagnosed patients were included, while in the remaining studies only patients with long standing diabetes were included. Though CVOT trials after FDA guideline have either shown benefit or they were neutral in terms of CV safety. But we need to have some data from the newly diagnosed patients of diabetes before extrapolating the findings from the CVOT to this group of patients. There are chances that even those drugs which have neutral outcome from the CVOT that they can have beneficial effect in this subgroup of newly diagnosed patients. Because GLP-1a, DPP-4 inhibitors have many pleiotropic effects apart from glucose lowering activity, real world data from patient with low CV risk are needed to demonstrate any CV benefit in this subgroup of patients [54,55].

The CV safety of sulfonylureas has not been established conclusively till date despite having several concerns for the same [56]. Between 30 and 50% of patients in different CVOT were on sulfonylureas, this may have some confounding effect on the outcome of these trials [11]. CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes), CARMELINA [Cardiovascular and Renal microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus] will come up with the answer in near future [19,20].

CVOT has shifted the focus on the secondary prevention of CVD in diabetes. As we know that primary prevention always is better than secondary prevention, so the research in the field of diabetes is in dire need of having strategies for primary prevention of diabetes and its associated complications. The CVOT are being carried out by the pharmaceutical industry, there is unmet need of research regarding the primary prevention of diabetes as well as cardiovascular disease in diabetes.

The neutral outcomes of some of the trials and superior outcomes of other trials suggest a unique effect of few drugs which is independent of its ability to lower serum glucose. It is possible that primary prevention of patients with type 2 diabetes for CV events can be expected with extended follow-up, if one exists. But such an approach does not appear feasible at this moment. A change in the regulatory guidelines is needed for this approach, for example by prolonging the patent protection to the manufacturers willing to pledge a durable drug development program [57].

Though complications of diabetes other than cardiovascular event have been included in many of the CVOT, but they still need more clarification. For example neuropathy is one of the most common complications of diabetes and it is a major cause of morbidity, autonomic neuropathy when present increases the risk of mortality. Recently diagnosed cases of diabetes should be included for assessment of microvascular complications. Like the CV benefit which appears independent of glucose lowering capacity, the similar effect on microvascular complication needs further evaluation [32].

Diabetes is a state of low grade inflammation, and it is invariably found to be associated with increased inflammatory cytokine levels. Further these elevated levels have been found to influence the mortality in a positive way. Increased IL-6 level have been to be associated with increased CV mortality [58]. The effect of these newer drugs on the cytokines levels needs further analysis.

Type 2 diabetes is characterized by relentless progression of beta cell failure. This failure is associated with loss of response to oral hypoglycemic drugs, increased glycemic variability, loss of glycemic control. The effect of newer medication on the beta cell survival needs exploration [59]. Also to assess the glycemic durability of these drugs, we need long term studies with prolong follow up.

The CVOT is not supposed to assess either glycemic effectiveness or glycemic effects, as possible components of drug superiority in lowering cardiovascular risk. Many question were raised while reviewing the saxagliptin and alogliptin trials, wisdom of enduring the burden of CVOT on all new diabetes medications in order to accomplish market approval, were questioned by multiple advisory members of the FDA committee [18,60].

The evidence obtained from the multiple CVOT needs to be incorporated into the whole of evidence to measure the effect and unintended consequences of the 2008 FDA guidance being applied to all new drugs. Should the current FDA guidance on cardiovascular safety be applied to all new diabetes drugs, especially when another drug from the same class has established CV safety profile?

FDA guideline issued in 2008 is aimed at CV safety of all new diabetes drugs and it is not aimed at the unanticipated safety concerns. To identify unexpected adverse events, the FDA has a variety of surveillance mechanisms in the postmarketing phase. A more targeted approach is needed taking into the account of all new available evidence and a discussion for the same, is needed between scientific community and the FDA [60]. After initial approval of a medication, the FDA can issue a directive for additional targeted postmarketing safety studies to address specific safety signals that arises either during drug development or during postmarketing phase. This strategy has been successfully applied to investigate the enhanced risks of pancreatitis and pancreatic cancer with DPP-4 inhibitors and GLP-1 receptor agonists. It could be more prudent to conduct such studies only when there is some concern in regarding the safety in preapproval period, and a credible mechanism for the hazard [61].

One more difficulty is that of comparing the results of different CVOT, because of the fact that the definition of CVD risk and/or CVD is different for each trial, and there is great variability in the severity of CVD among the participants of the different study. Along with the inclusion of the patients there is great variability while defining the endpoints. The trial duration is also different in different studies. Different approaches for glycaemic control have been utilised in the placebo arm of different CVOTs [43,60]. To improve the extrapolation of the results from the CVOT to the general population, there is need to improve the trial design of the CVOT. In the first summit of the Diabetes and CVD (D&CVD) EASD Study Group, it was agreed by the members that there should be uniformity in the primary endpoint of the CVOT [62].

The pathophysiology of the various CV events are different, thrombosis leads to myocardial infarction [63], arrhythmia is responsible for the majority of the CV death [64] while stroke can occur because of both thrombosis and bleeding [65,66]. These points should be considered while analysing the outcome the CVOT, because the finding in one outcome parameter can't be translated to another endpoint because of the different pathophysiology [67].

The result of EMPA-REG OUTCOME trial gives assurance regarding patients of diabetes and established CVD that they are likely to receive benefit of empagliflozin therapy similar to the patients in the trial [21]. But more evidence is required prior to assume that it will have similar effect in patients of diabetes without established CVD. CANVAS Program included patient of diabetes with and without established CVD, as one third of the participants had only CV risk factors. Less impressive benefit in CV death in the CANVAS Program when compared with EMPA-REG OUTCOME trial (HR for CV death 0.96 and 0.62 respectively for CANVAS and EMPA-REG) can be because of this fact only [23]. Similarly while analyzing the results of LEADER trial it was found that liraglutide was more effective in reducing the CV risk in patient with established CVD (HR 0.83 [95% CI 0.74–0.93] compared with HR 1.20 [95% CI 0.86–1.67]) in those without CVD, and the difference was statistically significant (P 0.04) [39]. So far FDA has approved liraglutide for CV benefit only in patients of diabetes with

established CVD.

The FDA mandated design of the current CVOT is an aberration to the natural history of diabetes. As mandated by the FDA and EMA, the recruited patients with diabetes have relatively short timelines. The completed as well as the ongoing CVOTs assess only short-term outcomes occurring within 5 years of treatment. The UKPDS and DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) trials have demonstrated that treatment early in the course of diabetes improves many outcomes including blindness, renal failure, amputation, CV death, and others. And the appearance of these beneficial effects usually occurs after five years of treatment [51,68,69]. As the occurrence of CV events are late in the course of disease so CV benefits of early intensive glycemic control were observed only after more than 10 years of follow-up. But the long-term benefit of early intensive glycemic control has been inferred from the observational studies and perhaps with incomplete data. So there is some doubt that this finding is a result of glycemic control only. Any nonglycemic benefit of these treatments in these trials cannot be determined. The discordant result of ACCORD, VADT and recent CVOTs including that of empagliflozin, canagliflozin, liraglutide, and semaglutide is suggestive of effects beyond simply lowering glucose in patients with advanced diabetes. In the trial involving semaglutide there was pronounced early decline in HbA1c which could modify the outcome. Can these benefits be replicated when the therapy with these agents starts at the diagnosis of diabetes or when there is no apparent CVD or CV risk factors, this needs to be seen. Any long term risk with these drugs can't be derived from the current CVOTs as they are of short duration. Apprehensions of long term risk may be higher for drugs which act at multiple sites and have many pleotropic actions which are currently not very clearly understood, including TZDs, DPP-4 inhibitors, and SGLT-2i [11].

There are some innocent appearing bystanders in the CVOTs. EMPAREG OUTCOME and CANVAS have shown that SGLT-2 therapy is associated with small increase in the LDL level. Empagliflozin has been found to be associated with increased risk of stroke. The CVOTs including GLP-1a have been found to be associated with increased heart rate. All these finding appears non-significant at this moment, but there long term effect needs prolonged follow-up [21,23,39].

7. Summary

After the FDA advisory in 2008 regarding the CV safety of drugs used in the treatment of diabetes, the data collection has improved a lot specially with reference to CV outcomes. As none of the completed trial revealed non inferior outcomes, while few have revealed strong evidence of CV benefit. Because of these evidences, now questions are raised that whether we should still vouch for the CV safety or move forward towards the assessment of efficacy in terms of CV outcomes. In addition to the CV safety data, these trials also provided other valuable information such as renoprotection and increased risk of lower extremity amputation, increased risk of heart failure with some agents. In presence of the current evidence more individualized approach might be suitable, where the necessity for cardiovascular outcome studies would be decided by watchdogs for each specific drug depending on its mechanism of action, phases 1,2 and preclinical data, and the safety database. There is always possibility of unexpected adverse events, and robust surveillance mechanisms in the postmarketing phase may identify those problems.

More data is needed from the real world where many patients have low CV risk, what is the effect of these drugs in this subgroup needs to be seen in long run.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2018.09.001.

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