The Design and Rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE) – TIMI 58 Trial

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Abstract

**Background:** Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT-2) inhibitor that reduces blood glucose in patients with type 2 diabetes mellitus (T2DM) by promoting glycosuria via inhibiting urinary glucose reabsorption. In addition to improving blood glucose control, treatment with dapagliflozin results in glucose-induced osmotic diuresis, weight loss, and blood pressure lowering. Previous trials of SGLT-2 inhibitors showed reductions in CV events, including CV death and hospitalization for heart failure, and ischemic events in patients with atherosclerotic cardiovascular disease (ASCVD), with less benefit apparent in those at risk for ASCVD.

**Research Design and Methods:** DECLARE – TIMI 58 [NCT01730534] is a phase 3b randomized, double-blind, placebo-controlled trial designed to evaluate the CV safety and efficacy of dapagliflozin that has completed enrollment of 17,160 patients with T2DM and a history of either established ASCVD (n=6971) disease or multiple risk factors for ASCVD (n=10,189). Patients were randomized in a 1:1 fashion to dapagliflozin 10 mg or matching placebo. The primary safety outcome is the time to the first event of the composite of CV death, myocardial infarction (MI), or ischemic stroke (major adverse cardiovascular events; MACE). The co-primary efficacy outcomes are the composite of CV death, MI, or ischemic stroke and the composite of CV death or hospitalization for heart failure. This event-driven trial will continue until at least 1390 subjects have a MACE outcome, thereby providing >99% power to test for the primary outcome of safety of dapagliflozin measured by rejecting the hypothesis that the upper bound of the confidence interval is > 1.3 for the primary outcome of MACE, as well as 85% power to detect a 15% relative risk reduction in MACE and an estimated 87% power to detect a 20% reduction in the composite of CV death or hospitalization for heart failure at a one sided alpha level of 0.0231.

**Conclusion:** The DECLARE – TIMI 58 trial is testing the hypotheses that dapagliflozin is safe (does not increase) and may reduce the occurrence of major CV events. DECLARE – TIMI 58 is the largest study to address this question with an SGLT2-inhibitor in both patients with established CV disease and in those without CV disease, but with multiple risk factors.

**Background**

Patients with diabetes are at increased risk of cardiovascular (CV) disease, and among patients with CV disease, those with diabetes have higher rates of acute ischemic events and death[1](#_ENREF_1). Decades of research have shown that glucose lowering in type 2 diabetes improves microvascular events in a proportional fashion, but uncertainty remains regarding a clear relationship between glucose lowering and macrovascular events such as myocardial infarction and stroke[2](#_ENREF_2),[3](#_ENREF_3). Indeed, currently available clinical trial data suggest that the mechanism of glucose lowering or that the specific therapy chosen may be more important than the extent of glucose lowering on cardiovascular outcomes[4](#_ENREF_4). With antihyperglycemic therapy a focus of treatment for type 2 diabetes, concerns regarding the CV safety of several classes of glucose lowering agents (GLAs) prompted the United States Food and Drug Administration to introduce guidance that requires the ascertainment of an adequate number of CV events in trials to exclude a CV safety risk with prescribed statistical precision[5](#_ENREF_5). Because of this guidance, there has been a remarkable increase in the number and size of CV outcomes trials for GLAs. For example, three large scale trials of dipeptidyl peptidase 4 (DPP4) inhibitors have been conducted and results published, evaluating more than 35,000 patients with or at risk for ASCVD[6-8](#_ENREF_6). These trials have demonstrated with clarity that there is neither an increase nor decrease in CV ischemic events with these agents; however, a concern regarding an increase in heart failure (HF) with some but not all members of this class has emerged[9](#_ENREF_9). This level of precision is in contrast to long-standing, often quoted data from trials such as UKPDS – a trial of multiple agents in patients, with the assertion that metformin improves cardiovascular outcomes based on sub-study of fewer than 400 patients randomized to metformin and few cardiovascular events[10](#_ENREF_10).

Dapagliflozin is among a class of compounds referred to as sodium-glucose

co-transporter-2 (SGLT2) inhibitors. Dapagliflozin is a highly selective and reversible inhibitor of SGLT2[11](#_ENREF_11). SGLT2 is localized to the renal proximal tubule where it reabsorbs most of the glucose normally filtered through the glomeruli each day[12](#_ENREF_12). SGLT2 inhibition leads to pharmacologically promoted glycosuria. Inhibition of urinary glucose reabsorption leads to direct, insulin-independent glycemic effects including lowering of plasma glucose and thus hemoglobin A1c (HbA1c)[13](#_ENREF_13).

Dapagliflozin has beneficial effects on CV risk factors in addition to its glucose-lowering effects[14](#_ENREF_14). Many potential mechanisms have been proposed for the CV benefits of SGLT-2 inhibition[15](#_ENREF_15),[16](#_ENREF_16). Dapagliflozin 10 mg (the dose studied in DECLARE – TIMI 58) lowers systolic blood pressure by 3 to 5 mmHg compared with placebo[17](#_ENREF_17). Dapagliflozin also results in loss of body weight compared with placebo or other GLAs, postulated to be related to both changes in fluid volume and to changes in calorie balance resulting in fat loss [15](#_ENREF_15),[18](#_ENREF_18).

In a meta-analysis of phase 2 and phase 3 studies of dapagliflozin, there was a suggestion of CV benefit, particularly a tendency toward reductions of a composite of CV events, including CV death, hospitalizations for HF and MI with no clear effect on stroke[19](#_ENREF_19). In these studies, a numerically higher rate of bladder cancer was observed with uncertainty regarding whether this finding was related to the drug, to detection bias due to increased urinary symptoms with an SGLT2 inhibitor, or simply to play of chance.

The DECLARE – TIMI 58 study was designed to test the hypotheses that dapagliflozin (1) does not increase MACE; and (2) will reduce the incidence of the CV events in patients with T2DM with established ASCVD or with multiple risk factors for ASCVD, but without established ASCVD. During the course of DECLARE-TIMI 58, new data emerged from two other large-scale cardiovascular outcomes trials of SGLT-2 inhibitors, the EMPA-REG OUTCOMES trial of empagliflozin[20](#_ENREF_20) and the Canagliflozin Cardiovascular Assessment Study (CANVAS) program for canagliflozin[21](#_ENREF_21). In the EMPA-REG Outcome Trial, empagliflozin reduced the composite of CV death, MI, or stroke by 14% over a median follow up of 3.1 years[20](#_ENREF_20). This included a marked reduction in CV death by 38%. Also observed was a reduction of hospitalization for HF by 35%. In the CANVAS program, canagliflozin reduced MACE by 14% and hospitalization for HF by 33%; there was a nonsignificant trend towards a reduction in CV death. The efficacy tended to be better in patients with established cardiovascular disease. The CANVAS trials program also showed a significant excess of amputations in patients treated with canagliflozin[21](#_ENREF_21). These external data led to several modifications of the DECLARE-TIMI 58 design as we note below. Moreover, they set the stage for the study to: validate the compelling but unexpected findings with SGLT2 inhibition reducing CV death and hospitalization for HF, clarify if the magnitude of benefit differs in patient with and without established cardiovascular disease, and provide important information on key safety outcomes such as amputation and bladder cancer.

**Study Design and Population**

DECLARE – TIMI 58 [NCT01730534] is a multicenter, multinational randomized, double blind, placebo-controlled, phase 3b-trial designed to evaluate whether treatment with dapagliflozin is safe and effective from a CV standpoint (Figure 1). Safety will first be assessed using a non-inferiority analysis of the triple composite endpoint of MACE with an upper bound of the 95% CI of the hazard ratio <1.3 of dapagliflozin compared with placebo (primary safety assessment). The trial was originally designed with a primary efficacy assessment to determine whether dapagliflozin reduces MACE, with hospitalization for HF as a key secondary endpoint. Following presentation of the empagliflozin CV outcomes trial, and completion of enrollment in DECLARE – TIMI 58, but *before any data monitoring committee (DMC) efficacy assessments*, the trial Executive Committee determined that because of compelling outside data, to elevate the composite of CV death or hospitalization for CHF to a co-primary efficacy endpoint, with an equal split of the alpha between the two outcomes. The intention to make this change was communicated to the US FDA on December 23, 2015 and the protocol was subsequently amended to reflect these changes. The description of the trial herein will be based on the amended protocol.

The duration of the trial was planned to be approximately 6 years, with a median follow up of 4.5 years. The actual duration of the trial will be based on accrual of at least 1390 subjects with MACE events. More than 25,000 subjects were enrolled in the run-in period to ultimately randomize 17,190 subjects aged at least 40 years, with a CrCl > 60 ml/min with documented T2DM, HbA1c between 6.5% and ≤12.0%, and either a history of established CV disease or multiple risk factors for vascular disease but without established CV disease were randomized. Full inclusion and exclusion criteria are presented in Appendix A. Subsequently, 30 subjects were excluded from all analyses because of significant GCP violations at a single site in a different trial of dapagliflozin, casting uncertainty on the validity of this site’s data, therefore the primary total for assessment was 17,160, referred to here as the randomized total.

A total of 6,971 subjects were randomized with established stable symptomatic CV disease (ischemic heart disease, cerebrovascular disease or peripheral artery disease). A total of 10,189 subjects were randomized without established CV disease with multiple cardiac risk factors. Multiple risk factor subjects were men aged > 55 and women aged > 60 with at least one additional traditional CV risk factors including dyslipidemia, hypertension, or tobacco use. Full disease state and risk factor descriptions are detailed in Appendix B.

Key exclusion criteria included acute cardiovascular or cerebrovascular event within 8 weeks of randomization, lifetime history of bladder cancer or recurrent urinary tract infections, history of any malignancy within 5 years, use of an open-label SGLT2 inhibitor, pioglitazone or rosiglitazone.

**Treatment Protocol and Follow-up Procedures**

Eligible patients were enrolled in the run-in period. During the 4-8 week run-in period, all subjects were assigned in a single blind fashion to placebo. Blood and urine testing were performed at the enrollment visit. If blood test revealed a result meeting an exclusion criterion, if patients did not show adequate adherence to therapy, or if patients did not wish to continue, the subject was not randomized. If hematuria was detected on either dipstick or microscopy, it was incumbent on the investigator to exclude bladder cancer using medically appropriate assessment per local standards of care. If bladder cancer was confirmed during run-in or could not be reasonably excluded, the patient was not randomized.

At the randomization visit, subjects were assigned either dapagliflozin 10 mg or matched placebo. The use of all other antihyperglycemic therapies (apart from excluded medications) at baseline and throughout the trial were at the discretion of the treating physician. If unexplained hematuria was detected at randomization or subsequent visits, evaluation for cause was mandated by the protocol. After randomization, subjects return for in-person study visits at 6-month to assess for clinical and safety events and for study drug adherence, and for clinical evaluation and laboratory testing. Subjects are contacted via telephone every 3 months between visits for clinical and safety event assessment and compliance. All subjects are intended to undergo a final visit at completion of the study. Subjects who prematurely discontinue study drug are followed up, ideally in person, but if not possible, by telephone or clinical records until the end of the study.

Based on the findings from other trials of SGLT2 inhibitors, additional efforts were initiated for data collection and characterization of heart failure. Sites were asked to review each subject’s baseline HF status and provide ejection fraction, if measured, in all subjects, and to report CHF status and cardiac function measurements at each visit. Fracture and peripheral artery, diabetic ketoacidosis (DKA) and non-traumatic amputation events were also evaluated in detail with specific data collection and reporting. In addition to these efforts, guidance regarding clinical evaluation and prevention of DKA and events leading to amputation were provided.

**Study Objectives and Endpoints**

*Primary Endpoint and Objectives*

The primary safety and co-primary efficacy endpoint of the trial is the composite endpoint of CV death, MI, or ischemic stroke (MACE). This primary objective will be evaluated in two steps. The first step will determine if dapagliflozin is non-inferior to placebo for the incidence of MACE assessed with a non-inferiority margin of 1.3. If non-inferiority is statistically confirmed, the second step will be to determine if dapagliflozin reduces the incidence of the co-primary endpoints.

The co-primary efficacy endpoints are (1) MACE and (2) the composite of CV death or hospitalization for heart failure. The event definitions are consistent with the Standardized Definitions for End Points Events in Cardiovascular Trials created by the Standardized Data Collection for Cardiovascular Trials Initiative collaboration between academics, industry and regulators[22](#_ENREF_22). Event definitions are found in Appendix C. All elements of the primary safety and efficacy endpoints will be adjudicated by members of an independent clinical events committee (CEC, appendix E) unaware of treatment assignment. Analytic details are discussed below.

*Secondary Objectives*

Two secondary efficacy objectives are prespecified. The first is to determine whether treatment with dapagliflozin reduces the risk of a composite renal endpoint consisting of a confirmed, sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m2 and/or ESRD (dialysis ≥90 days or kidney transplantation or confirmed sustained eGFR <15ml/min/1.73m2) and/or renal or CV death. The second is to determine whether treatment with dapagliflozin reduces the risk of all-cause mortality.

*Additional safety objectives*

In addition to the primary safety assessment, safety and tolerability will be assessed from adverse events, serious adverse events, adverse events of special interest including liver events, fractures, malignancies (particularly bladder), hypersensitivity, urinary infections, non-traumatic amputations and other vascular events, diabetic ketoacidosis, and major hypoglycemic events.

*Exploratory objectives*

Other efficacy and safety objectives include whether dapagliflozin compared with placebo when added to current background therapy will result in a reduction of: the individual components of the co-primary efficacy endpoints (CV death, MI, ischemic stroke and hospitalization for HF) and a broader clinical composite endpoint of cardiovascular death, MI, ischemic stroke, hospitalization for HF, hospitalization for unstable angina pectoris, or hospitalization for coronary or non-coronary revascularization. Other efficacy objectives include change in HbA1c, initiation of insulin, increase in anti-hyperglycemic therapy, major hypoglycemia and/or hospitalization for hypoglycemia, development of albuminuria, regression of albuminuria, change in body weight, and change in blood pressure.

**Statistical Considerations**

The primary analyses for safety and efficacy will be based on time to first event for the noted composite endpoints in all randomized patients (i.e. intent-to-treat principal) using events adjudicated and confirmed by the CEC. Hazard ratios (HR) and confidence intervals (CIs) will be derived from a Cox proportional hazards model with a factor for treatment group in the overall population as well as stratified by: (1) CV risk category (established CV disease, or multiple risk factors without established CV disease) and (2) baseline hematuria. A sensitivity analysis of the primary objectives will be performed using an on-treatment analysis. Aside from the primary non-inferiority safety assessment, all safety outcomes will be assessed using a safety analysis dataset, defined as all patients receiving at least 1 dose of randomized study treatment with data recorded after the first dose and corrected for actual treatment received in the event of erroneous treatment assignment. Key prespecified subgroups of interest are noted in the statistical analysis plan and include but are not limited to enrollment stratum (CV disease, multiple risk factors), history of heart failure, renal function, age, gender, duration of diabetes, and diabetes treatments. Subgroups will be assessed without adjustment for multiple testing.

*Control of Type 1 Error:*

The testing of the primary safety and efficacy outcomes will be assessed in a closed testing procedure to preserve alpha (Table 1). To account for 2 data monitoring committee interim analyses to evaluate for overwhelming efficacy at approximately 33% and 67% of anticipated primary efficacy events, using an O’Brien-Fleming spending rule, an alpha penalty will be taken leaving a one sided alpha of 0.0231 (two-sided 0.0462) to establish nominal significance. First, the primary non-inferiority analysis will assess whether the upper bound of the confidence interval of the composite of CV death, MI or ischemic stroke is <1.3 using the full one-sided alpha of 0.0231. If the null hypothesis regarding the non-inferiority analysis is rejected, then the alpha will be split evenly between the two co-primary efficacy composites (MACE and CV death or hospitalization for HF). If either is significant at a one sided alpha level of 0.0115, alpha-recycling will be performed[23-25](#_ENREF_23) to allow assessment of the other composite using the full one sided alpha of 0.0231.

*Data Safety Monitoring*

Periodic assessments of safety and efficacy are performed in DECLARE – TIMI 58 by an independent Data Monitoring Committee (DMC). The DMC is composed of 5 members with appropriate expertise, as noted in Appendix E, and appointed jointly by the sponsor and the academic leadership of the trial. Periodic safety analyses are performed to review for safety including bladder cancers, based on accrued enrollment, incident bladder cancers (every 8 events until 32), and accumulation of 33, 50, 67% of efficacy events. Two interim analyses for overwhelming efficacy in terms of reducing MACE and all-cause mortality were pre-specified to occur after accrual of 33% and 67% of the planned MACE outcomes. The one-sided alpha thresholds for the analyses are 0.000095 and 0.00614, respectively, resulting in the alpha penalties noted above.

*Sample Size Determination*

A total of 1390 subjects with MACE events will be required to have 85% power to demonstrate superiority of dapagliflozin to placebo if the true HR is 0.85, i.e., a 15% relative risk reduction, with a one-sided alpha of 0.0231. To achieve this number of MACE events, the study was designed based on the following assumptions. Approximately 17,150 randomized patients will be required for the study, with an assumed annual event rate of 2.1% on placebo, and an annual study withdrawal rate of 1.0% over a 3-year accrual period and 3-year minimum follow-up. With above assumptions and 1390 MACE events, it is estimated to have >99% power to test the hypothesis of non- inferiority. The trial was not formally powered for the second of the co-primary endpoints, CVD or HHF. However, we anticipate that approximately 770 events for this composite will correspond to the 1390 MACE events. This event number would provide 87% power to detect a hazard ratio of 0.80 with a one-sided alpha of 0.0231. As noted above, for the alpha to be recycled (ie, for a hypothesis to be tested at 0.0231), the other hypothesis must achieve significance at 1-sided threshold of 0.01155. At the 0.01155 level, the power to detect a 20% reduction in CV death or hospitalization for heart failure is approximately 80%. If a reduction of 25- 30% were seen in CVD/HHF as was observed in EMPA-REG Outcomes[20](#_ENREF_20) and CANVAS[21](#_ENREF_21), there would be greater than 90% power at either alpha level.

The Executive Committee of the trial will monitor the aggregate event rate and rate of study drug discontinuation and may alter the number of primary endpoint events or duration of the trial in accordance with the goals of the trial. Such changes will be made in consultation with the sponsor.

**Biomarkers and Genetic Analyses**

Biological samples were collected and stored for future analysis. Future analyses of stored biosamples will be used to assess biomarkers that reflect inflammatory, thrombotic, metabolic, vascular, and hemodynamic markers of risk in subjects with diabetes and atherosclerotic risk. Key objectives will be to evaluate the ability of biomarkers alone or in combination to predict CV risk in the population, to identify groups with a greater absolute/relative benefit of dapagliflozin, and to assess the effects of dapagliflozin on biomarker levels over time. An additional objective was to collect and store serum and deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response, (e.g., distribution, safety, tolerability and efficacy) to treatment with dapagliflozin or other drugs and genetic factors that may influence susceptibility to T2DM and/or associated cardiovascular conditions and their risk factors.

*Study Organization*

The DECLARE – TIMI 58 Trial is a large-scale CV outcomes trial conducted world-wide with 882 investigative sites in 33 countries. The first patient was enrolled in April 2013. Key participating members are listed in Appendix E. The trial was designed and implemented by an Executive Committee (EC) which consisted of a collaboration between members of the TIMI Study Group, the Hadassah Medical Organization, additional leading academic medical experts and the sponsors [initially Astra Zeneca (Wilmington, DE and Gothenburg Sweden) and Bristol Myers Squibb (Princeton, NJ) and subsequently at the time of the protocol update and submission of this manuscript by Astra Zeneca alone]. The Executive committee was responsible for the protocol design and overall scientific guidance and supervision of the trial. A steering committee including the EC members, world-wide country lead investigators, operational staff, and additional content experts was responsible for scientific guidance and local implementation of the protocol. The authors are responsible for drafting and editing of this design paper and its contents.

Data analysis will be conducted in parallel between the Sponsor and the TIMI Study Group. The TIMI Study Group and The Hadassah Medical Organization will have complete access to the study database, and will submit results for presentation and publication of the primary results in a peer-reviewed medical journal. The trial was funded by and research grants for trial activities were provided to the Brigham and Women’s Hospital (TIMI) and the Hadassah Medical Organization from Astra Zeneca.

**Additional Responses to External Events:**

As noted above, the results of two other large-scale outcomes trials of SGLT-2 inhibitors (EMPA-REG OUTCOMES trial[20](#_ENREF_20) and the CANVAS program[21](#_ENREF_21)) led to changes in the endpoints and data collection in DECLARE-TIMI 58. In addition, results summaries were prepared and distributed to all sites to ensure all investigators were aware of these external data. In the case of EMPA-REG OUTCOME, with a mortality benefit observed, all subjects were informed and were required to sign an updated informed consent document to continue participation in the trial. The data safety and monitoring board was made aware of external trial results and asked to consider these data (both benefits and risks) in their review of the safety and appropriateness of DECLARE – TIMI 58. In addition, there were interactions with regulators regarding external trial results, ethics of ongoing placebo-controlled study of SGLT-2 inhibitors, safety reviews, and reporting to sites and subjects of updates to drug labels.

**Discussion**

CV disease is the leading cause of death among people with diabetes[1](#_ENREF_1), therefore finding antihyperglycemic therapies that are at the very least safe and ideally effective in reducing risk of CV events in this population is a key treatment goal. In addition to atherothrombotic cardiovascular events, such as MI and stroke, patients with T2DM are at increased risk of morbidity and mortality related to HF[1](#_ENREF_1),[26](#_ENREF_26). Though both ischemic and HF risks have been known for decades, demonstrating CV benefit from oral blood glucose lowering agents during treatment has proven elusive in T2DM.

Based on mechanism, SGLT-2 inhibitors represent a promising class of agents for glycemic control with low risk of hypoglycemia in patients with T2DM and CV disease. These agents reduce blood sugar in an insulin independent manner, and tend to have favorable effects on blood pressure, blood volume, and weight[15](#_ENREF_15). In addition, there are mechanistic data that suggest that SGLT-2 inhibition may directly improve vascular function, renal function, have anti-inflammatory effects, and favorable effects on the sympathetic nervous system which could be expected to reduce CV events[12](#_ENREF_12),[15](#_ENREF_15). However, there are several classes of drugs where clinical CV outcomes were discordant with mechanistic expectations for both atherothrombotic events and HF[27](#_ENREF_27).

The EMPA-REG Outcome trial demonstrated, for the first-time, in a well-powered trial that an oral GLA could reduce cardiovascular events including cardiovascular death in a population of patients with CV disease receiving indicated background preventive therapies[20](#_ENREF_20). Further, there were early and marked reductions in HF events[28](#_ENREF_28) among patients with and without HF at baseline. Despite these exciting results, uncertainty remains. In the setting of many prior antihyperglycemic agents with neutral or unfavorable CV results, some have remained skeptical of fully accepting the implications of the results of a single trial[29](#_ENREF_29), especially given that CV mortality was not a prespecified primary or secondary outcome. Though some guidelines have recommended SGLT-2 inhibition for cardioprotection, guideline committees have not uniformly endorsed empagliflozin or SGLT-2 inhibitors as preferred therapy for CVD patients[3](#_ENREF_3), though the US FDA has granted an indication for the prevention of CV death in patients with established CV disease. The CANVAS program of 10142 subjects with or at risk for vascular disease and affirmed a CV benefit with a significant reduction in CV death, MI, or stroke[21](#_ENREF_21). Benefits seemed to be predominantly seen in patients with established CV disease, and not in those with multiple risk factors alone. Based on the hierarchal statistical testing, no definitive statement on significant reduction in heart failure could be made, but nominal reductions were qualitatively similar to those seen in EMPA-REG. In addition to the benefits seen in CV events, there was also a nearly two-fold increase in amputations, primarily of the toe or at the level of the metatarsal, and an increase in bone fractures.

The DECLARE – TIMI 58 trial is a large-scale, CV outcomes trial that will determine the cardiovascular safety and efficacy of dapagliflozin. In addition, this trial could both validate and extend the results of prior SGLT-2 inhibitor studies in important ways. If an additional well-powered, rigorously conducted, CV outcomes trial within a class of agents was to show CV benefit, this would increase the level of evidence in support of SGLT-2 inhibition being cardioprotective. Moreover, DECLARE – TIMI 58 is the largest and most well powered trial to study the effect of SGLT-2 inhibition on CV outcomes in patients with T2DM, with similar numbers of subjects with established CVD as in EMPA-REG outcomes and CANVAS as well as more than 10,000 with multiple risk factors. DECLARE – TIMI 58 is anticipated to report nearly twice the number of CV outcomes compared with the other trials. Further, unlike EMPA REG, DECLARE – TIMI 58 has enrolled large populations of both patients with established CV disease and patients without established CV disease but with multiple risk factors for CV disease. Thus, this trial will have the opportunity to assess whether there is a consistent effect in these two important groups of patients with T2DM in contrast to the observations on MACE in CANVAS. DECLARE – TIMI 58 will have the largest population of patients without established CV disease treated with SGLT-2 inhibition as primary prevention. In part building off prior data, DECLARE – TIMI 58 will have better-characterized assessments of HF history and outcomes than prior studies to provide greater granularity regarding natural history and potential prevention of and treatment of coincident HF and T2DM. Furthermore, DECLARE – TIMI 58 has a robust collection of biosamples and genetics that may help to improve the understanding of the pathophysiology of CV disease in patients with T2DM, and further increase the understanding of drug effects, and benefits and risks in specific populations. Additionally, DECLARE – TIMI 58 can further clarify uncertainty regarding potential risks of SGLT-2 inhibitors that have been raised in large and smaller studies or post-approval monitoring such as volume depletion, acute kidney injury, bladder cancer, limb ischemic events/amputations, and diabetic ketoacidosis.

**Summary**

DECLARE – TIMI 58 is a global, phase 3b, randomized, double blind, placebo controlled CV outcomes trial designed to evaluate the effect of dapagliflozin on CV outcomes in patients with T2DM and either established CV disease or multiple risk factors for CV disease. The trial is well-powered to demonstrate clinical safety and efficacy, and has robust data and biosample collection to help extend the understanding of pathobiology of CV disease in diabetes.

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Tables and Figures:

Figure 1: Trial Schema

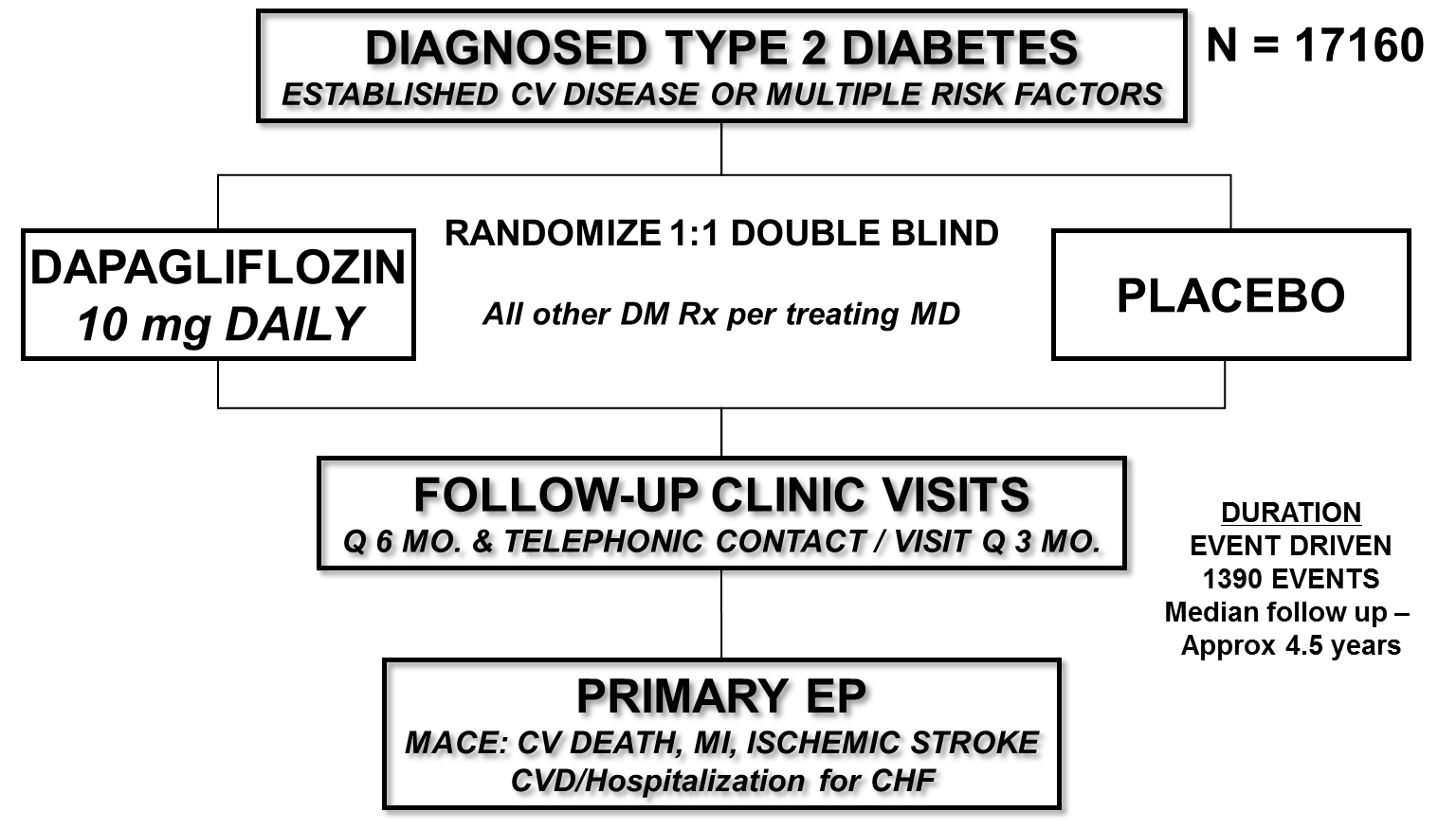
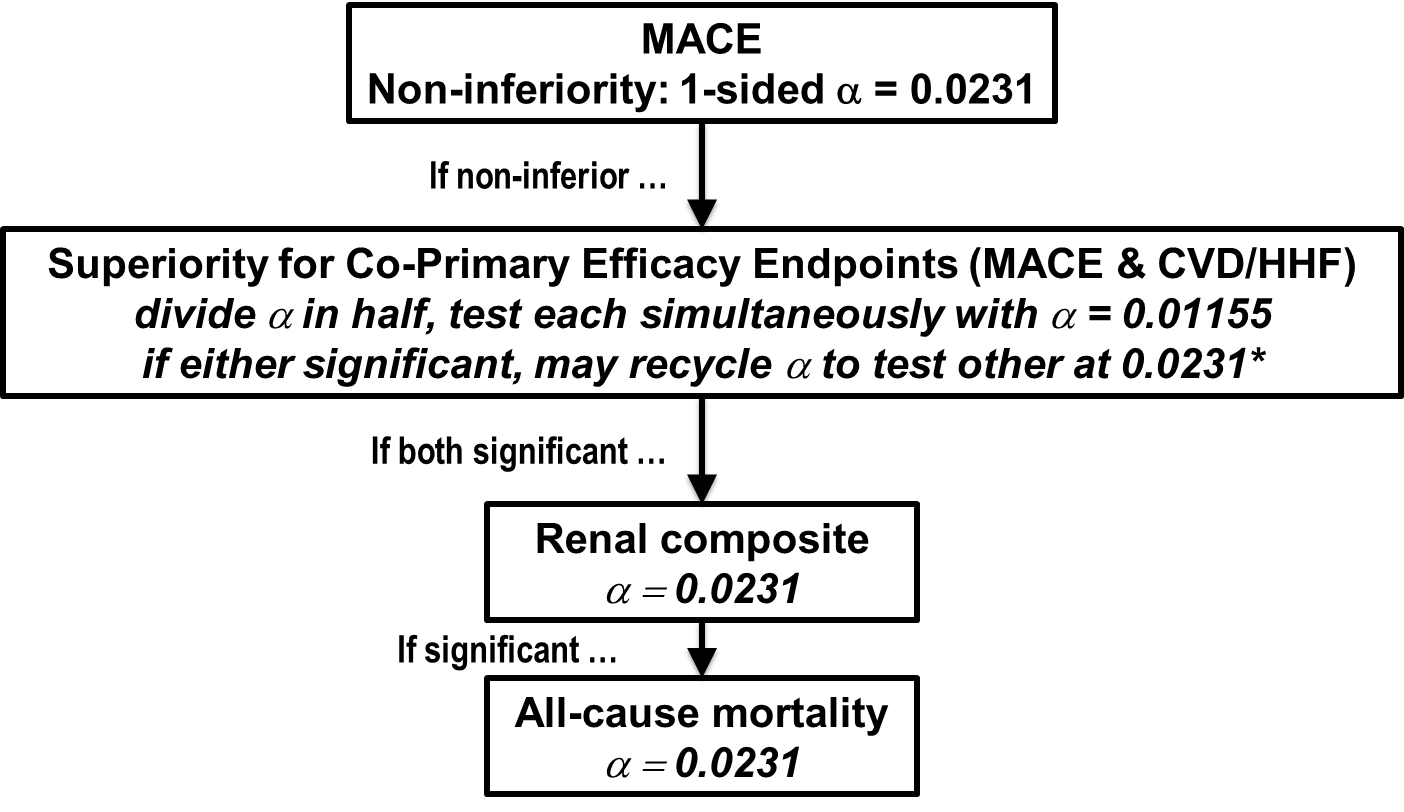


Figure 2: Key Outcomes and Alpha Allocation. All alphas are presented as one sided. \*If either is significant at 0.01155, alpha may be recycled and full 0.0231 can be used for the other co-primary endpoint according to the Holm Procedure.



Appendix A: Full Inclusion/Exclusion Criteria

**Inclusion Criteria:**

For inclusion in the study patients should fulfill the following criteria:

1. Provision of informed consent prior to any study specific procedures (including run-in)

2. Female or male aged ≥ 40 years

3. Diagnosed with T2DM

4. High Risk for CV event defined as having either established CV disease and/or multiple

risk factors:

− Established CV Disease (See Appendix E for details)

OR

No known cardiovascular disease AND at least two cardiovascular risk factors in addition to

T2DM, defined as:

− Age > 55 years in men and > 60 in women

AND presence of at least 1 of the following additional risk factors (see Appendix E for details)

− Dyslipidemia

− Hypertension

− Tobacco use

-

5. WOCBP must take precautions to avoid pregnancy throughout the study and for 4 weeks

after intake of the last dose.

− WOCBP must have a negative urine pregnancy test. WOCBP include any female who has

experienced menarche and who has not undergone successful surgical sterilization

(hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not

postmenopausal.

− WOCBP must be willing to use a medically accepted method of contraception that is

considered reliable in the judgment of the Investigator.

For inclusion in the optional genetic research, patients must fulfill the criterion specified in

**Exclusion Criteria:**

Patients should not meet any exclusion criteria at the time of randomization. If at the time of enrollment, it is known that the patient will not meet criteria after a successful run-in period he/she should not be entered into run in.

1. Use of the following excluded medications:

• Current or recent (within 24 months) treatment with pioglitazone and/or use of

pioglitazone for 2 years or more at any time

• Current or recent (within 12 months) treatment with rosiglitazone

• Previous treatment with any SGLT2 inhibitor

• Any patient currently receiving chronic (>30 consecutive days) treatment with an

oral steroid at a dose equivalent to oral prednisolone ≥10 mg (e.g., betamethasone

≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day

2. Acute cardiovascular event [e.g., acute coronary syndrome (ACS), transient ischemic

attack (TIA), stroke, any revascularization, decompensated HF, sustained tachycardia

<8 weeks prior to randomization. Patients with acute cardiovascular events can be

enrolled in the run-in period as long as randomization does not occur within 8 weeks

of the event.

3. Systolic BP >180 or diastolic BP >100 mmHg at randomization

4. Diagnosis of Type 1 diabetes mellitus, MODY, or secondary diabetes mellitus

5. History of bladder cancer or history of radiation therapy to the lower abdomen or

pelvis at any time

6. History of any other malignancy within 5 years (with the exception of successfully

treated non-melanoma skin cancers)

7. Chronic cystitis and/or recurrent urinary tract infections (3 or more in the last year)

8. Any conditions that, in the opinion of the Investigator, may render the patient unable

to complete the study including but not limited to cardiovascular (NYHA class IV

CHF, recurrent ventricular arrhythmias) or non-cardiovascular disease (e.g., active

malignancy with the exception of basal cell carcinoma, cirrhosis, chronic lung disease,

severe autoimmune disease) and/or a likely fatal outcome within 5 years

9. Pregnant or breast-feeding patients

10. Involvement in the planning and/or conduct of the study or other dapagliflozin studies

(applies to AZ, BMS, Hadassah and Thrombolysis in Myocardial Infarction [TIMI] or

representative staff and/or staff at the study site)

11. Previous randomization in the present study

12. Active participation in another clinical study with IP and/or investigational device

13. Individuals at risk for poor protocol or medication compliance during run-in period

(reasonable compliance defined as 80 – 120%, unless a reason for non-compliance is

judged acceptable by the Investigator). If for any reason, the Investigator believes that

the patient will not tolerate or be compliant with IP or study procedures, the patient

should not be randomized and considered a run-in failure.

Patients will be excluded during run-in and should not be randomized if the following are

observed from laboratory or observation during enrollment and run-in assessments:

14. HbA1c ≥12% or HbA1c<6.5%

15. AST or ALT >3x ULN or Total bilirubin >2.5 x ULN

16. CrCl < 60 ml/min (based on the Cockroft-Gault equation)

17. Hematuria (confirmed by microscopy at Visit 1) with no explanation as judged by the

Investigator up to randomization. If bladder cancer is identified, patients are not

eligible to participate.

18. Any reason the Investigator believes the patient is not likely to be compliant with the study medication and protocol.

APPENDIX B: Disease State Definitions:

1. Type 2 Diabetes Mellitus (T2DM)

• Diagnosis of T2DM can be based on the following:

− Prior documentation of type 2 diabetes AND/OR

− Treatment with anti-hyperglycemic medications and/or diet AND/OR

− ADA criteria: plasma random glucose >200 mg/dl (11.1

mmol/L) or fasting >126 mg/dl (7.0 mmol/L) or HbA1C ≥6.5%

2. Cardiovascular disease:

2.1 Established Vascular Disease

• Ischemic heart disease (any of the following):

− Documented Myocardial Infarction

− Percutaneous Coronary Intervention

− Coronary Artery Bypass Grafting

− Objective Findings of Coronary Stenosis (> 50%) in at least 2 coronary arteries

• Cerebrovascular disease (any of the following):

− Documented ischemic Stroke

− Known transient ischemic attack, primary intracerebral hemorrhage or

subarachnoid hemorrhage do not qualify.

− Carotid stenting or endarterectomy

• Peripheral Arterial Disease (any of the following):

− peripheral arterial stenting or surgical revascularization

− lower extremity amputation as a result of peripheral arterial obstructive disease

− Current symptoms of intermittent claudication AND ankle/brachial index

(ABI) < 0.90 documented within last 12 months

2.2 Multiple Cardiac Risk Factors

No known cardiovascular disease AND

− Age >≥ 55 years in men and >≥ 60 in women

AND presence of at least 1 of the following additional risk factors

− Dyslipidemia (at least one of the following)

− Low-density lipoprotein cholesterol (LDL-C) >130 mg/dl (3.36 mmol/L)

within last 12 months

− On lipid lowering therapy prescribed by a physician for dyslipidemia

− Hypertension (at least one of the following)

− BP >140/90 mm/Hg at enrollment visit

− On anti-hypertensive therapy prescribed by a physician for blood pressure

lowering

− Tobacco use (5 cigarettes/day or more for at least 1 year at randomization)

APPENDIX C: Definitions of Key Trial Outcomes:

**CARDIOVASCULAR DEATH**

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

1. **Death due to Acute Myocardial Infarction** refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days[[1]](#footnote-1) after a MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. There may be assessable mechanisms of cardiovascular death during this time period, but for simplicity, if the cardiovascular death occurs ≤ 30 days of the MI, it will be considered a death due to myocardial infarction.

Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis.

Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI.

1. **Sudden Cardiac Death** refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:
2. Death witnessed and occurring without new or worsening symptoms
3. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
4. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
5. Death after unsuccessful resuscitation from cardiac arrest
6. Death 30 days after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
7. Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient’s clinical status preceding death should be provided, if available)

**General Considerations**

* + Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤ 24 hours of being found dead, sudden cardiac death (criterion **2**f) should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of deathshould be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days).

1. **Death due to Heart Failure** refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology (see Heart Failure Event Definition). Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions (unless ≤30 days after an MI, see definition for Death due to Acute MI above), ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.
2. **Death due to Stroke** refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke (see Cerebrovascular Event Definition).
3. **Death due to Cardiovascular Procedures** refers to death caused by the immediate complications of a cardiac procedure unless procedure is to treat a myocardial infarction.
4. **Death due to Cardiovascular Hemorrhage** refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (see Cerebrovascular Event Definition), non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.
5. **Death due to Other Cardiovascular Causes** refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

**NON-CARDIOVASCULAR DEATH**

**Non-cardiovascular Death** is defined as any death without a specific cause that is not thought to be cardiovascular in nature. The following is a suggested list of non-CV causes of death:

* Pulmonary
* Renal - *defined as death occurring after a patient refuses or a physician withholds renal replacement therapy (i.e., initiation of chronic dialysis or renal transplantation) or in cases where dialysis is unavailable. Deaths due to another primary process and/or when another cause is adjudicated (e.g., sepsis, end-stage heart failure, malignancy) will be adjudicated as death resulting from the primary process and will not be considered renal death.*
* Gastrointestinal
* Hepatobiliary
* Pancreatic
* Infection (includes sepsis)
* Inflammatory (e.g. Systemic Inflammatory Response Syndrome (SIRS)/Immune (including autoimmune)
* Hemorrhage that is neither cardiovascular bleeding nor a stroke
* Non-CV procedure or surgery
* Trauma
* Suicide
* Non-prescription drug reaction or overdose
* Prescription drug reaction or overdose
* Neurological (non-cardiovascular)
* Malignancy
* Other non-CV, specify: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**UNDETERMINED CAUSE OF DEATH**

**Undetermined Cause of Death** refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is “patient died”) or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV.

**CARDIAC ISCHEMIC / ACUTE CORONARY SYNDROMES**

1. **General Considerations**

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

In general, the diagnosis of MI requires the combination of:

* + Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and
  + Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

The term acute myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

* Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
* Symptoms of ischemia
* New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
* Development of pathological Q waves in the ECG.
* Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
* Identification of an intracoronary thrombus by angiography or autopsy

1. **Criteria for Myocardial Infarction**
2. **Clinical Presentation**

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, heart failure, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

1. **Biomarker Elevations**

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer’s listed reference limits in an assay’s instructions for use. *In general, troponins are preferred. CK-MB should be used if troponins are not available, and total CK may be used in the absence of CK-MB and troponin.*

For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL.

1. **Electrocardiogram (ECG) Changes**

Electrocardiographic changes can be used to support or confirm a diagnosis of MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

* + **ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):**
* ST elevation

New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.

* + ST depression and T-wave changes

New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or new T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

* **Criteria for pathological Q-wave**
* Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
  + Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, and aVF)a

aThe same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

* **ECG changes associated with prior myocardial infarction**
* Pathological Q-waves, as defined above
* R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect
* **Criteria for prior myocardial infarction**

Any one of the following criteria meets the diagnosis for prior MI:

* Pathological Q waves with or without symptoms in the absence of non-ischemic causes
* Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
  + Pathological findings of a prior myocardial infarction

**Criteria for universal classification of myocardial infarction**

**Type 1: Spontaneous myocardial infarction**

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

**Type 2: Myocardial infarction secondary to an ischemic imbalance**

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.

**Type 3: Myocardial infarction resulting in death when biomarker values are unavailable**

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

**Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)** Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

**Type 4b: Myocardial infarction related to stent thrombosis**

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

**Type 4c:** **Myocardial infarction related to restenosis**

Restenosis is defined as ≥50% stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values .99th percentile URL and no other significant obstructive CAD of greater severity following: (i) initially successful stent deployment or (ii) dilatation of a coronary artery stenosis with balloon angioplasty (<50%).

**Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)**

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

*Note: As noted in criterion 2b, although language states troponin, CKMB can be used with similar cut points.*

**ST-Segment Elevation MI versus Non-ST-segment Elevation MI**

All events meeting criteria for MI\* will also be classified as either ST-segment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), or unknown.

* **STEMI** – To be classified as a STEMI the event must meet all of the above criteria for myocardial infarction and one of the four criteria below.
  + New ST segment elevation at the J point in ≥2 contiguous leads, defined as: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads. Subjects must have an interpretable ECG (i.e., without evidence of left ventricular hypertrophy or pre-existing left bundle branch block), *or*
  + New left bundle branch block
* **NSTEMI** – To be classified as a NSTEMI the event must meet all of the above criteria for myocardial infarction and not meet criteria for classification as STEMI. In order to be classified as NSTEMI there must be adequate interpretable ECG documentation associated with the event.
* **Unknown** – Events which meet criteria as specified above for MI but do not meet criteria for STEMI or NSTEMI. All cases where ECG documentation of the acute event is missing, inadequate, or uninterpretable should be classified as Unknown.

*Note: All events adjudicated as MI will be classified as STEMI, NSTEMI, or Unknown; however, it is acknowledged that a significant proportion of peri-procedural (PCI or CABG) events may have missing, inadequate or uninterpretable ECG documentation.*

**Categorization of MI**

Categorization of MI will include measures of MI size and severity including biomarker values, MI type, and post-MI cardiac function.

**HOSPITALIZATION FOR UNSTABLE ANGINA**

**Unstable angina requiring hospitalization** is defined as:

1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring

* at rest, or
* in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity.

AND

1. Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay (or a change in calendar date if the hospital admission or discharge times are not available).

AND

1. At least one of the following:
2. New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as LBBB or LVH)

* Transient ST elevation (duration <20 minutes)

New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply:   
≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or   
≥ 0.15 mV in women.

* ST depression and T-wave changes

New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.3 mV in two contiguous leads with prominent   
R wave or R/S ratio > 1.

1. Definite evidence of inducible myocardial ischemia as demonstrated by:

* an early positive exercise stress test, defined as ST elevation or ≥ 2 mm ST depression prior to 5 mets

OR

* stress echocardiography (reversible wall motion abnormality) OR
* myocardial scintigraphy (reversible perfusion defect), OR
* MRI (myocardial perfusion deficit under pharmacologic stress).

and believed to be responsible for the myocardial ischemic symptoms/signs.

1. Angiographic evidence of new or worse ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.
2. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.

AND

1. Negative cardiac biomarkers and no evidence of acute MI

**General Considerations**

1. Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive but not diagnostic of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient to support classification as hospitalization for unstable angina.
2. If subjects are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as unstable angina.
3. Planned hospitalization or rehospitalization for performance of an elective revascularization in patients who do not fulfill the criteria for unstable angina should not be considered a hospitalization for unstable angina. For example,
   * Hospitalization of a patient with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for unstable angina.
   * Rehospitalization of a patient meeting the criteria for unstable angina who was stabilized, discharged, and subsequently readmitted for revascularization, does not constitute a second hospitalization for unstable angina.
4. A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina end point.

**CEREBROVASCULAR EVENTS**

The distinction between a Transient Ischemic Attack and an Ischemic Stroke is the presence of infarction. Persistence of symptoms is an acceptable indicator of acute infarction.

**Transient Ischemic Attack**

Transient ischemic attack (TIA) is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, *without* acute infarction.

**Stroke**

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

* infarction may be documented by brain imaging or,
* persistence of symptoms beyond 24 hours

**Classification:**

1. **Ischemic Stroke** is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

1. **Hemorrhagic Stroke** is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.
2. **Undetermined Stroke** is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B.

**General Considerations**

1. Evidence of vascular central nervous system injury without recognized neurological dysfunction including microhemorrhage, silent infarction, and silent hemorrhage, if appropriate, will not be adjudicated as cerebrovascular events in this trial.

Subdural hematomas are intracranial hemorrhagic events and not strokes.

**HEART FAILURE**

A **Heart Failure Event** includes hospitalization for heart failure and may include urgent outpatient visits. HF hospitalizations should remain delineated from urgent visits.

A **Heart Failure Hospitalization** is defined as an event that meets ALL of the following criteria:

1. The patient is admitted to the hospital with a primary diagnosis of HF
2. The patient’s length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)
3. The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:
   1. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
   2. Decreased exercise tolerance
   3. Fatigue
   4. Other symptoms of worsened end-organ perfusion or volume overload
4. The patient has objective evidence of new or worsening HF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including:
5. Physical examination findings considered to be due to heart failure, including new or worsened:
   1. Peripheral edema
   2. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
   3. Pulmonary rales/crackles/crepitations
   4. Increased jugular venous pressure and/or hepatojugular reflux
   5. S3 gallop
   6. Clinically significant or rapid weight gain thought to be related to fluid retention
6. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
   * 1. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
     2. Radiological evidence of pulmonary congestion
     3. Non-invasive or invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e’ > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration

OR

* + 1. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m2

1. The patient receives initiation or intensification of treatment specifically for HF, including at least ONE of the following:
   1. Augmentation in oral diuretic therapy
   2. Intravenous diuretic, inotrope, or vasodilator therapy
   3. Mechanical or surgical intervention, including:
      1. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device)
      2. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

Using available information, Heart Failure will be categorized based on the following:

1. Left ventricular ejection fraction (LVEF)
2. Type
3. Etiology

An **Urgent Heart Failure Visit** is defined as an event that meets all of the following:

1. The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization.
2. All signs and symptoms for HF hospitalization (i.e., 3) symptoms; 4) physical examination findings/laboratory evidence of new or worsening HF, as indicated above) must be met
3. The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

**MALIGNANCIES**

All reported neoplasms, with the exception of those confirmed as benign and non-melanoma skin cancers that are diagnosed after randomization or that were present prior to randomization and then worsened or recurred post randomization will be reviewed and classified as follows using pathology data as the primary source of classification.

* Malignant neoplasm - an abnormal mass of tissue that can invade and destroy nearby tissue, and that may spread (metastasize) to other parts of the body.
* Benign neoplasm – an abnormal mass of tissue that cannot invade/destroy nearby tissue or metastasize.
* Not a neoplasm – neither of the above.

In addition, the CEC will determine the following:

1. Timing of malignancy

* Clinically evident at time of randomization
* Diagnosed after randomization

1. Site of malignancy

* Bladder
* Bowel
* Brain
* Breast
* Esophageal
* Genital
* Leukemia
* Lip, oral, pharynx
* Liver, gall bladder
* Lung
* Lymphoma
* Pancreatic
* Prostate
* Renal
* Skin
* Stomach
* Thyroid
* Uterine
* Other

1. Extent of malignancy

* Solid Neoplasm
  + Local disease only, no spread beyond the primary organ
  + Spread to contiguous organs
  + Metastatic
* Leukemia, lymphoma and other blood malignancy
  + Acute
  + Chronic
  + Unknown

**HEPATIC EVENTS**

Event triggers can be found in the trial Data Management Plan. Each event will be assessed for causality, severity and patterns of liver injury.

**Causality Scale**

When completing the adjudication forms, the HAC members will express their opinions regarding the probability of Drug-Induced Liver Injury (DILI) using the five-point likelihood causality scale described by Rockey et al. in the table below. This includes both numerical and descriptive terms to grade cases as definitely, highly likely, probable, possibly, or unlikely related to DILI below.

* Definite: Causality should be considered to be definite if attribution of the study drug to the liver injury is believed to exceed 95% likelihood with an association beyond a reasonable doubt.
* Highly Likely: The designation highly likely should be applied when there is an estimated 75% to 95% likelihood of an association and a clear and convincing evidence for the association.
* Probable: Cases should be considered probable when the likelihood of an association is considered to be between 50% and 75%, with an indication that the association is supported by the predominance of the evidence. Although appearing to show an association, such cases should not be graded higher because of an atypical course, the absence of essential clinical information, or the presence of another possible explanation or diagnosis.
* Possible: Cases should be considered to be possible if they are believed to have a 25% to

50% likelihood of an association because, although it was still possibly related, the involvement by the study drug is equivocal and not supported by the preponderance of the evidence.

* Unlikely: Cases should be ranked as unlikely if they are regarded to have less than a 25% likelihood of resulting from the medication, and another etiology is considered to be responsible.

Table: Clinical Assessment of Causality Scale:

|  |  |  |
| --- | --- | --- |
| **Causal Relationship** | **Likelihood** | **Description** |
| Definite | > 95% | The evidence for the study drug causing the  injury is beyond a reasonable doubt |
| Highly Likely | 75 - 95% | The evidence for the study drug causing the  injury is clear and convincing but not definite |
| Probable | 50 - 74% | The preponderance of the evidence supports the  link between the study drug and the liver injury |
| Possible | 25 - 49% | The evidence for the study drug causing the  injury is equivocal but present |
| Unlikely | < 25% | There is evidence that an etiological factor other  than the study drug caused the injury is clear |

a Rockey D.C., et al. for the US Drug-Induced Liver Injury Network. Causality Assessment in Drug-Induced Liver Injury Using a Structured Expert Opinion Process: Comparison to the Roussel-Uclaf Causality Assessment Method. HEPATOLOGY 2010;51:2117-2126

For cases that do not meet any of the above description, two additional likelihood causality scale terms will be included, as described below:

Excluded: Cases should be ranked as excluded if there is a definite and documented alternative cause for the abnormality.

Not Assessable: Cases should be ranked as not assessable if critical data is missing that interferes with a fair assessment.

Only one option can be selected for each case.

**Severity Scale**

For each case, the HAC members will also express their opinions regarding the severity using the scoring system described below, which has been used by the Food and Drug Administration in the past, including as part of the dabigatran Advisory Committee.

Table: Severity Scale

|  |  |
| --- | --- |
| **Scale** | **Definition** |
| 1 | ALT or AST > 3X ULN, usually transient and reversible by adaptation (mild) |
| 2 | Also TB > 2X ULN, after or concurrent, indicating early functional loss (Hy’s Law Case) |
| 3 | Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction |
| 4 | Acute liver failure, with secondary failure of brain or kidney function due to liver injury |
| 5 | Fatal, or requiring liver transplantation due to liver failure |

In addition to the above scale, the option “not applicable and/or no liver injury” will be

available for cases where options 1 to 5 do not apply. Only one option can be selected for

each case for options 1 to 5, however, the option “not applicable and/or no liver injury”

can be selected in conjunction with one option from 1 to 5.

**Patterns of Liver Injury**

For each case, the pattern of liver injury will be assessed and reported on the adjudication

form in accordance with the below definitions, as described by Farrell G, Schiff’s

Diseases of the Liver, 11th edition (in press).

Table: Definition of Patterns of Liver Injury

|  |  |  |
| --- | --- | --- |
| Hepatocellular | Cholestatic | Mixed |
| ALT >2-3 XULN and  Normal ALP  **OR**  ALT/ALP ratio ≥ 5a | ALT >2 XULN  **OR**  ALT/ALP ratio ≤ 2a | ALT >2-3 XULN and ALP >2 XULN  **OR**  ALT/ALP ratio between 2 and 5a |

a The ALT and SAP values are expressed as multiples of the upper limit of normal

For cases that do not meet any of the above description, 2 additional patterns of liver

injury terms will be included:

Other Type: Pattern of liver injury not meeting any of above definitions.

Not Applicable: For cases where there is no liver injury noted.

Only one option can be selected for each case.

For each case, the adjudicators will also indicate whether the pattern of liver injury

involves hepatic adaptation by selecting “yes”, “no” or “possible” for hepatic adaptation.

Hepatic adaptation has been defined as abnormal liver test results without symptoms or

biochemical evidence of significant liver disease.

APPENDIX D: Trial Organization

Appendix E. Trial organization

• TIMI Study Group—M. Sabatine (study chair), S. Wiviott (co-principal investigator), M. Bonaca (steering committee), P. Fish, S. Morin, E. Toda Kato (steering committee), M. Silverman, S. Bansilal, A. McCourt, S. Ahern, R. Guaraldi, J. Lamp

• Hadassah Medical Organization—I. Raz (co-principal investigator), O. Mosenzon, A. Cahn, A. Buskila, A. Weiss, G. Leibowitz

• AstraZeneca—A. Langkilde, I. Gause Nilsson, M. Fredriksson, P. Johansson, Y. Fox, B. Faber, C. Karup, S. Ranft, C. Casselgård, A. Mellander, U. Callsen, E. Johnsson, K. Rohwedder, A. Katz, K. Koontz, J. Neubauer, M. Wallander, U. Allgén

• Bristol-Myers Squibb—D. Liaw, B. Frederich

**Executive Committee**

M Sabatine (Chair), S Wiviott (Co-PI), I Raz (Co-PI), D. Bhatt, L. Leiter, D. McGuire, J. Wilding, I Gause Nilsson, A Langkilde

Steering committee

D. Bhatt (USA), L. Leiter (Canada), D. McGuire (USA), J. Wilding (UK), and M. Abola (Philippines), D. Ardissino (Italy), O. Averkov (Russia), P. Aylward (Australia), C. Bode (Germany), F. Bonnici (South Africa), E. Bonora (Italy), A. Budaj (Poland), S. Cernea (Romania), C. Chiang (Taiwan), M. Cooper (Australia), A. Dalby (South Africa), C. Deerochanawong (Thailand), M. Dellborg (Sweden), R. Diaz (Argentina), D. Dimulescu (Romania), J. Dwyer (United States), F. Eliaschewitz (Brazil), S. Goto (Japan), A. Goudev (Bulgaria), S. Hadjadj (France), M. Herrera Marmolejo (Mexico), Y. Huo (China), G. Jermendy (Hungary), L. Ji (China), T. Kadowaki (Japan), T. Khue (Vietnam), R. Kiss (Hungary), A. Kooy (Netherlands), P. Kumar (India), B. Lewis (Israel), L. Litwak (Argentina), J. López-Sendón (Spain), R. Ma (Hong Kong), P. Merlini (Italy), G. Montalescot (France), M. Nauck (Germany), J. Nicolau (Brazil), C. Östgren (Sweden), T. Oude Ophuis (Netherlands), F. Padilla (Mexico), P. Pais (India), K. Park (Republic of Korea), A. Parkhomenko (Ukraine), K. Ray (United Kingdom), J. Rosenstock (United States), M. Ruda (Russia), I. Satman (Turkey), M. Shestakova (Russia), A. Smahelova (Czech Republic), J. Spinar (Czech Republic), K. Strojek (Poland), R. Sy (Philippines), T. Tankova (Bulgaria), P. Theroux (Canada), I. Tkáč (Slovakia), L. Van Gaal (Belgium), and J. Wainstein (Israel).

Data monitoring committee

Chair: R. Harrington (USA); members: J. Tuomilehto (Finland), R. Nesto (USA), M. Droller (USA), K. Lee (USA)

Clinical events committee

TIMI Study Group—Chair: C. Ruff; Administrative Staff: C. Lowe, L. Zahn, N. Fisher, E. Gershman; Medical Review: D. Forni, T. Zhargalova, K. Barrera, Z. Khan, M. Shimmer; Members (Cardiology): E. Awtry, C. Berger, K. Croce, A. Desai, E. Gelfand, C. Ho, D. Leeman, M. Link, A. Pande, F. Ruberg; (Neurology): A. Norden, N. Rost, S. Silverman, A. Singhal; (Oncology): G. Gignac, W. Goessling, E. Hochberg, A. Lane, C. Rosenberg, A. Wagner, B. Wolpin; (Hepatic) D. Larrey, J. Lewis, E. Schiff

1. [↑](#footnote-ref-1)