Table 1
Laboratory findings on admission

	Laboratory results on admission	Reference range*
Platelet count (K/L)	217	150-450
D-dimer (ng/mL)	>4000	<500
Prothrombin time (sec)	14.6	11.5-14.5
International normalized ratio	1.2	0.9-1.1
Activated partial-thromboplastin time (sec)	26.6	23.8-36.6
Fibrinogen (mg/dL)	320	200-450
Lactate dehydrogenase (U/L)	642	135-225
Ferritin (ug/L)	617	13-150
High-sensitivity C-reactive protein (mg/L)	95	0-10
B2 glycoprotein 1 Ab, IgG (CU)	<6.4	0-19
B2 glycoprotein 1 Ab, IgM (CU)	12	0-19
Cardiolipin Ab, IgG (CU)	3	0-19
Cardiolipin Ab, IgM (CU)	53	0-19
Protein C Resistance	4.2	>2.2
Dilute Russell's viper venom time	Positive	Negative
Lupus anticoagulant (hexagonal phase)	Positive	Negative

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Brigham and Women's Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

angiogram revealed extensive arterial thromboses including nonocclusive thrombus of the infrarenal abdominal aorta near the aortic bifurcation, occlusion of the left common iliac artery, internal iliac artery, and external iliac artery to the level of the iliac ligament with complete occlusion of the popliteal artery below the knee and its branches (Figure 1, *left panel*). The patient had no history of venous or arterial clots, no known vasculopathy, minimal underlying atherosclerosis, no personal or family history of hypercoagulable disease, no aortic compression as nidus for thrombus formation, and evaluation for malignancy has been negative to date. An initial hypercoagulable workup (Table 1) found a positive lupus anticoagulant by dilute Russell's viper venom time and hexagonal phase assays.

Hypercoagulability and endothelial injury have been described as features of coronavirus disease 2019 (Covid-19). While asymptomatic or symptomatic venous thromboembolism has been frequently observed, arterial thrombosis and acute limb ischemia have less commonly been described.[1] Lupus anticoagulant has been identified commonly in Covid-19,[2] and if persistent, is known to be associated with thrombosis in antiphospholipid syndrome. In this case, lupus anticoagulant may have been a false-positive test result in context of acute illness and the receipt of unfractionated heparin. Critical illness and marked inflammatory response in the setting of Covid-19 likely increased propensity for thrombus formation and acute limb ischemia in this patient.

She underwent emergent thrombectomy and thrombolysis and 4-compartment fasciotomy, with limb salvage and revascularization (Figure 1, *right panel*). She was initially treated with unfractionated heparin and was bridged to warfarin for maintenance anticoagulation, and discharged to rehabilitation for ongoing recovery. Heightened clinical vigilance is needed for early identification of this potentially serious complication of Covid-19 to facilitate prompt intervention targeting limb salvage,[3–6] Further research is needed to determine the role of hypercoagulability in Covid-19, and to identify strategies to prevent and treat venous and arterial thrombosis in this setting.

Disclosures

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Meta-analysis Assessing the Effect of Sodium-Glucose Co-transporter-2 Inhibitors on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) has evolved as a pandemic of the 21st century, while cardiovascular disease (CVD) affects almost one third of patients and represents the cause of death

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in more than half cases, with coronary artery disease, heart failure (HF), and stroke being the main contributors.[1] Hallmark cardiovascular outcome trials published during the last five years have established a novel class of antidiabetics, namely sodium-glucose co-transporter-2 (SGLT-2) inhibitors as a primary treatment option in patients with HF, atherosclerotic cardiovascular disease, or chronic kidney disease, along with the use of metformin (unless not tolerated or contraindicated).[2] Of note, the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial demonstrated significant cardiovascular benefit (risk for HF decompensation or cardiovascular death) for patients with HF with reduced ejection fraction, regardless of T2DM status, extending the therapeutic potential of this drug class beyond diabetic subjects.[3] Despite the undoubted cardiovascular benefits observed with SGLT-2 inhibitors, the underlying mechanisms of their action remain largely unknown.

Left ventricular (LV) hypertrophy, expressed by LV mass and quantified either with echocardiography or cardiac magnetic resonance imaging (cMRI), has been established as an independent predictor of cardiovascular morbidity and mortality.[4–6] A previously published analysis of data concerning 10 patients participating in the Empagliflozin Cardiovascular Outcome Event Trial in T2DM Patients (EMPA-REG OUTCOME) trial supported the potential of empagliflozin to promote LV remodeling by decreasing LV mass, speculating that this action might be implicated into the observed cardiovascular benefit in the trial.[7] A few, recently published randomized controlled trials (RCTs), have assessed the effect of SGLT-2 inhibitors on LV mass and other indices of LV remodeling. Thus, we sought to determine whether the administration of this drug class in patients with T2DM might confer a significant effect on LV mass and remodeling.

We searched for RCTs enrolling adult patients with T2DM, investigating the effect of SGLT-2 inhibitors on LV mass and other indices of LV remodeling. We excluded studies enrolling patients with type 1 diabetes mellitus or patients aged less than 18 years. We did not impose any restriction regarding study duration, study design (parallel or cross-over), study blinding (single-blind, double-blind, or open-label), setting, sample size and method of LVMI assessment (either cMRI or echocardiography).

We performed a systematic search in two major electronic databases, PubMed and Cochrane Central Register of Controlled Trials (CENTRAL), for eligible RCTs, from their inception to July 2020, along with grey literature sources. We used both free text words and MeSH terms. Our search was restricted to human studies. We did not impose any filter regarding language, text-availability, and publication date. Search strategy in the 2 major databases is provided in supplementary appendix (Supplementary Table 1).

All retrieved reports were imported into reference software manager (Mendeley) for deduplication. After that, remaining reports were reviewed at title and abstract level by 2 independent reviewers (D.P. and C.P.). Potentially eligible studies were full-text assessed. Any discrepancies among the 2 reviewers at any stage were resolved by discussion, consensus or arbitration by a third senior reviewer (M.D.). Eligible reports from grey literature were cross-checked with the results retrieved from electronic databases. The study selection process is depicted in the flow diagram (Supplementary Figure 1).

Two independent reviewers (D.P. and C.P.) extracted the data from the eligible reports, by using a pilot tested, data extraction form developed in Microsoft Excel. Our primary efficacy outcome was change in LV mass and LV mass index (LVMI), while our secondary efficacy outcome was change in LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV). We did not assess any safety outcomes. We preferred utilizing data retrieved from intention-to-treat (ITT) analyses, if available.

As we assessed only continuous variables, we calculated mean differences (MD) with 95% confidence intervals (CI), using an inverse variance weighted random effects model. Statistical heterogeneity among studies was assessed by using I^2 statistics. Heterogeneity was considered to be low if I^2 was between 0% and 25%, moderate if I^2 was between 25% and 50%, or high if I^2 was greater than 75%.[8] All analyses were performed at the 0.05 significance level, while they were undertaken with RevMan 5.3 software.[9]

Two independent reviewers (D.P. and M.K.) assessed the quality of the included RCTs, by using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) for the primary efficacy outcome.[10] Discrepancies between reviewers were solved by discussion, consensus or arbitration by a third senior reviewer (M.D.).

Our search yielded 125 results in total. After deduplication and initial screening, we ended up with 10 records eligible for full-text screening. Finally, 3 records were included in our quantitative analysis. In the REFORM trial, Singh et al assessed the effect of 12-month treatment with dapagliflozin on LV remodeling in patients with T2DM and LVEF <45%.[11] They showed that dapagliflozin did not result in significant change in LVESV, LVEDV, and LVMI; however, it decreased diastolic blood pressure and increased hemoglobin and fasting b-hydroxybutyrate levels, leading to a significant decrease in loop diuretic requirements.[11] Unfortunately, no numeric data regarding the effect of dapagliflozin on LV mass were provided.[11] In the EMPA-HEART CardioLink-6 trial, enrolling adults with T2DM and established coronary artery disease without LV systolic dysfunction (mean baseline LVEF 58%), Verma et al demonstrated that 6-month treatment with empagliflozin did not affect significantly LVESV and LVEDV; however, it produced a significant decrease in LVMI.[12] Of note, the researchers showed that the change in LVMI was not associated with the observed changes in 24-hour ambulatory blood pressure and hematocrit.[12] Finally, in the recently published DAPA-LVH trial enrolling patients with T2DM and LV hypertrophy with preserved systolic function, Brown et al showed that 12-month treatment with dapagliflozin produced a significant decrease in LV mass; however, it did not affect LVMI, LVESV, and LVEDV compared with placebo, despite the fact that it significantly decreased 24-hour systolic blood pressure, body mass index, visceral, and subcutaneous adipose tissue.[13] Notably, all studies utilized cMRI for the assessment of LV mass and LVMI. Participants' baseline characteristics across the selected studies are summarized in Supplementary Table 2. Risk of bias is considered as low across all studies, as presented in Supplementary Table 3.

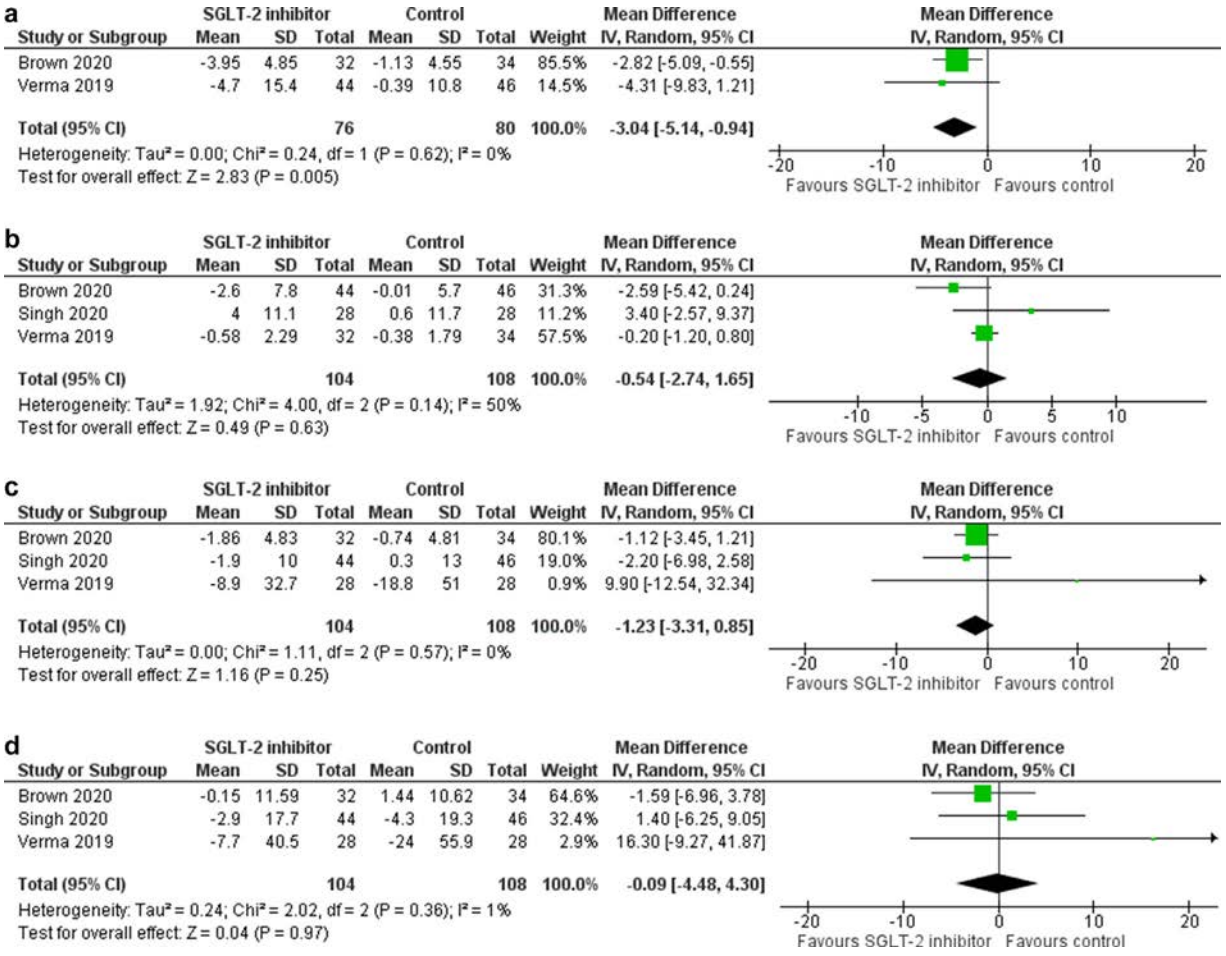

Figure 1. Effect of SGLT-2 inhibitors compared with control on: (a) LV mass, (b) LVMI, (c) LVESV, and (d) LVEDV.

Our analysis in a total of 212 patients showed that SGLT-2 inhibitor treatment produced a significant decrease in LV mass by 3.04 g (MD = −3.04, 95% CI −5.14 to −0.14, $I^2 = 0\%$), as shown in Figure 1a, and a nonsignificant decrease in LVMI by 0.54 g/m^2 (MD = −0.54, 95% CI −2.74 to 1.65, $I^2 = 50\%$), as shown in Figure 1b. In addition, SGLT-2 inhibitor treatment did not decrease significantly neither LVESV (MD = −1.23 mL, 95% CI −3.31 to 0.85, $I^2 = 0\%$) nor LVEDV (MD = −0.09 mL, 95% CI −4.48 to 4.30, $I^2 = 1\%$), as shown in Figure 1c and d.

Despite the small number of included studies and of enrolled subjects, our meta-analysis demonstrates that SGLT-2 inhibitor treatment in patients with T2DM has a favorable effect on LV mass, which might be implicated into the cardioprotection observed with this drug class. Of course, besides structural remodeling, T2DM is also associated with metabolic LV remodeling.[14] It has been previously shown in a small cohort of patients with T2DM without hypertension or CVD that myocardial triglyceride content is a strong, positive and independent predictor of concentric LV remodeling.[14] There is only a small, relevant observational study published so far, which failed to prove a significant effect of empagliflozin either on structural or metabolic LV remodeling.[15]

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.08.002.

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COVID-19 and the Prehospital Incidence of Acute Cardiovascular Events (from the Nationwide US EMS)

A substantial reduction has been reported in the number of patients admitted to hospitals with acute cardiovascular events—including ST-elevation myocardial infarctions, cardiac arrests, and strokes—coinciding with the onset of the COVID-19 pandemic. For example, there has been a 40% decrease in STEMI volume among 81 centers in Spain,[1] a 38% reduction in cardiac catheterization lab activations for STEMI among 9 high-volume centers across the United States,[2] and a decrease in weekly hospitalization for acute myocardial infarction in Northern California of up to 48%.[3] In Northern Italy, there has been an increase in out-of-hospital cardiac arrests[4] but also a significant decrease in hospitalizations related to acute coronary syndrome.[5] One proposed explanation is that patients are afraid and reluctant to visit hospitals and access healthcare systems during a pandemic. In the prehospital setting, EMS clinicians are often the first point of contact and caregivers to the victims of acute cardiovascular events, and understanding patterns seen by EMS might provide a better perspective of the occurrence of acute cardiovascular events during the pandemic.

We surveyed the National Emergency Medical Services Information System (NEMSIS) database, which contains millions of EMS activations throughout the United States. Inclusion criteria were calls when EMS clinicians documented the presence of rhythms suggestive of a STEMI; ventricular fibrillation or ventricular tachycardia (VF/VT); asystole; or a stroke pre-arrival alert. The frequency of these calls during January, February, March, and April of 2020 were compared amongst each other and with historic trends (Figure 1).

There was an overall 10.33% decrease in EMS calls between January and March 2020, a 4.62% decrease from February to March 2020, and a 12.96% decrease between March and April. Cardiac calls similarly decreased, with an even-greater magnitude. STEMIs and stroke alerts both decreased across all months. Interestingly, both the incidence of VF/VT and asystole decreased from January to March but increased from March to April: VF/VT increased 3.04%, while asystole increased 27.34% to a year-to-date high. These trends identified in 2020 are not seen in the databases' previous years, eliminating the possibility of this variability being indicative of seasonal variation and suggesting unique patterns coinciding with the COVID-19 pandemic.

These data seem to confirm a decrease in the number of patients seeking care for acute cardiovascular events, a trend seen within many healthcare centers. It is unclear whether or not reductions in overall EMS calls, cardiac-specific calls, stroke alerts, and STEMIs are related to actual decrease in these events or an unwillingness of patients to seek medical care. The spike in asystole and VF/VT calls could be due to the pathophysiological effects of the virus. However, it is also possible that the increase in asystole and VF/VT following a decrease in STEMI, stroke, and general cardiac calls might indicate patients are avoiding seeking care in time-sensitive conditions, resulting in less-favorable outcomes. Although it would be rather difficult to investigate if patients have been reluctant to visit hospitals, a continued trend of VT/VF or asystole following decreases in STEMI, strokes, and cardiac calls might support such a notion. Further physiological studies should attempt to better understand the link between COVID-19 and acute cardiovascular events, and the public health community should examine patients' willingness to self-triage and seek care during the pandemic.

Disclosures

The authors have no conflicts of interest to disclose.