Timing of Nonculprit Percutaneous Coronary Intervention after ST-Elevation Myocardial Infarction

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Keywords

Primary percutaneous coronary intervention · ST-elevation myocardial infarction · Culprit artery

Abstract

Introduction: Complete revascularization of ST-elevation myocardial infarction (STEMI) patients with multivessel disease (MVD) has recently shown to reduce risk of adverse cardiovascular events, including cardiovascular death. Optimal timing of revascularization of nonculprit lesions remains controversial. We aimed to measure cardiac outcomes related to duration between primary percutaneous coronary intervention (pPCI) of the culprit lesion and staged PCI (sPCI) of nonculprit lesions. **Methods:** From a prospectively collected consecutive registry of 3,002 patients treated for STEMI by pPCI, 1,555 patients with MVD requiring sPCI were identified. Patients were placed into quartiles of duration to sPCI: 0–7 days (Q1), 7–22 days (Q2), 22–42 days (Q3), >42 days (Q4), excluding those who had complete revascularization at the index event. Major adverse cardiac events (MACEs) included all-cause mortality, myocardial infarction, target vessel revascularization, and coronary artery bypass surgery. Cox regression and propensity score matching were performed correcting for confounding factors. **Results:** The av-

erage age at presentation was 65.7 ± 11.5 years. 333 were female (21.4%). Mean time between pPCI and sPCI was 28.3 days (± 24.8). Rates of MACE were Q1 - 16.5%, Q2 - 21.2%, Q3 - 25.8%, and Q4 - 30.1% (log-rank < 0.001). Following regression analysis, sPCI remained an independent risk factor for MACE (hazard ratio [HR] = 1.226 [95% confidence interval {CI}: 1.129–1.331, $p < 0.001$]). There was no association between the time interval up to sPCI with all-cause death (HR = 1.022 [95% CI: 0.925–1.129, $p = 0.671$]). **Conclusions:** Patients with MVD are at increased risk of experiencing MACE after revascularization of nonculprit vessels with increasing time delay between pPCI and sPCI.

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Introduction

For patients suffering from ST-elevation myocardial infarction (STEMI), timely revascularization with primary percutaneous coronary intervention (pPCI) of the infarct-related artery (IRA) is the treatment of choice. Of these patients, multivessel disease (MVD) identified angiographically upon intervention of the culprit lesion is common, with some studies suggesting a prevalence of approximately 50% [1, 2]. MVD in patients with STEMI

has been shown to be a predictor of short- and long-term mortality rates as well as reinfarction when compared to patients with single-vessel disease [3–5]. Whether these patients would benefit from intervention of non-IRA has long been controversial [6, 7]. Recently, data from the COMPLETE trial showed a significantly reduced risk of cardiovascular events when complete revascularization of STEMI patients with MVD is achieved [8]. Other smaller randomized studies have also suggested reduced adverse cardiac events for patients receiving complete revascularization, including the Cvlpit [9], PRAMI [10], DANAMI-3-PRIMULTI [11], and Compare-Acute trials [12]. Furthermore, a recent meta-analysis of available randomized trials comparing multivessel versus culprit only revascularization found similar reduction in risk of reinfarction [13].

Studies have shown patients are at increased risk of ischemic events [14–16] and mortality [17, 18] when one-time complete revascularization is attempted compared to staged PCI (sPCI), suggesting that sPCI is the safer method for addressing nonculprit lesions [19]. However, what is considered a “reasonable time” following pPCI until completion of coronary revascularization is still a matter of great uncertainty and debate. Because there are conflicting data on this issue [20], the need for clear guidelines for optimal management of these patients is vital. Whether it is necessary to revascularize non-IRA as soon as possible or to delay procedures remains controversial [10, 21]. Thus, we aimed to evaluate the rate of major adverse cardiac events (MACE) over time for STEMI patients with MVD undergoing pPCI and whether patients are at increased risk of adverse outcomes as time between the procedures lengthens.

Materials and Methods

Patients and Setting

Since 2004, all consecutive STEMI cases at the Rabin Medical Center, Israel, have been prospectively entered into a comprehensive registry for purposes of monitoring patient-related parameters and clinical events. This study is therefore based on clinical data of consecutive patients presenting with STEMI and treated by pPCI between January 2004 and January 2018. The Rabin Medical Center includes 2 campuses: the Beilinson and Hasharon medical centers. Of the 3,002 patients in the registry, 1,555 were eligible for the study: patients who were found to have a nonculprit lesion, defined as the presence of at least 1 angiographically significant lesion that was amenable to successful treatment with PCI and was located in a vessel with a diameter of at least 2.5 mm. Lesions were considered angiographically significant if they were associated with at least 70% stenosis of the vessel diameter on visual estimation (e.g., taken during the pPCI angiography) or with moderate

stenosis accompanied by a fractional flow reserve measurement of 0.80 or less at the time of sPCI.

Patients were divided into quartiles of duration from pPCI to sPCI: 0–7 days (Q1), 7–22 days (Q2), 22–42 days (Q3), and >42 days (Q4). We excluded all patients who were treated for their nonculprit artery during the index procedure or sent to coronary bypass surgery (CABG) for revascularization of the non-IRA. We also excluded those who were treated urgently for the nonculprit artery due to an acute coronary syndrome during their wait for a scheduled sPCI. Other exclusion criteria were presentation with cardiogenic shock during STEMI, treatment by thrombolysis (<1% of patients), and ineligibility for year-long dual antiplatelet pharmacotherapy. The study and registry were approved by the Institutional Review Boards of the medical center.

Interventional Procedure

All patients provided explicit written informed consent before undergoing cardiac catheterization. Pretreatment consisted of aspirin 300 mg and unfractionated heparin (70 U/kg); clopidogrel 300 or 600 mg, prasugrel 60 mg, or ticagrelor 180 mg was administered as a loading dose before or immediately after pPCI. The utilization of glycoprotein IIb/IIIa inhibitors and the choice of the type of coronary stent and other adjunct therapy were left to the discretion of the primary operator. All stents were implanted with moderate-to-high deployment pressure (12–16 atm). All patients received dual antiplatelet therapy with aspirin 100 mg daily and a P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor) for at least 12 months after the sPCI according to STEMI guidelines directed management.

Study End Points

Immediate and in-hospital clinical events were prospectively recorded in the institutional database. During the follow-up, patients completed standardized questionnaires on clinical events at 6-month intervals either by telephone or in the outpatient clinic. When indicated, records from peripheral hospitals were acquired to verify the data. All events were further confirmed and adjudicated by the institutional clinical events adjudication committees. Survival status was assessed by municipal civil registries after 1 and 2 years.

Primary outcomes included all-cause mortality and MACE following sPCI, at the median time of each quartile which comprised death, repeat myocardial infarction (MI), need for target vessel revascularization (TVR), and/or CABG. Renal failure was defined as glomerular filtration rate below 50 mL/min/1.73 m² (calculated according to the Modification of Diet in Renal Disease formula). Anemia was defined as hemoglobin levels lower than 13.0 g/dL for men and 12.0 g/dL for women.

Statistical Analysis

Continuous data are summarized as mean and standard deviation, or median and interquartile range, and categorical data as frequency (%). Student *t* test or analysis of variance was used to compare continuous variables between groups, and χ^2 or Fisher's exact test was used for categorical variables. The normality of variable distributions was assessed using the Kolmogorov-Smirnov test. Time-to-event curves were constructed using the Kaplan-Meier method and compared using log-rank test. Stepwise variable selection of significant univariate predictors ($p < 0.1$) was used to identify variables for inclusion in the multivariate model. Cox regression analysis was performed to determine independent predictors of the primary end point, accounting for known baseline cardiovascular risk differences,

Table 1. Baseline characteristics

	Total (n = 1,555)	Q1 (n = 423)	Q2 (n = 382)	Q3 (n = 379)	Q4 (n = 371)	p value
Age, years	65.7±11.5	64.7±12.0	65.7±11.8	65.7±10.8	67.1±11.1	0.368
Gender, % female	21.4	22.2	18.8	20.1	24.5	0.240
DM, %	46.3	39.5	44.2	47.2	55.3	<0.001
Hypertension, %	76.8	70.9	70.9	80.2	86.0	<0.001
Smoking, %	37.8	41.6	35.9	37.2	36.1	0.294
CHF, %	10.4	10.2	10.5	7.4	13.5	0.057
COPD, %	8.0	6.4	8.4	7.9	9.4	0.454
PVD, %	3.5	1.7	3.1	3.2	6.2	0.005
CVA, %	6.8	6.6	6.8	5.8	7.8	0.938
Atrial fibrillation, %	33.6	35.8	32.1	30.9	34.6	0.001
Malignancy, %	11.1	10.2	9.9	11.3	13.2	0.462
Dementia, %	1.7	1.9	1.6	1.1	2.2	0.671
CABG, %	6.6	3.3	7.1	6.1	10.5	0.001
eGFR <60, %	20.1	19.6	20.4	17.7	22.9	0.251
Estimated EF, %	53.3	51.0	53.3	54.4	54.9	<0.001

CABG, coronary artery bypass graft surgery; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disorder; CVA, cerebrovascular accident; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; PVD, peripheral vascular disease.

Table 2. Procedural characteristics for pPCI

	Total (n = 1,555)	Q1 (n = 423)	Q2 (n = 382)	Q3 (n = 379)	Q4 (n = 371)	p value
Number of diseased vessels	2.18	2.24	2.15	2.13	2.20	0.198
Radial approach, %	52.1	50.3	52.8	52.7	52.0	0.270
CTO, %	4.4	2.5	5.6	5.4	4.4	0.077
Bifurcation, %	17.7	23.0	18.0	15.5	12.8	0.325
Left main PCI, %	3.7	3.8	2.6	4.0	4.3	0.630
Anterior AMI, %	47.2	47.8	45.6	46.3	49.3	0.439
Inferior-posterior AMI, %	32.5	32.0	32.6	33.1	31.6	0.562
Lateral/infero-lateral AMI, %	13.7	13.1	12.9	14.1	13.4	0.816
Venous graft AMI, %	4.5	2.4	3.3	3.7	4.1	0.126
Calcification, %	13.4	16.8	11.3	15.8	8.4	0.003
Long lesion, %	26.8	26.2	26.1	27.7	26.0	0.286
GP2B3A inhibitors, %	2.7	2.4	3.1	3.0	2.8	0.231
IABP, %	1.2	1.2	1.1	1.4	1.3	0.430
Statin, %	96.8	98.3	96.1	96.2	95.9	0.214
VKA, %	4.0	4.2	1.9	4.8	5.0	0.892
NOAC, %	2.8	3.4	2.3	2.8	2.5	0.193
Aspirin, %	97.0	97.1	97.1	96.2	97.5	0.921
Clopidogrel, %	74.8	71.3	72.3	73.9	81.7	0.078
Prasugrel, %	18.2	23.3	18.6	21.0	15.6	0.082

AMI, acute myocardial infarction; CTO, chronic total occlusion; IABP, intra-aortic balloon pump; NOAC, nonvitamin K antagonist oral anticoagulants; pPCI, primary percutaneous coronary intervention; VKA, vitamin K antagonist.

which included: age, sex, diabetes mellitus, renal failure, hypertension, obesity, peripheral vascular disease, and cerebrovascular accident. Effect sizes are presented as hazard ratio (HR) and 95% confidence interval (CI). As a secondary analysis, propensity score was then computed using a multivariable logistic regression model with

receipt of patients treated after the median (over 22 days) 3 versus controls as the independent variable and all pre-PCI and intraprocedural variables as covariates. The propensity score matching was performed using a “closest neighbor, greedy” algorithm, attempting to match to each patient above the median time to sPCI with a cohort

Fig. 1. Kaplan-Meier curves showing unadjusted rates of MACEs for each delayed PCI quartile group of patients. PCI, percutaneous coronary intervention; MACEs, major adverse cardiac events.

patient from the rest of the cohort with the closest propensity score. To control for adequate matching, we also calculated the standardized differences of means and of dichotomous variable distributions for the covariates used for the matching. We regarded a cutoff value of $\pm 0.96 \times [\sqrt{(2/n)}]$ to assume the prevalence of a covariate is equal between 2 groups with equal number of subjects. All standardized differences were below that cutoff value (see online suppl. Table 1; see www.karger.com/doi/10.1159/000517295 for all online suppl. material). Each pair was used once. Unpaired patients were discarded from the analysis. The propensity score was then used to select 296 well-matched pairs of patients in each group (delayed sPCI = 296 vs. early sPCI = 296) were selected. All statistical analyses were performed with IBM SPSS V. 27. A *p* value of <0.05 was considered statistically significant.

Results

In total, 1,555 patients were included in our analysis. The average age at presentation was 65.7 ± 11.5 , 333 were female patients (21.4%). The average time between pPCI and sPCI was 28.3 days (± 24.8). 46.3% had diabetes mel-

litus, 76.8% had hypertension, 10.4% were diagnosed with heart failure, and 3.5% had a previous diagnosis of peripheral vascular disease (PVD). Patients were separated into quartiles based on days elapsed following pPCI until day of sPCI: quartile 1 (Q1) 0–7 days (423 patients), quartile 2 (Q2) 7–22 days (382 patients), quartile 3 (Q3) 22–41 days (379 patients), and quartile 4 (Q4) >42 days (371 patients). Differences in rates of diabetes ($p < 0.001$), hypertension ($p < 0.001$), PVD ($p = 0.005$), and prior CABG ($p = 0.001$) existed between the quartiles (Tables 1, 2).

Patients in Q1 experienced 70 MACE (16.5%), patients in Q2 experienced 81 MACE (21.2%), patients in Q3 experienced 98 MACE (25.8%), and patients in Q4 experienced 112 MACE (30.1%) (log-rank <0.001, Fig. 1). When unadjusted rates of MACE were compared between all groups, all MACE outcome components were significantly associated with increasing time between pPCI and sPCI, including: re-MI ($p = 0.008$), TVR ($p < 0.001$), CABG ($p = 0.041$), and all-cause death ($p < 0.001$) (online

suppl. Table 2). Differences in unadjusted all-cause mortality rates were statistically significant ($p < 0.001$) between the quartiles (online suppl. Fig. 1).

Multivariate cox regression analysis was performed, adjusting for variables such as comorbid conditions between the quartiles. This analysis revealed delayed sPCI as an independent factor for risk of MACE (HR = 1.226 [95% CI: 1.129–1.331, $p < 0.001$]). Other factors associated with increased risk of MACE included: age at PCI (HR = 1.015 [95% CI: 1.005–1.025, $p = 0.002$]), history of diabetes mellitus (HR = 1.272 [95% CI 1.050–1.541, $p = 0.014$]), decreased estimated ejection fraction (HR = 0.978 [95% CI 0.968–0.988 $p < 0.001$]), and renal insufficiency (HR = 2.260 [95% CI 1.823–2.801, $p < 0.001$]) (Table 3). A multivariate cox regression analysis assessing death as the primary end point revealed a nonsignificant association (HR = 1.022 [95% CI: 0.925–1.129, $p = 0.671$]) with delay length. Patient age at PCI (HR = 1.043; 1.03–1.056, $p < 0.001$), history of diabetes mellitus (HR = 1.402 [95% CI: 1.102–1.784, $p = 0.006$]), prior PVD (HR = 1.768 [95% CI: 1.133–2.758, $p = 0.012$]), decreased estimated ejection fraction (HR = 0.974 [95% CI 0.962–0.986 $p < 0.001$]), renal insufficiency (HR = 2.759 [95% CI 2.134–3.568, $p < 0.001$]), and prior stroke (HR = 1.501 [95% CI 1.076–2.092, $p = 0.017$]) were all found to be associated with increased risk of death (online suppl. Table 3).

We then performed a secondary analysis, following propensity matching, which compared those treated before and after the median time (22 days) between pPCI and sPCI, again revealing delayed sPCI as an independent factor for risk of MACE (HR = 1.503 [95% CI: 1.192–1.896, $p = 0.001$]) (Fig. 2). Other factors associated with increased risk of MACE included: congestive heart failure (HR = 1.976 [95% CI: 1.525–2.561, $p < 0.001$]), prior PVD (HR = 1.635 [95% CI: 1.092–2.450, $p = 0.017$]), and renal insufficiency (HR = 2.034 [95% CI: 1.604–2.580, $p < 0.001$]) (Table 4). When mortality was assessed as the end point, delayed sPCI was not found to be a significant independent risk factor (HR = 1.163 [95% CI: 0.890–1.521, $p = 0.269$, online suppl. Table 4 and Fig. 3]).

Discussion

The goal of the current study is to better understand the effects of timing between primary intervention of culprit lesions in STEMI patients and staged interventions of nonculprit lesions. With growing trends toward complete revascularization of patients with MVD, the need for accurate information on the optimal timing of revascular-

Table 3. Cox regression MACE

	HR	Range	<i>p</i> value
Age, years	1.015	1.005–1.025	0.002
Gender (female)	1.064	0.862–1.314	0.561
DM	1.272	1.050–1.541	0.014
HTN	1.049	0.801–1.375	0.727
CHF	1.161	0.908–1.375	0.234
PVD	1.373	0.923–2.044	0.118
Estimated EF	0.978	0.968–0.988	<0.001
eGFR <60	2.260	1.823–2.801	<0.001
Prior stroke	1.227	0.911–1.654	0.178
Radial	1.070	0.845–1.354	0.575
Time between quartiles	1.226	1.129–1.331	<0.001

CHF, congestive heart failure; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HTN, hypertension; PVD, peripheral vascular disease; MACE, major adverse cardiovascular event; HR, hazard ratio.

ization is necessary. A clearly defined protocol for management has not emerged due to the lack of robust evidence and conflicting data. Our study showed that increased time to staged intervention of nonculprit lesions was associated with higher rates of MACE.

The ESC/EACTS guidelines on myocardial revascularization highlight a lack of evidence on optimal timing of staged procedures [14]. When considering the proper timing for sPCI, the clinician must consider many variables, including risk of recurrent ischemic events, contrast exposure, severity of initial infarction, patient symptoms, and other comorbidities. Two recent studies have shown improved outcomes and reduction of MACE for patients with MVD receiving sPCI within 1–2 weeks of initial presentation [22, 23]. Other studies suggest that a more conservative approach with longer wait times (>3 weeks) can improve outcomes [24]. A sub-analysis of the COMPLETE trial assessing timing showed consistent improvement in outcomes irrespective of timing of secondary interventions [25], and a recent meta-analysis similarly demonstrated consistent benefits for STEMI patients regardless of whether the complete revascularization was achieved during the index procedure or as a staged intervention (≤ 45 days) [26].

In this study, the risk for MACE increased as duration between primary and staged procedures increased. This may be due to the fact that patients with non-IRA coronary artery disease are inherently at increased risk for adverse events and mortality [4], and these events were a manifestation of this burden over time. Other studies have

Fig. 2. Kaplan-Meier curves showing rates of MACEs for sPCI groups following propensity matching. sPCI, staged percutaneous coronary intervention; HR, hazard ratio; MACEs, major adverse cardiovascular events.

shown that complex coronary plaques [27] and concomitant plaque ruptures [28, 29] were already present in non-culprit arteries at presentation of STEMI, increasing the urgency of revascularization of high-risk plaques. Patients within our dataset who had their secondary interventions delayed had significantly more comorbidities. Despite our adjustment for available comorbidities, these patients may have experienced higher rates of MACE because they had a larger burden of coronary artery disease and/or comorbid conditions contributing to the likelihood of adverse events. This may have also contributed to the clinician's decision to delay sPCI. However, when both Cox regression and propensity matching were done within each

quartile for isolation of timing as an independent variable, delayed sPCI remained a risk factor for MACE.

The consideration of timing is inherent in decision-making when clinicians are presented with patients having STEMI and MVD. Studies discuss the decreased or similar risk of adverse effects [19, 30, 31] if flow is restored within nonculprit lesions during the index procedure, while others show planning a separate intervention to be more efficacious [14–17]. Potential benefits of sPCIs include time to properly assess complex nonculprit lesions with noninvasive testing and fractional flow reserve [21], as well as a proposed time for myocardial recovery [17]. Of consideration, revascularization of non-

Table 4. Cox regression propensity matched MACE

	HR	Range	p value
Age, years	1.009	0.996–1.021	0.187
DM	1.183	0.922–1.518	0.186
HTN	0.801	0.526–1.221	0.302
CHF	1.976	1.525–2.561	<0.001
PVD	1.635	1.092–2.450	0.017
Estimated EF	0.990	0.978–1.002	0.105
eGFR <60	2.034	1.604–2.580	<0.001
Gender factor	0.520	0.2061.315	0.167
Median time to sPCI	1.503	1.191–1.896	0.001

CHF, congestive heart failure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HTN, hypertension; sPCI, staged percutaneous coronary intervention; PVD, peripheral vascular disease; MACE, major adverse cardiovascular event; HR, hazard ratio.

culprit arteries soon after STEMI, either during the index procedure or during an early sPCI, may have added risk due to the fact that the myocardium is undergoing remodeling. This must be weighed against complications associated with performing a duplicate procedure such as increased contrast burden and nephropathy risk [32], a potentially higher incidence of procedural complications from higher patient loads of anticoagulant and antithrombotic therapies in early sPCI [17], as well as the inherent risk associated with prolonged patient exposure to vulnerable plaque burden when intervention is delayed.

Following infarction, a multifactorial process involving inflammatory mediators, the renin-angiotensin-aldosterone system, and the sympathomimetic nervous system causes myocyte hypertrophy and dilation [33]. Noninfarcted areas that surround the infarcted lesion are under increased stress, due to a multitude of factors, and undergo a detrimental form of hypertrophy [34]. Furthermore, the plaques harbored in non-IRA obstructive lesions have been found to be, more often than not, of vulnerable plaque morphology (thin-cap fibroatheroma) as detected by optical coherence tomography [35] which have been most commonly implicated as the cause of acute coronary events [36, 37]. The presence of thin-cap fibroatheroma lesions as detected by optical coherence tomography can also be predictive of post-procedural MI occurrence, further strengthening the need to intervene in such lesions [38]. This may be compounded in patients with MVD and perhaps could be mitigated by intervening on non-IRA lesions, which

could be suggested by other studies showing improved short-term [39] and long-term [40] outcomes for patients who undergo complete revascularization more urgently. If patients require secondary procedures to intervene on non-IRA, those with an increased burden of comorbidities should be evaluated sooner and undergo early revascularization.

Study Limitations

One main limitation of this study is that it is an observational, single-center, and post hoc analysis of our cohort. This is an initial hypothesis-generating study. It is not conclusive or adequate to change practice per se. Although based on an all-comer prospective registry, biases may have influenced the selection of data, the method of therapy and other factors associated with outcome, although our primary outcome measures remained significant after multivariate analysis. The observational nature of the study weakens our ability to report on a causal relationship between time duration between the index event and sPCI and outcomes. Patient baseline characteristics also significantly differed between quartiles; nevertheless, after multivariate analysis, delayed sPCI remained a significant risk factor for MACE. In this large real-world registry, our data support an early approach to sPCI in patients suffering from STEMI presenting with MVD.

Conclusions

Patients who presented with STEMI and MVD and who underwent complete revascularization were at increased risk of experiencing MACE with increased time interval between primary intervention and staged intervention. These data should be taken into account when treating patients with STEMI and MVD using the staged approach geared toward complete coronary revascularization.

Statement of Ethics

The Institutional Review Board for Rabin Medical Center approved this process prior to beginning the data collection. All patients gave written informed consent prior to participation. The IRB reference number is RMC-3741.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Fig. 3. Kaplan-Meier curves showing rates of mortality over time for sPCI groups following propensity matching. sPCI, staged percutaneous coronary intervention; HR, hazard ratio.

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Author Contributions

All authors fulfill the ICJME criteria for authorship. J.H.A. was responsible for the writing, conception, and revision of the manuscript. T.B. was responsible for data analysis and acquisition. G.G. and H.V.A. were responsible for critical revision of the manu-

script. R.K. was responsible for the conception and revision of the manuscript, and L.P. was responsible for the conception and design, data analysis, and revision of the manuscript. All the authors have read and approved the final version of this work.

Data Availability Statement

All data generated or analyzed during this study are not publicly available on legal or ethical grounds. Further inquiries can be directed to the corresponding author.

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