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Restoring mortality data in the FOURIER cardiovascular outcomes trial of evolocumab in patients with cardiovascular disease: a reanalysis based on regulatory data

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ABSTRACT

Objective The FOURIER trial showed a benefit of the PCSK9 inhibitor evolocumab over placebo with respect to cardiovascular outcomes in patients with cardiovascular disease. However, we observed some inconsistencies between the information in the Clinical Study Report (CSR) and that in the 2017 primary trial results publication. We aimed to restore the mortality data in the FOURIER trial based on the information contained in the death narratives in the CSR.

Methods Mortality data in the primary results publication were compared with that in the CSR. In cases of discrepancy between the sources, an independent committee blindly readjudicated and restored the cause of death according to the information in the CSR narratives.

Results For 360/870 deaths (41.4%), the cause of death adjudicated by the FOURIER clinical events committee differed from that declared by the local clinical investigator. When comparing the CSR information with the 2017 primary results publication, we found 11 more deaths from myocardial infarction in the evolocumab group (36 vs 25) and 3 less deaths in the placebo group (27 vs 30, respectively). In the CSR, the number of deaths due to cardiac failure in the evolocumab group was almost double those in the placebo group (31 vs 16). While cardiac and vascular deaths were not assessed as separate outcomes in the original trial analysis, after readjudication, we noted that cardiac deaths were numerically, but non-significantly, higher in the evolocumab group (113) than in the placebo group (88; relative risk (RR) 1.28, 95% CI 0.97 to 1.69, p=0.078), whereas non-cardiac vascular deaths were similar between groups (37 in each; RR 1.00, 95% CI 0.63 to 1.58, p=0.999). The reported HR for cardiovascular mortality in the original trial analysis was 1.05 (95% CI 0.88 to 1.25); after readjudication, we found a greater (although still non-significant) relative increase in cardiovascular mortality in the evolocumab treatment group (RR 1.20, 95% CI 0.95 to 1.51, p=0.13).

Conclusion After readjudication, deaths of cardiac origin were numerically higher in the evolocumab group than in the placebo group in the FOURIER trial, suggesting possible cardiac harm. At the time the trial was terminated early, a non-significantly higher risk of cardiovascular mortality was observed with evolocumab, which was numerically greater in our readjudication. A complete restoration of the FOURIER trial data is required. In the meantime, clinicians should be sceptical about prescribing evolocumab for patients with established atherosclerotic cardiovascular disease.

Trial registration numbers NCT01764633.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is a reanalysis of mortality data from the FOURIER trial based on information in the original Clinical Study Report (CSR), which provides relevant insight into the effects of evolocumab on mortality in patients with established cardiovascular disease.
⇒ We provide detailed information on the causes of mortality that were not previously available.
⇒ This readjudication showcases the need for independent scientific access to regulatory documents to assess drug effects and confirm or refute published observations.
⇒ Because autopsies were not performed in the FOURIER trial, the cause of death could not be determined for about one third of all deaths.
⇒ Non-fatal primary and secondary outcomes could not be readjudicated and recalculated, since the CSR did not include the corresponding clinical event narratives; additionally, we calculated relative risks instead of the HRs, since it was not possible to calculate the latter without individual patient data.

INTRODUCTION

Government regulators licensed evolocumab in 2015 based on its ability to reduce LDL-cholesterol, not its effect on cardiovascular disease or mortality. The FOURIER trial,[1] the primary results of which were published in 2017 in the *New England Journal of Medicine* (*NEJM*), examined the impact of evolocumab

on cardiovascular outcomes by randomising 27 564 patients with clinically evident atherosclerotic cardiovascular disease and LDL-C>70 mg/dL (1.8 mmol/L) on statin therapy, to subcutaneous evolocumab 140 mg every 2 weeks or 420 mg monthly, or to placebo.

The FOURIER trial utilised the composite outcome of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularisation, whichever occurred first. The trial was planned for 56 months (4.7 years). However, it was terminated early for apparent benefit after a median follow-up of 2.2 years.[2]

According to the *NEJM* publication,[1] adding evolocumab to a statin reduced the incidence of the primary composite endpoint (9.8% vs 11.3%, HR 0.85 (95% CI, 0.79 to 0.92)). Evolocumab reduced LDL-C by 59% (from baseline median 92 mg/dL (2.4 mmol/L) to 30 mg/dL (0.78 mmol/L), whereas LDL-C did not change in the placebo group. However, both total mortality and CV death were numerically increased in the evolocumab group. Most cardiovascular deaths (n=372/491; 75.8%) were classified as 'other cardiovascular death', not as myocardial infarctions or congestive heart failure, which typically predominate among cardiovascular deaths.

The Clinical Study Report (CSR) provides more abundant and detailed evidence than was published in the *NEJM* report. This is a technical document prepared by the manufacturer and submitted to regulators as part of the approval package for drug evaluation. It contains information about the trial's protocol, amendments, inclusion and exclusion criteria, outcome definitions and measurement, efficacy and safety results and statistical analysis plan. The main FOURIER CSR is over 25 000 pages.

When we first browsed the narratives in the CSR, we could identify some cases where the cause of death established by the trial investigator did not match that adjudicated by the clinical events committee. We also observed that in the 2017 *NEJM* publication, a statistically significant reduction in myocardial infarction and stroke was reported but this did not translate into a benefit in all-cause mortality or cardiovascular mortality, being both numerically higher in participants treated with evolocumab. Additionally, we noted significant inconsistencies and misreporting when comparing the information on mortality in the published article with that in the CSR. Consequently, we deemed that a thorough reanalysis of data was necessary. Additionally, the lead author initially declared no conflicts of interest, something inconsistent with other available information (but addressed in a subsequent correction).

The Restoring Invisible and Abandoned Trials (RIAT) initiative is an international effort to tackle bias in research reporting. Its goal is to provide more accurate information to patients and other healthcare decision makers.[3] Our main objective for a RIAT reappraisal was to present the restored mortality data from the FOURIER trial based on the information provided by the manufacturer in the CSR.

METHODS

Application for regulatory documents

On 22 May 2018, a RIAT team was established and applied to the European Medicines Agency (EMA) for the CSR of the FOURIER trial. Our request was handled in accordance with Article 7 of Regulation (EC) No 1049/2001 regarding public access to European Parliament, Council and Commission documents, and Article 6 of the Rules for the Implementation of Regulation (EC) No 1049/2001 on access to European Medicines Agency documents.[4]

The team also applied to the US FDA for the CSR under the Freedom of Information Act. However, we were notified by telephone on 18 October 2019 that it would take FDA 3–4 years to address the petition, and another 2–3 years to release the information. Finally, we requested the FOURIER CSR from Health Canada. In early 2020, in compliance with the Protecting Canadians from Unsafe Drugs Act 2014 (Vanessa's Law),[5] Health Canada made the CSR publicly available through its internet portal.[6]

Overview of the Clinical Study Report

Enrolment in the FOURIER trial began on 5 September 2012. The trial protocol, reproduced in the FOURIER CSR, was amended on six occasions. Amendment 2 was adopted on 24 September 2012, after enrolment had commenced. A key change from the original protocol was exclusion of some outcomes defined as efficacy endpoints from characterisation as Serious Adverse Events: *Clarify that all cause death, myocardial infarction, stroke, revascularisation, hospitalisation for unstable angina, hospitalisation for heart failure, and TIA will not be considered as Serious Adverse Events in this study but will be handled as efficacy endpoints and that the Data Monitoring Committee will be requested to follow the occurrence of these events to see if specific action needs to be taken during the course of the study.*

This protocol amendment allowed the trial managers to split cardiovascular events into two different groups, namely 'efficacy' and 'safety' endpoints. We discovered that the FOURIER CSR only provided detailed patient information for death outcomes (including cardiovascular deaths, one component of the composite primary endpoint) and for non-fatal serious adverse events tagged as 'safety' endpoints. Detailed information was not provided in the CSR for non-fatal cardiovascular outcomes defined as 'primary endpoints'. Consequently, we could restore only the mortality outcomes for all patients. We were not able to restore non-fatal serious adverse events, unless they were tagged as safety endpoints.

The FOURIER CSR provides narratives for 870 death outcomes (in 939 pages, from 23 766 to 24 705). Each narrative consists of a brief summary of the clinical record for each death. Most important to our readjudication process, it provides the cause of death declared by *the main local investigator* (as both 'reported' and 'coded'

terms). Death narratives also include categorisation of the death into one of the three permitted 'causes of death' assigned by the *FOURIER clinical-events committee* ('cardiovascular', 'non-cardiovascular' or 'undetermined' death). Finally, death narratives include the 'adjudicated cause of death', the specific cause of cardiovascular death adjudicated by the *FOURIER clinical-events committee* (eg, myocardial infarctions, congestive heart failure). Reference 6 includes the link to the FOURIER CSR (Study 20110118, documents Body 1, 2a and 2b).

RIAT methodology

In order to initiate a project to restore a clinical trial, authors must fulfil three main requisites. First, they have to contact the trial main author and invite him/her to restore data. If the main author refuses to do it or is not responsive, RIAT authors can kick off the restoration project by publishing a 'call-to-action' at BMJ. Finally, RIAT authors must provide evidence to the RIAT support centre that they have enough information to undertake the restoration project.[3]

Following this established RIAT methodology, the RIAT team emailed the main author of the *NEJM* FOURIER trial publication on 13 February 2019, inviting him to republish the article in order to restore missing information. When we had no reply from the main author, we emailed two reminders on 18 March and 8 April 2019. We obtained a 'read' receipt for each request. When we still received no response, the RIAT team emailed the main author a fourth time to advise him of our intention to restore the FOURIER trial. We published this email as a 'call to action' in the *British Medical Journal* on 10 April 2019.[7] We never obtained any response from the main FOURIER trial author to any of our emails and we commenced work on 1 September 2020.

Establishment of the readjudication and validation committees and data reanalysis

In September 2020, we established a *RIAT readjudication committee* composed of researchers from the University of British Columbia (JW, Chair; KB, CJ, MB-E; TLP, Supervisor; JE, Secretary). The *RIAT readjudication committee* first reviewed and approved the protocol for this RIAT project (available from the corresponding author on request). The *readjudication committee's* principal role was to evaluate clinical information in the CSR narratives to either confirm the *FOURIER clinical-events committee's* 'adjudicated cause of death', or when necessary, to readjudicate the cause of death by consensus. In order to assess the death narratives in a blinded manner, the Secretary (JE) then extracted all 870 death outcomes from the CSR narratives, but redacted the treatment arm, sex, age, race and page number from the CSR. Remaining members of the *readjudication committee* evaluated all death narratives during scheduled weekly meetings. The Secretary created a RIAT project database for death outcomes, including the original FOURIER 'adjudicated cause of death' and the readjudicated cause of death. All death readjudications in this database include the readjudication committee's consensus justification for a change in categorisation of deaths, and reference to the CSR page of the original death narrative. The RIAT readjudication committee used the same clinical definitions for readjudication of death cases as did the original study authors, which are available in the appendix of the original 2017 *NEJM* publication.[1]

We also established a *Validation Committee* composed of researchers from the Navarre Health Service, Spain (LCS, LL and MG-V). This committee ensured that information entered into our RIAT project database was consistent with the original CSR. This verification was not blinded as it entailed validation of information on treatment arm, patient characteristics, etc. The *Validation Committee* also confirmed that all potential cases for readjudication had been evaluated, and that readjudications achieved by consensus of the *Readjudication Committee* were consistent with the information in the CSR narratives.

In 308 cases (35.4% of total deaths), the readjudicated cause of death was 'undetermined' due to lack of information in the CSR narratives to justify the cause of death adjudicated by the *FOURIER clinical-events Committee*. On 8 March 2021, the Vancouver research team emailed the main author of the FOURIER trial, to request additional clinical information that might clarify the cause of death in these cases. We received a 'read' receipt on the same day, but never received any response to our request for further information.

Having completed the readjudication, we broke blinding for analysis of the incidence of events in each group as reported in the *NEJM*, and after readjudication. We describe below the inconsistencies in death adjudication when comparing mortality information reported in the CSR with that reported in the 2017 *NEJM* article. We also compared the readjudicated cause of death with mortality information presented in the *NEJM* article. The χ^2 test was used to calculate relative risk (RR) of outcomes after readjudication.

Patient and public involvement

None.

RESULTS

Internal inconsistencies in the 'type of death' classification within the CSR

In the CSR narratives, all deaths were assigned to one of the three categories: 'cardiovascular', 'non-cardiovascular' or 'undetermined'. We designated this as the 'death classification'. In addition, a more specific cause was stated for all cases, designated by FOURIER as the 'adjudicated cause of death'.

For 226 of 870 deaths (26.0%), 'death classification' and 'adjudicated cause of death' were inconsistent, within the FOURIER CSR. For example, among 24 deaths classified as 'cardiovascular', the 'adjudicated cause of death' was 'Non-cardiovascular' for 12 and 'Undetermined' for 12.

Among 66 deaths classified as 'Non-cardiovascular', the 'adjudicated cause of death' was 'Cardiovascular' for 56 and 'Undetermined' for 10. Among 136 deaths classified as 'Undetermined', the 'adjudicated cause of death' was 'cardiovascular' for 101 and 'Non-Cardiovascular' for 35 (table 1).

Death outcome after readjudication

For 360/870 deaths (41.4%), the cause of death adjudicated by the *FOURIER clinical-events committee* differs from the cause declared by the local clinical investigator in the corresponding CSR death narrative. Figure 1 illustrates this inconsistency. For a death that we adjudicated as having been reported clearly by the responsible physician as due to a myocardial infarction, the myocardial infarction was neglected by the *FOURIER clinical-events committee* and misreported as a Sudden Cardiac death. Figure 2 shows an example of a death we adjudicated as resulting from myocardial infarction that was misadjudicated and misreported by the *FOURIER clinical-events committee* as a non-cardiovascular death.

The RIAT Secretary (JE) assessed all death narratives (CSR pages 23 766 to 24 705). Based on these death narratives, the RIAT researchers readjudicated the cause of death whenever information in the narratives was discordant with the adjudication reported by the *FOURIER clinical-events Committee*. Online supplemental table S1 summarises our readjudication of death outcomes and online supplemental table S2 lists all readjudicated deaths, including the justification for readjudication by consensus of our *RIAT Readjudication Committee*. References to the CSR page(s) relevant to these decisions are included. Both online supplemental tables S1 and S2 are available as supplementary materials along with the death outcomes narratives in the CSR (online supplemental table S3).

Table 2 summarises the readjudicated causes of death, compared with the information in the 2017 *NEJM* publication, categorised by treatment group. The total number of deaths is the same. However, categorisation of cardiovascular deaths is very different. Readjudication of the deaths provides much more information than is available from the original publication in the *NEJM*. After readjudication, 'undetermined' cause of death accounted for 308/870 deaths (35.4%), 'non-cardiovascular' death for 287/870 (33.0%) and 'cardiovascular' death for 275/870 (31.6%).

Cardiac and vascular death was not assessed as separate outcomes in the original trial analysis. When comparing the CSR information with the 2017 NEJM publication, we found 11 more deaths from myocardial infarction in the evolocumab group (36 vs 25) and 3 less deaths in the placebo group (27 vs 30, respectively). One of the most frequent causes of death we identified by readjudication was 'cardiac failure'. The 2017 *NEJM* article did not report this outcome. Readjudication indicated that deaths attributable to cardiac failure in the evolocumab group were almost double those in the placebo group (31 vs 16, respectively).

Our readjudication also showed that the number of deaths of cardiac origin was higher in the evolocumab group (113) than in the placebo group (88). Non-cardiac vascular deaths were similar between groups (37 in each); table 2).

The 2017 *NEJM* publication reported that cardiovascular mortality was non-significantly increased in the evolocumab group (251) versus placebo (240), HR=1.05 (95% CI, 0.88 to 1.25), p=0.62. After readjudication, we found a greater (although still non-significant) relative increase in cardiovascular mortality in the evolocumab treatment arm: RR=1.20 (95% CI 0.95–1.51), p=0.13. Cardiac mortality was also higher in the evolocumab group although statistical significance was not reached, RR=1.28 (95% CI 0.97–1.69), p=0.078, whereas vascular mortality was similar between groups, RR=1.00 (95% CI 0.63–1.58), p=0.999 (note that cardiac and non-cardiac vascular mortality were not assessed as separate outcomes in the original trial analysis).

After readjudication, we found that the leading cause of 'non-cardiovascular' deaths was cancer, followed by infectious diseases (including sepsis; table 2). We identified no significant differences between treatment groups.

DISCUSSION

The FOURIER trial is particularly important because evolocumab is the first in a new drug class. When first licensed, its effects on clinical outcomes were unknown. The 2017 *NEJM* publication and regulatory approval are the basis for treatment of many people around the world.

The 2017 *NEJM* publication reported that evolocumab decreased non-fatal myocardial infarctions and strokes. Readjudication of the FOURIER data confirmed the 2017 *NEJM* report findings that both total and cardiovascular mortality were numerically higher in the evolocumab group. However, the number of cardiovascular deaths observed after readjudication was higher than reported in the 2017 *NEJM* article. It would be surprising for myocardial infarctions and strokes, which account for most cardiovascular deaths, to decrease while cardiovascular mortality was increased by evolocumab.

When we applied to the EMA and to Health Canada for the FOURIER trial CSR, we also requested access to anonymised individual patient Case Report Forms (CRFs). These are the primary documents filed by local investigators for every participating patient. They contain all relevant clinical information, including descriptions and documentation of clinical events plus laboratory, electrocardiographic/echocardiographic and radiologic data. Both the EMA and Health Canada responded that they had not requested these documents from the company for the approval process; consequently, they have no legal right to ask the manufacturer for this information postauthorisation. We also requested the CSR and CRFs from the FDA, which replied that due to work overload,

Table 1 Inconsistencies between 'death classification' and 'adjudicated cause of death' in the CSR death narratives

Death classification	Adjudicated cause of death	No	CSR page
Cardiovascular (n=24)	Undetermined	12	23 840; 23 852; 23 987; 24 038; 24 183; 24 189; 24 197; 24 291; 24 378; 24 476; 24 646; 24698
	Non-cardiovascular (infection; includes sepsis)	6	23 882; 24 203; 24 216; 24 370; 24 582; 24662
	Non-cardiovascular (trauma)	3	23 825; 24 562; 24703
	Non-cardiovascular (renal)	2	23 916; 24596
	Non-cardiovascular (malignancy)	1	23964
Non-cardiovascular (n=66)	Cardiovascular (due to stroke)	28	23 772; 23 864; 23 946; 23 948; 23 974; 24 002; 24 050; 24 055; 24 060; 24 074; 24 079; 24 101; 24 117; 24 140; 24 147; 241 49; 24 176; 24 265; 24 379; 24 381; 24 451; 24 454; 24 483; 24 572; 24 590; 24 591; 24 635; 24687
	Cardiovascular (sudden cardiac)	12	23 781; 23 866; 24 000; 24 020; 24 029; 24 164; 24 213; 24 227; 24 321; 24 374; 24 426; 24518
	Cardiovascular (due to heart failure)	5	24 091; 24 241; 24 424; 24 644; 24677
	Cardiovascular (due to other cardiovascular causes/ pulmonary embolism)	5	23 969; 24 367; 23 924; 24 092; 24436
	Cardiovascular (due to cardiovascular haemorrhage)	3	23 911; 24 258; 24573
	Cardiovascular (due to an acute myocardial infarction)	2	23 919; 24247
	Cardiovascular (due to other cardiovascular causes/ intestinal ischaemia)	1	24157
	Undetermined	10	23 806; 23 828; 23 950; 24 107; 24 187; 24 205; 24 395; 24 430; 24 536; 24673

Continued

Table 1 Continued

Death classification	Adjudicated cause of death	No	CSR page
Undetermined (n=136)	Cardiovascular (sudden cardiac)	91	23 789; 23 818; 23 859; 23 861; 23 862; 23 881; 23 903; 23 918; 23 922; 23 923; 239 38; 23 945; 23 958; 23 963; 23 970; 23 971; 24 007; 24 013; 24 016; 24 051; 24 052; 24 057; 24 065; 24 083; 24 124; 24 131; 24 132; 24 136; 24 152; 24 160; 24 162; 24 173; 24 179; 24 180; 24 186; 24 193; 24 200; 24 201; 24 209; 24 211; 24 218; 24 219; 24 242; 24 250; 24 254; 24 255; 24 259; 24 261; 24 266; 24 268; 24 294; 24 297; 24 312; 24 333; 24 337; 24 343; 24 348; 24 357; 24 376; 24 377; 24 380; 24 383; 24 384; 24 390; 24 391; 24 409; 24 410; 24 416; 24 419; 24 434; 24 445; 24 463; 24 465; 24 480; 24 490; 24 531; 24 537; 24 555; 24 594; 24 619; 24 620; 24 625; 24 626; 24 649; 24 651; 24 654; 24 655; 24 664; 24 667; 24 674; 24685
	Cardiovascular (due to stroke)	4	24 195; 24 577; 24 647; 24657
	Cardiovascular (due to heart failure)	3	24 631; 24 668; 24671
	Cardiovascular (due to an acute myocardial infarction)	2	24 256; 24331
	Cardiovascular (due to other cardiovascular causes/ peripheral arterial disease)	1	23791
	Non-cardiovascular (malignancy)	15	23 855; 23 885; 23 889; 23 894; 23 930; 24 037; 24 184; 24 397; 24 420; 24 488; 24 508; 24 509; 24 517; 24 550; 24570
	Non-cardiovascular (infection; includes sepsis)	6	23 884; 24 030; 24 273; 24 551; 24 650; 24679
	Non-cardiovascular (pulmonary)	4	24 249; 24 576; 24 578; 24695
	Non-cardiovascular (hepatobiliary)	2	24 270; 24624
	Non-cardiovascular (non-cardiovascular procedure or surgery)	2	23 961; 24366
	Non-cardiovascular (trauma)	2	24 306; 24669
	Non-cardiovascular (gastrointestinal)	1	24385
	Non-cardiovascular (neurological)	1	24489
	Non-cardiovascular (pancreatic)	1	24192
	Non-cardiovascular (suicide)	1	24123
Total inconsistencies		226	
Total deaths		870	

CSR, Clinical Study Report.

Product: Evolocumab
Clinical Study Report: 20110118
Date: 10 April 2017 Page 24461

Study ID: 20110118
Subject: PPD
Randomized Arm: AMG 145
Actual Arm: AMG 145

Death Endpoint (coded term [reported term]): MYOCARDIAL INFARCTION [MYOCARDIAL INFARCTION]

Subject ID	Adjudication	Adjudicated cause of death
PPD	Cardiovascular Death	Death - Cardiovascular (Sudden Cardiac)

Subject PPD was a P -year-old PPD male who was participating in Study 20110118. His medical history included PPD

The subject received the first dose of investigational product (IP) on PPD (Day 1). On PPD (Day 624) the subject experienced myocardial infarction. The event was considered serious for the following reasons: results in death, and is life threatening. The event occurred 8 days after the last dose of any study medication. No treatment medications were reported for the event.

Concomitant medications taken at the onset of the myocardial infarction and up to 30 days prior to event onset included: atorvastatin.

The subject had the following abnormal laboratory test results at baseline: high blood urea nitrogen [10 mmol/L, range = (2.86 - 8.21)], high glucose [10.7 mmol/L, range = (4.6 - 6.4)], high HbA1c [0.07 fraction of 1, range = (0.04 - 0.06)], low platelets [126 10^9/L, range = (140 - 450)], and high protein [1+, range = NEGATIVE]. **On the closest laboratory test results day on or prior to the start of the event (**PPD **Day 506), the subject had the following on-study laboratory test results with results different than baseline:** normal blood urea nitrogen [7.14 mmol/L, range = (2.86 - 8.21), BL =high], normal platelets [160 10^9/L, range = (140 - 450), BL =low], high potassium [5.2 mmol/L, range = (3.3 - 5.1), BL =normal], and normal protein [negative, range = NEGATIVE, BL =high].

The investigator considered the event to be not related to IP and not related to statin. The event ended on PPD (Day 624) with an outcome of fatal.

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Figure 1 Example of myocardial infarction death misreported as sudden cardiac death. PPD, protection of personal data. AMG 145: evolocumab (experimental group). Death endpoint: report by local clinical investigator. Adjudication: FOURIER Clinical-events Committee classification (CV, non-CV, unknown). Adjudicated cause of death: FOURIER Clinical-events Committee specific classification of death.

Study ID: 20110118
Subject: PPD
Randomized Arm: AMG 145
Actual Arm: AMG 145

Death Endpoint (coded term [reported term]): CARDIOGENIC SHOCK [CARDIOGENIC SHOCK]

Subject ID	Adjudication	Adjudicated cause of death
PPD	Cardiovascular Death	Death - Non-Cardiovascular (Trauma)

Subject PPD was a P -year-old PPD male who was participating in Study 20110118. His medical history included PPD

The subject received the first dose of investigational product (IP) on PPD (Day 1). On PPD (Day 267) the subject was reported with myocardial infarction (Grade 4) and on PPD (Day 267) the subject experienced cardiogenic shock (Grade 4). The event was considered serious for the following reasons: results in death. The event occurred 14 days after the last dose of any study medication. No treatment medications were reported for the event.

Concomitant medications taken at the onset of the cardiogenic shock and up to 30 days prior to event onset included: ACE inhibitor, acetylsalicylic acid, beta blocker, glycemic control medication, insulin, and simvastatin.

The subject had the following abnormal laboratory test results at baseline: low calcium [2.15 mmol/L, range = (2.2 - 2.55)], low calcium corrected [2.18 mmol/L, range = (2.2 - 2.55)], high creatinine [126 umol/L, range = (62 - 106)], low glucose [<2.2 mmol/L], high glucose [1+, range = NEGATIVE], high HbA1c [0.09 fraction of 1, range = (0.04 - 0.06)], high protein [1+, range = NEGATIVE], and high urate [440 umol/L, range = (202 - 416)]. **On the closest laboratory test results day on or prior to the start of the event (PPD Day 169), the subject had the following on-study laboratory test results with results different than baseline:** normal calcium [2.2 mmol/L, range = (2.2 - 2.55), BL =low], normal calcium corrected [2.2 mmol/L, range = (2.2 - 2.55), BL =low], high glucose [6.6 mmol/L, range = (4.6 - 6.4), BL =low], normal glucose [negative, range = NEGATIVE, BL =high], and high hematocrit [0.52 fraction of 1, range = (0.37 - 0.5), BL =normal].

The investigator considered the event to be not related to IP and not related to statin. The event ended on PPD (Day 267) with an outcome of fatal.

AMGEN

Figure 2 Example of myocardial infarction death misreported as non-cardiovascular death. PPD, protection of personal data. AMG 145: evolocumab (experimental group). Death endpoint: report by local clinical investigator. Adjudication: FOURIER Clinical-events Committee classification (CV, non-CV, unknown). Adjudicated cause of death: FOURIER Clinical-events Committee specific classification of death.

Table 2 Cause of death: readjudication (RA) vs original *NEJM* publication

	EVO (RA)	EVO (*NEJM*)	PLA (RA)	PLA (*NEJM*)
Cardiac death				
Sudden cardiac	43	n.r.	43	n.r.
Acute myocardial infarction	36	25	27	30
Heart failure	31	n.r.	16	n.r.
Acute coronary syndrome	1	n.r.	0	n.r.
Ischaemic heart disease	1	n.r.	0	n.r.
Postinfarction cardiosclerosis	1	n.r.	0	n.r.
Ventricular tachycardia	0	n.r.	1	n.r.
Other causes	0	n.r.	1	n.r.
Subtotal	113	n.r.	88	n.r.
Non-cardiac vascular death				
Stroke	23	31	25	33
Pulmonary embolism	7	n.r.	7	n.r.
Cardiovascular haemorrhage	5	n.r.	3	n.r.
Cardiovascular procedures	1	n.r.	1	n.r.
Intestinal ischaemia	1	n.r.	0	n.r.
Mesenteric ischaemia	0	n.r.	1	n.r.
Subtotal	37	n.r.	37	n.r.
Non-cardiovascular death				
Malignancy	80	n.r.	72	n.r.
Infection; includes sepsis	34	n.r.	32	n.r.
Pulmonary	7	n.r.	12	n.r.
Hepatobiliary	3	n.r.	2	n.r.
Non-cardiovascular haemorrhage	3	n.r.	2	n.r.
Non-cardiovascular procedure or surgery	3	n.r.	0	n.r.
Pancreatic	3	n.r.	1	n.r.
Suicide	3	n.r.	3	n.r.
Trauma	3	n.r.	6	n.r.
Renal	2	n.r.	2	n.r.
Other causes	9	n.r.	5	n.r.
Cause of death after readjudication				
Death—cardiovascular	150	251	125	240
Death—non-cardiovascular	150	n.r.	137	n.r.
Death—undetermined	144	n.r.	164	n.r.
Total	444	444	426	426

n.r., not reported; RA, data after readjudication.

we would have to wait at least 5 years for the requested information. It is thus possible that none of the regulators requested and reviewed the CRFs before approving evolocumab for marketing. If so, we find this an unacceptable lack of due diligence.

The information registered in the CRF is usually employed by the manufacturer to build the individual-patient database including the full information of the trial. The CSR is elaborated according to these raw data, but, though extensive, it may not include all necessary information to appropriately assess results. For example, independent analysis in some outcomes or time-to-event analysis may not be possible. Nonetheless, most probably, observed discrepancies between the 2017 *NEJM* publication and the CSR information are not related to the unavailability of CRFs. The cause of death determined by the principal investigator and the final adjudicated cause of death according to the clinical events committee are registered both in the CRF and CSR, and we could access this information through the latter document. Anyway, independent researchers should be granted access to the raw data of all trials to verify the validity of the CSR among other issues.

Who validates the work of clinical events committees?

The 26% of inconsistencies we identified through the RIAT process puts into question the validity of cause of death adjudication by the *FOURIER clinical-events committee*. Discrepancies in the death adjudication process affected both treatment arms, but the misadjudications improperly reduced cardiovascular deaths in the evolocumab group. The 2017 *NEJM* publication reported that cardiovascular mortality was non-significantly increased in the evolocumab group (251) versus placebo (240), HR=1.05 (95% CI, 0.88 to 1.25), p=0.62. After readjudication, we found a greater (although still non-significant) relative increase in cardiovascular mortality in the evolocumab treatment arm: RR=1.20 (95% CI 0.95–1.51), p=0.13.

Clinical trials of treatments for cardiovascular diseases usually report results for both 'cardiovascular' and 'total' mortality. One exception is the 2008 *NEJM* report of the JUPITER trial,[8] which failed to report cardiovascular mortality, even though this was the single most important component of the predefined composite primary outcome. The US FDA and the manufacturer of rosuvastatin were aware that the trial did not identify a significant difference in CV mortality and considered the apparent difference in total mortality to be spurious.[9] Readers may assume that the difference between 'total' mortality and 'cardiovascular' mortality reflects 'non-cardiovascular' mortality. However, we were surprised to learn from readjudication of FOURIER that the cause of death was 'Undetermined' for 35.4% of all deaths. Similar unrecognised uncertainties probably apply to the apparent results of many other trials. During our review and readjudication of all deaths, we were surprised to find no evidence that autopsy was performed after any death. Autopsies are the most effective tool to discover unexpected adverse events and causes of death, especially in pivotal trials of new drugs.[10]

When reviewing the death narratives in the CSR, we observed 91 deaths classified by the local investigator as 'Undetermined', but subsequently adjudicated by the *FOURIER clinical-events committee* as 'Sudden Cardiac' deaths without any clinical evidence to support this change. It is misleading to categorise deaths of unknown

cause as 'Sudden Cardiac', because the latter term implies a relationship to acute myocardial infarction or dysrhythmia of ischaemic origin. A Cochrane systematic review provides evidence against that assumption[11] and a study of 1000 sudden deaths investigated by autopsy showed that only 41% of sudden deaths are due to myocardial infarction.[12] Therefore, a critically important error in the *NEJM* reporting of FOURIER is the adjudication of all 'sudden' deaths as sudden cardiac deaths, without supporting evidence.

Clinical trialists should thus abstain from including cardiovascular mortality as part of a primary endpoint, and steering committees should abstain from terminating trials early on the basis of cardiovascular mortality. If a drug is suspected to reduce cardiovascular mortality, then it should be suspected to reduce all-cause mortality as well, and trial sample sizing should thus incorporate all-cause mortality instead.

The 2017 *NEJM* article reported cardiovascular deaths poorly, accounting only for myocardial infarctions and strokes. All other cardiovascular deaths were classified only as 'other', despite comprising 75.8% of the total. The exceptionally large proportion of cardiovascular deaths classified only as 'other' indicates that in most instances neither the trialists nor the *FOURIER clinical-events committee* knew the true cause of death.

Our readjudication found that the number of deaths of cardiac origin was higher in the evolocumab group (113) than the placebo group (88), whereas there was no difference between groups in total vascular deaths (table 2). This raises the possibility that evolocumab might have specific adverse cardiac effects, a hypothesis consistent with pharmacovigilance reports (FAERS, Eudravigilance or VigiAccess databases) and other publications,[13] but inconsistent with the FOURIER trial finding that evolocumab decreased non-fatal myocardial infarctions. Table 3 shows cardiovascular reports on evolocumab registered at the FDA Adverse Event Reporting System (FAERS) as of 30 June 2022. Cardiovascular fatal cases account for 18% of total deaths reported, and cardiovascular serious adverse events (including deaths) account for 23% of total serious adverse events (including all reaction groups). The only way to shed light on this issue is for the narratives of clinical events tagged as 'efficacy endpoints' in the FOURIER trial to be made available by regulatory bodies, AMGEN, or by the original investigators, who attested in *NEJM* to having complete access to all data from the trial.

As readjudicated, we found that total cardiovascular deaths were significantly lower than the number published in 2017 by the *NEJM*. Since cardiovascular mortality is included in the composite primary endpoint, an exaggerated assessment of cardiovascular mortality could have contributed to inappropriate early termination of the trial 'for benefit'. Assuming that the point estimate we identified of a 20% RR increase in cardiovascular mortality were maintained, the non-significant increase in cardiovascular mortality from evolocumab might have reached statistical significance before the end of the prespecified 56-month follow-up. Therefore, we cannot exclude the possibility that evolocumab would have increased cardiovascular mortality significantly over the planned full trial duration.

Finally, last 5 October 2021, we emailed the *NEJM* editors to inquire whether they would be interested in learning about our RIAT project on the FOURIER trial,

Table 3 Cardiovascular reports on evolocumab registered at the FDA Adverse Event Reporting System (FAERS) (as of 30 June 2022)

	No reports	Fatal	Serious (incl. death)
Cardiac disorders	2241	137	1875
Myocardial infarction	651	55	620
Heart failure*	189	12	183
Vascular disorders	1886	35	991
Nervous system disorders—stroke and TIA	641	33	622
Stroke†	541	31	526
Transient ischaemic accident (TIA)	100	2	96
Stroke+TIA	641	33	622
Cardiovascular disorders‡	4768	205	3488
Total adverse event reports (all reaction groups)	89366	1132	14986
CV events out of total adverse events	5.3%	18.1%	23.3%

*Cardiac failure congestive, cardiac failure, cardiac failure acute, cardiac dysfunction, cardiac failure chronic.
†Cerebrovascular accident, cerebral infarction, cerebral haemorrhage, haemorrhagic stroke, subaracnoid haemorrhage, ischaemic stroke, haemorrhage intracraneal, cerebral thrombosis, embolic stroke, haemorrhagic cerebral infarction, cerebral venous thrombosis, cerebral artery thrombosis, brain stem stroke, brain stem infarction, brain stem haemorrhage, lacunar stroke, lacunar infarction, thrombotic stroke, basilar artery thrombosis, stroke in evolution and embolic cerebral infarction.
‡Cardiac disorders, vascular disorders, stroke and transient ischaemic accident.

and also willing to correct the original article. In addition to the above-mentioned email, we also sent a reminder on 20 October 2021, but never obtained any response.

Limitations

A limitation of this study is that the CSR did not include the narratives for the non-fatal primary and secondary outcomes and CRF were not available from regulators. This is why we could not recalculate results in these outcomes. Another limitation is that we could not recalculate HRs for cardiovascular mortality since we had no access to time to event information from individual-patient data. We have calculated RR after re-adjudication.

Future directions

This study shows the need for independent scrutiny of medical literature based on regulatory documents. It also indicates that the CSR is a valuable source to assess trials but still relevant information may be absent. All narratives for events registered in the trials should be included in the CSR, regardless the case was tagged as an efficacy or safety outcome. Most regulators do not require individual-patient data from the companies, but they should hold this information for an appropriate assessment, and also make it available to independent researchers. This should include both CRFs and the full individual-patient database.

CONCLUSIONS

The FOURIER trial showed no reduction in total or cardiovascular mortality. Our readjudication of mortality outcomes showed that deaths of cardiac origin were numerically higher in the evolocumab group (113) than with placebo (88), suggesting possible cardiac harm from evolocumab. At the time, the trial was early terminated, a non-significant higher risk of cardiovascular mortality was observed after readjudication as compared with that reported in the 2017 *NEJM* publication. Our findings indicate that complete restoration of all clinical outcomes from the FOURIER trial is required. Meanwhile, clinicians should be sceptical about benefits versus harms of prescribing evolocumab for patients with established atherosclerotic cardiovascular disease.

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