Real-life LDL-C treatment goals achievement in patients with heterozygous familial hypercholesterolemia in the Czech Republic and Slovakia: Results of the PLANET registry

Michal Vrblík, Katarina Raslová, Branislav Vohnout, Vladimir Blaha, Martin Satnya, Ondrej Kyselak, Martina Vavlova, Robin Urbanek, Jana Maskova, Vladimir Soska, Tomas Freiberger

ABSTRACT

Background and aims: Despite the high prevalence of familial hypercholesterolemia (FH) and available effective lipid-lowering therapy, most of the individuals with this disorder remain undiagnosed and undertreated. The aim of the PLANET registry was to assess the real-life attainment of low-density lipoprotein cholesterol (LDL-C) therapeutic target level in patients with heterozygous FH, to characterize prescribed lipid-lowering therapy with assessment of its efficiency according to the attainment of the target LDL-C level, and to characterize cardiovascular events observed in this patient population again in relation to LDL-C target level attainment.

Methods: PLANET registry was designed as a non-interventional, retrospective, cross-sectional, multicentre disease registry for adult patients with heterozygous FH in the Czech Republic and Slovakia.

Results: Overall, 1755 patients were enrolled at 32 sites specialized in FH treatment. 15.4% of patients attained the target LDL-C value. The proportion of patients with LDL-C goal achievement increased to 17.3% in the subgroup of patients receiving high-intensity statin therapy (54.6% of study population). Out of 55 patients receiving inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), 61.8% reached the LDL-C treatment goal. Of all cardiovascular events reported, 14.0% occurred in patients attaining the LDL-C goal, while it was 86.0% in the not-at-target group. It was documented (p = 0.004) that the longer is the patient in care at the specialized FH centre, the higher is the probability that he/she will attain the target LDL-C level.

Conclusions: Although target LDL-C level attainment remains relatively low, the likelihood of LDL-C goal attainment increases with duration of specialized care.
1. Introduction

Familial hypercholesterolemia (FH) is one of the most frequent genetic disorders and it is associated with severe elevation of cholesterol in the blood, specifically, low-density lipoprotein cholesterol (LDL-C) that leads to premature atherosclerotic cardiovascular disease. Furthermore, individuals with FH often die from sudden cardiovascular death at a young age [1], therefore aggressive lipid management is needed.

Despite the high prevalence of FH estimated to be around 1 in 250 for heterozygotes, most of individuals with this disorder remain undiagnosed and undertreated (reviewed in Ref. [2]). Often, individuals are not screened or diagnosed until after they experience a premature cardiovascular event [3]. Moreover, even when using all currently available treatment options to lower LDL-C, most FH patients do not reach recommended target LDL-C levels [4,5].

In 1989, the MedPed (Make early diagnoses to Prevent early deaths in Medical Pedigrees) project was initiated with the aim to identify subjects with FH that are either undiagnosed or inadequately treated and help them treat their disorder by advising them and their doctors on the best possible medical therapies available [6]. The Czech Republic joined the MedPed project in 1998. A network of national and regional centres, specialized centres and professional collaborators has gradually been established, all of which are dedicated to the identification and treatment of FH patients. Till 30 November, 2016, the Czech National MedPed Database has registered 7001 FH patients from 5223 different families, representing 17.4% of the expected patients in the Czech Republic, considering the 1:250 FH prevalence. Slovakia was invited to participate in the MedPed project in 1997. To 14 December, 2016, 23 MedPed centres in 14 different districts had been established [7,8]. Till 30 November, 2016, the Slovak National MedPed Database has registered 2246 FH patients from 1184 different families that was 12.23% of the expected patients in Slovakia, considering 1:250 FH prevalence. Although the Czech and Slovak Republic belong to the most successful countries with respect to FH detection, FH still remain undiagnosed [9].

Although MedPed is a well-established project of active search for FH patients in the Czech Republic and Slovakia that includes a very large FH population, no evaluation of long-term patient outcomes after inclusion at MedPed has been performed to date. The aim of the PLANET registry was to assess the attainment of therapeutic target level of low-density lipoprotein cholesterol (LDL-C) according to the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines 2011 [10], in the settings of everyday medical practice. Furthermore, PLANET registry enabled to characterize lipid-lowering therapy prescribed to patients with heterozygous FH, assessing its efficiency according to attainment of the target LDL-C level as well as to characterize cardiovascular events observed in this patient population again in relation to LDL-C target level attainment.

The data were collected during visit V1 (the date of patient enrolment to the PLANET registry), when required information was recorded from medical documentation to an electronic case report form (eCRFs) retrospectively, including data from entry to the MedPed project and recent laboratory findings (within 1 month before V1). Data for the PLANET registry were collected from 21 October, 2015 to 30 June, 2016.

2. Patients and methods

2.1. Patient population and participating sites

Selected sites were out-patient departments participating in the MedPed project. All sites were specialized in internal medicine, or even in cardiology, or lipidology. Overall, 1755 patients were enrolled and analysed. 1421 patients were enrolled in 24 Czech sites and 334 patients were enrolled in 8 Slovak sites. Patients in the PLANET registry were recruited from participants of the MedPed project and they were enrolled on the consecutive basis to reduce selection bias. Inclusion criteria: males and females ≥18 years old, heterozygous FH, signed informed consent with registry participation. Exclusion criteria: homozygous FH and other hypercholesterolemia than FH. FH was diagnosed using MedPed criteria, but also patients with elevated LDL-C levels in serum not exceeding MedPed cut-offs or patients with untreated levels unavailable, with high clinical suspicion of FH based on personal history and/or family history of premature coronary heart disease and/or elevated total and LDL cholesterol serum levels in the first degree relatives, were included.

Sample size calculation was based on the proportion of patients with attained target LDL-C level according to ECS/EAS guidelines 2011 [10] that was 10–30% with expected value 20%. To achieve a confidence interval range of 2%–10% of expected value (with probability of 83.6%), we needed to analyse 1600 evaluable subjects.

2.2. PLANET registry design and collected data

PLANET registry was designed as a non-interventional, retrospective, cross-sectional, multicentre disease registry for patients with heterozygous FH in the Czech Republic and Slovakia.

The primary objective of the registry was to assess the attainment of LDL-C therapeutic target level according to the ESC/EAS 2011 guidelines [10] in the settings of everyday medical practice. The secondary objectives were to characterize lipid-lowering therapy prescribed to patients with heterozygous FH, assessing its efficiency according to attainment of the target LDL-C level as well as to characterize cardiovascular events observed in this patient population again in relation to LDL-C target level attainment.

The null hypothesis that the distribution of MedPed participation was not different from the overall Czech and Slovak distribution of FH prevalence was tested using data from MedPed centres and the Slovak National MedPed Database.

2.3. Ethics

PLANET registry was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964), including all subsequent amendments, and in compliance with all national laws and regulations of the countries in which the registry was performed, as well as with Guidelines for Good Pharmacoepidemiology Practices [11] and Good Epidemiological Practice [12]. The registry was approved by the independent ethic committee and informed consent form had to be signed by the patient before any data collection to the registry.

2.4. Statistical analysis

Analysis of collected data was based on descriptive statistics including absolute and relative frequencies of discrete variables. Continuous variables were described by: count, mean, standard deviation, median and 25th–75th percentile range. Discrete variables were described by count (absolute frequency), and percentages (relative frequency). All missing data were accounted for each analysis. No imputation of missing data was performed.

The null hypothesis that the distribution of MedPed participation duration is the same across both subpopulations with respect to target LDL-C level attainment was tested using independent samples, Mann-Whitney U test on the level of significance of 0.05. We chose non-parametrical test after normal distribution of analysed data had been examined by Shapiro-Wilk test on the level of significance 0.05.
3. Results

3.1. Characteristics of the patient population

In total, 1755 patients were included in the study and descriptive statistics of the patient population is summarized in Supplementary Table 1. 40.9% of participants (n = 717) were males while 59.1% (n = 1038) were females and the mean age at the time of heterozygous FH diagnosis in 1744 subjects (11 had missing value) was 46 years.

3.2. Attainment of therapeutic target LDL-C level in the study population

The primary endpoint was to evaluate LDL-C treatment targets attainment as recommended by the ESC/EAS 2011 guidelines [10]. The target value was attained in 267 patients (15.4%). Better attainment was observed in patients with LDL-C target value \( \leq 2.5 \) mmol/L (184 patients (19.5%)) compared to LDL-C target value \( \leq 1.8 \) mmol/L (83 patients (10.4%)). Table 1 summarizes LDL-C levels in subgroups of patients by the target value and by the target value attainment. Supplementary Tables 2, 3 and 4 summarize total cholesterol levels, high density cholesterol (HDL-C) and triglycerides in the PLANET patient population at the time of inclusion in the PLANET registry.

3.3. LDL-C level in the study population at inclusion in the PLANET registry

Frequency of patients in categories by LDL-C level at inclusion in the PLANET registry is described in Table 2. Frequency of subjects with LDL-C up to 3.00 mmol/L was 43.4% at inclusion in the PLANET registry. However, 26.4% of registry patients have the value of LDL-C higher than 4.1 mmol/L. Furthermore, Supplementary Fig. 1 shows the bar chart of LDL-C level categories and Supplementary Fig. 2 shows the bar chart of LDL-C level categories by target LDL-C value.

3.4. Lipid-lowering treatment and dose by attainment of target value

Participating patients with heterozygous FH were treated with monotherapy (49%) or combination of medications (43%). Some of the observed subjects were newly diagnosed patients (8%) without therapy to date. Statins were used by 1578 patients (98%), however, information on whether patients receive any statin was missing for 144 patients. Ezetimibe was prescribed to 42.1% patients with reported lipid-lowering therapy. History of statin intolerance was reported in 16.7% of subjects with recorded lipid-lowering therapy, nevertheless, 92.6% of these patients were using statin.

To simplify efficacy assessment of a very complex variety of lipid-lowering therapy used in the real life setting, we separately analysed patients with high-intensity [13] lipid-lowering therapy only, as described in Table 3. In comparison to the proportion of patients with target value attainment in the whole patient population (15.4%), 13.6% of patients reached target LDL-C value with the highest dose of the two most potent statins, atorvastatin 80 mg, or rosuvastatin 40 mg, administered as the only lipid-lowering treatment. Adding ezetimibe 10 mg to the same therapy increased the proportion of patients with attainment of target LDL-C value to 14.6%. Of note, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, a new treatment option approved recently, resulted in 61.8% of patients with target value attained. All patients used PCSK9 inhibitors in combination with.
the other lipid-lowering drugs, and they all were participants in PCSK9 inhibitors clinical trials as reimbursement rates had not been stated yet at the time of data collection. When assessing patients with high-intensity lipid-lowering therapy defined as atorvastatin in dose 40–80 mg or rosuvastatin in dose 20–40 mg alone or in combination with other lipid-lowering medication, the proportion of patients with attained target value is 17.3%. In total, 958 of patients used this high-intensity lipid-lowering therapy, that is 54.6% of the whole PLANET registry population.

### 3.6. Cardiovascular events

At least one cardiovascular event (CVE) was experienced 15.3% (n = 266) by patients from the PLANET registry population with reported information (n = 1739). Of all patient registry population, the most frequent CVE was revascularisation (10.5%), followed by myocardial infarction - MI (10.0%), unstable angina pectoris (1.5%), and stroke (3.2%) (Table 5). Lifetime prevalence of CVE was collected in the Cardial infarction - MI (10.0%), unstable angina pectoris (1.5%), and most frequent CVE was revascularisation (10.5%), followed by myocardial infarction - MI (10.0%), unstable angina pectoris (1.5%), and stroke (3.2%). Overall, 14% of CVEs occurred among patients with target value attained, while it was 86.0% in the subgroup without treatment target attained.

#### 3.7. Duration of MedPed participation

Duration of participation in the MedPed project for each patient was also collected in the Planet registry. Therefore, we were able to test null hypothesis that the distribution of MedPed participation duration is the same across both subpopulations with respect to target LDL-C level attainment. Normal distribution of participation duration in both subgroups was rejected by Shapiro-Wilk test with p < 0.001 on significance level 0.05. Using non-parametrical independent samples Mann-Whitney U test on the level of significance 0.05, the null hypotheses was rejected with p = 0.004. The data thus suggests the longer the patient participates in the MedPed project, the higher is the probability he/she would attain the target LDL-C level. As summarized in Supplementary Table 5, median participation of patients with attained target value was 4 years, while median participation of patients without attained target value was 2 years.

### 4. Discussion

FH represents the most frequent inherited metabolic disorder, as the most recent prevalence data from Europe have newly suggested the disease is as frequent as 1:250 in the general population [14]. Despite the long standing efforts for its proper and early detection and effective screening supported by local and national collaborations, the detection rate of FH remains to be relatively low, reaching up to 35% of identified cases in the Netherlands while being still below 1% in most other countries [2]. Thanks to continuous efforts of nation-wide FH screening programme MedPed, being coordinated by the Czech Society for Atherosclerosis, there have been more than 17% of the predicted number of FH patients identified in the Czech Republic till 2017 [9]. In Slovakia, MedPed project coordinated by the Coordination Centre for Familial Hyperlipidemias of Slovak Medical University in Bratislava has

### Table 4

<table>
<thead>
<tr>
<th>Changes in any lipid-lowering therapy</th>
<th>Changes in therapy with any statin</th>
<th>Changes in therapy with added ezetimibe</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Increased dose</td>
<td>198</td>
<td>37.2%</td>
</tr>
<tr>
<td>Changing statin</td>
<td>174</td>
<td>32.7%</td>
</tr>
<tr>
<td>Decreased dose</td>
<td>28</td>
<td>5.3%</td>
</tr>
<tr>
<td>Other change in treatment</td>
<td>132</td>
<td>24.8%</td>
</tr>
<tr>
<td>Total</td>
<td>532</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

### Table 5

<table>
<thead>
<tr>
<th>At least one CVE</th>
<th>Yes</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>target value attained</td>
<td>target value not attained</td>
<td>total</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>26</td>
<td>14.8%</td>
<td>150</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>0</td>
<td>0.0%</td>
<td>26</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
<td>16.1%</td>
<td>47</td>
</tr>
<tr>
<td>Revascularisation</td>
<td>27</td>
<td>14.7%</td>
<td>157</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>14.0%</td>
<td>380</td>
</tr>
</tbody>
</table>

<sup>a</sup> % counted from the total number of CVEs in patients with at least one CVE.
<sup>b</sup> % counted from the total number of patients in the PLANET registry.
successfully implemented systematic FH screening and helped create a system of FH centres throughout the country [7]. Despite all the evidence, guidelines and therapeutic options, even the FH population identified and under therapy does not seem to be optimally managed. The recent SAFEHEART registry data from Spain showed only 11.2% of FH individuals being followed by specialized services were at LDL-C targets [4]. Thus, as nobody doubts the value and usefulness of long-term and nation-wide FH registries as very powerful sources of data to demonstrate natural development of the disease under changing therapeutic options as well as the environment, we need to make a move further towards improving quality of care for FH patients. With this aim, we designed the PLANET registry as a cross-sectional survey within the MedPed Czech and Slovak national FH registries to describe the current situation of LDL-C goal attainment and its relation to clinical outcomes and atherosclerotic vascular events rates.

Primary goal of the PLANET registry – LDL-C goal levels attainment – was reached in 15.4% of the overall registry population. Not surprisingly, slightly more patients with LDL-C goal of less than 2.5 mmol/L have reached the target than the ones with LDL-C goal of less than 1.8 mmol/L (19.5% vs. 10.4%). This data is not surprising and well in line with previous observations [5,15]. One may believe this rather unsatisfactory treatment result might be, to the largest extent, attributed to severity of hypercholesterolaemia in FH and efficacy limits of currently available lipid lowering therapies. However, the analysis of treatment patterns revealed just another explanation. 49% of the patients included in the PLANET registry were treated with statin monotherapy. Most frequently, high-potency statins (atorvastatin and rosuvastatin) were used. However, the analysis of statin dosing revealed substantial underutilization of high intensity statin treatment, which was prescribed to only 54.6% of the patients. Of course, when compared to the results of other surveys (e.g. EUROASPIRE IV or DYSIS), these data might be interpreted as a successful implementation of practice guidelines, as the use of high intensity statin treatment is far more frequent than in the aforementioned non-interventional studies [16,17]. However, given the PLANET programme was conducted in centres specialized in FH diagnosis and management, greater penetration of high intensity statin treatment would have been expected. This finding might be, to a certain extent, explained by the relatively high proportion of subjects reporting statin intolerance. Interestingly, most of the FH subjects with a history of statin intolerance were able to tolerate alternate statin treatment (e.g. statin switch, dose adjustment) – a finding indicative of greater motivation of FH individuals to adhere to statin treatment when compared to the general population. This holds true particularly in those with genetically confirmed diagnosis that has been identified as an important determinant of patients’ long-term adherence to therapy [18]. Ezetimibe was used in 42.1% of patients, which once again suggests important underutilization of this treatment modality. Based on the conclusions of the largest outcomes study, proving ezetimibe efficacy and safety in the very high cardio-vascular disease (CVD) risk setting (the IMPROVE-IT trial [19]), the latest guidelines changed its position and recommended that concomitant use of statin and ezetimibe should be used in those not at goal with statin monotherapy [20]. In light of this, it seems surprising that ezetimibe was not used more frequently in the PLANET registry. Several possible explanations might be offered. First, the PLANET registry was performed only a few months after the publication of the IMPROVE-IT trial and, thus, its greater penetration was about to start gaining this new trial evidence. Second, the guidelines (2011 version [10]) valid at the time of the registry data collection had lower level of ezetimibe evidence, which might have also played its role. Third, and perhaps the most important reason, it is the cost of ezetimibe that is more than twice as high as the cost of high intensity statin treatment. Given the budget restrictions for health care providers, this seems to be the most plausible explanation. On the other hand, comparison of ezetimibe use at baseline of recently published outcome trials with PCSK9 inhibitors shows the utilization of this treatment modality in the PLANET registry was more than 10 times more frequent [21,22].

Analysis of CVE prevalence in the PLANET cohort documented favourable changes observed in FH cohorts in recent years. Compared to original observations from pre-statint era, the prevalence of atherosclerotic vascular complications in our cohort was markedly lower [23]. However, even more recent studies report significantly greater CVD burden in FH individuals. The Danish study documented 33% of FH individuals with overt coronary artery disease [24]. Importantly, only 48% of the individuals in the study were treated with a statin. Our findings match the results of the Spanish SAFEHEART registry that demonstrated CVD prevalence of 14% among FH individuals despite the fact 84% of them had been on statin treatment. It is noteworthy, only 13.6% of the SAFEHEART population were treated with maximum statin dose and ezetimibe as the most effective LDL-lowering treatment option at the time of the analysis [25].

Subgroup analysis of CVE occurrence in those at LDL-C goal and those above the recommended LDL-C level brought another evidence for the guidelines-recommended emphasis on LDL-C lowering in FH individuals. Vast majority (86%) of all CVE occurred in the PLANET patients who were not at their LDL-C target. This crucial finding underlines the importance of the need to pursue the treat-to-target strategy and emphasises the use of the most powerful LDL-C lowering options, which nowadays includes also inhibitors of PCSK9 [26,27]. A very small number of patients included in the PLANET registry were treated with this novel drug class (n = 55) but their goal LDL-C concentration attainment reached 61.8%, which is four-fold greater success rate compared to the general population included in the PLANET. A number of predictors of target LDL-C values in FH have been proposed, from the type of underlying mutation to the presence of other genetic and environmental factors modulating baseline LDL-C level and, of course, treatment patterns [28,29]. Interestingly, patients who achieved their LDL-C goal in the PLANET registry had significantly longer duration of follow up (p = 0.004) at sites of the Czech and Slovak MedPed project (where the PLANET registry was conducted). Thus, specialized and focused care as provided by such centres finally results in greater LDL-C goal attainment and, most importantly, to reduced risk of atherosclerotic vascular complications.

One of the PLANET registry limitations is that inclusion criterion in the registry was clinically diagnosed heterozygous FH and not only molecularly confirmed heterozygous FH. Therefore, it is likely that some patients meeting these criteria may have phenocopies of heterozygous FH.

Results of the PLANET registry could be also influenced by a cross-sectional design when the duration of the therapy was not considered. Furthermore, 8% of enrolled patients were newly diagnosed patients without therapy to date. Therefore, LDL-C level at inclusion to the MedPed project and change in the treatment within the last year were also collected in the PLANET registry to enable evaluation of selected endpoints over a period of time. However, the aim of the PLANET registry – primarily to characterize level of LDL-C and treatment pattern in heterozygous FH patients in clinical practice – was fulfilled with the planned design. Furthermore, results of the PLANET registry fully correspond to situation in the other countries.

Last but not least, multivariate analysis was not performed to investigate a causal relationship between the duration of patient participation in the MedPed project and LDL-C treatment goal attainment as the PLANET registry aimed mainly to map FH patient characteristics and real-life treatment outcomes. Therefore, we cannot exclude other confounding factors, e.g. baseline patient characteristics that could affect this association.

4.1. Conclusion

Data from the PLANET registry thoroughly describe contemporary management of heterozygous FH in the Czech Republic and Slovakia. The study may serve as a quality control, auditing the standards of
clinical management of heterozygous FH in everyday practice of specialized FH (MedPed) centres. While the PLANET registry documents some positive achievements, e.g. much higher use of high-intensity statin treatment and greater penetration of ezetimibe compared to the general clinical practice, the goal LDL-C level attainment remains relatively low. Importantly, the data suggests the likelihood of LDL-C goal attainment increases with the duration of specialized care within the FH MedPed centres. However, multivariate analysis to confirm these assumptions has to be completed to account for potential confounders. Overall, results from the PLANET registry emphasize the potential of national registries not only in characterization of patients’ population and in assessing the trends of FH management but also in demonstrating opportunities to improve the standard care of FH patients.

Conflicts of interest

M. Vrablik received honoraria for consultancy and lectures from: Abbott, Actavis, AstraZeneca, BMS, Genzyme, Krika, MSD Idea, Novartis, Pfizer and Sanofi-Regeneron. T. F. and V. B. received honoraria for sponsored lectures from Amgen and Sanofi. K. R. received honoraria for consultancy/lectures from Sanofi, Amgen, Mylan, AstraZeneca, and research grants from Amgen, Pfizer, and Sanofi. V. S. received honoraria for consultancy/lectures from Sanofi, Amgen, Mylan, MSD, Servier, Egis and PharmaSwiss. J. M. is an employee of NEOX Clinical Research, clinical research organization. NEOX Clinical Research provided the following services funded by the sponsor: data management, administration, statistical analysis and medical writing.

Financial support

This registry - protocol number DIREGL07340 - was funded by Sanofi-Aventis, Czech Republic.

Author contributions

All authors except J.M. were involved in PLANET registry concept and design and protocol development. All authors were involved in evaluation and interpretation of the study results and review and approval of the manuscript. J.M. and M. Vrablik prepared the manuscript with coordination of all co-authors comments. M. Vrablik was also International Registry Coordinator and Scientific Advisor for the PLANET registry and National Coordinator for the Czech Republic. K. R. was National Registry Coordinator for Slovakia. T.F. was National MedPed Registry Coordinator for the Czech Republic.

Acknowledgements

Data collection, analysis, and medical writing of Clinical Summary Report was performed by NEOX Clinical Research, clinical research organization, and funded by Sanofi-Aventis, Czech Republic. The authors had unrestricted access to study data, were responsible for all content and editorial decisions, and received no honoraria related to the development of this publication.

Authors would like to thank to all investigators of the PLANET registry for their devotion and effort during participation in the PLANET registry (participating physicians are listed in Supplementary Table 6).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.08.008.

References


