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Evaluating the utility of fasting lipid panel in addition to random lipid panel in determining lipid-lowering therapy in acute ischemic stroke or TIA patients

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ABSTRACT

Background: Hyperlipidemia is one of the major risk factors for cerebrovascular disease and it is common practice to obtain fasting lipid profile prior to starting lipid lowering therapy (LLT). Recent AHA Guidelines published in 2018 allow for a non-fasting value to be used.
Objective: To determine if obtaining fasting lipid levels in addition to random lipid levels prompts changes in hyperlipidemia management of acute stroke patients.
Methods: 206 patients met the study criteria which included a diagnosis of acute ischemic stroke or transient ischemic attack on admission and availability of both random and fasting LDL levels collected within 72 h of each other. Patients were divided into three groups based on random LDL at admission: Group A: LDL < 70, Group B: LDL 70 – 99, and Group C: LDL ≥ 100 mg/dL. The dataset was analyzed to conform to the 2018 AHA/ACC guidelines using an LDL cutoff of 70 mg/dL.
Results: In 206 patients, statin management would change based on the fasting LDL level in 12 patients, 11 of whom were in Group B. Our data suggests that lipid management is more likely to change if the initial random LDL falls between 70 – 99 mg/dL as compared to a value outside of this range ($P < 0.001$). We present a decision algorithm to guide lipid management in acute stroke patients.
Conclusions: Foregoing a fasting lipid panel to guide LLT in patients with ischemic stroke is appropriate in most cases but for select patients with random LDL levels between 70 and 99, fasting lipid profile should be obtained prior to deciding upon LLT.

1. Introduction

Stroke is a leading cause of morbidity and mortality in the United States with approximately 800,000 strokes occurring every year [1,2]. Secondary prevention of stroke by controlling stroke risk factors remains a staple of stroke management. One of the major risk factors for cerebrovascular disease is hypercholesterolemia. The association between low-density lipoprotein cholesterol (LDL-C) and risk for acute ischemic stroke (AIS) or transient ischemic attacks (TIA) has been evaluated in multiple large cohort studies. For example, Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed a 28 % reduction in stroke risk, without a significant increase in hemorrhagic stroke, by achieving an LDL-C level lower than 70 mg/dL [3]. More recently, Amarenco et al. established that target LDL of < 70 mg/dL for secondary stroke prevention results in a lower risk of subsequent cardiovascular events than higher targets [4,5].

Current stroke guidelines recommend "high intensity statin therapy should be initiated or continued with the aim of achieving a 50 % or greater reduction in LDL-C levels" [6]. While the current Stroke guidelines do not recommend a target LDL level [6], based on above-mentioned studies, we believe that LDL < 70 mg/dL is a target that should be aimed for in Stroke patients for optimal secondary prevention.

It is common practice to obtain a fasting lipid profile for all stroke

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and TIA patients prior to starting lipid lowering therapy. In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released guidelines noting that non-fasting lipid levels can be used for assessing cardiovascular risk, but still recommended a fasting lipid panel prior to statin initiation [7]. Additionally, the 2019 guidelines recommend "measurement of fasting lipids" every 3–12 months to adjust therapy.

1.1. Objective

In this study, we compare the LDL value obtained from the random lipid profile that is collected upon arrival to the ER to the value obtained from the fasting lipid profile, to determine if obtaining fasting levels changes hyperlipidemia management of the patient.

2. Materials and Methods

2.1. Patient Sample

Our hospital, a suburban academic medical center with a Comprehensive Stroke Center certified by the State of New York Department of Health, sees approximately 1000 patients with a stroke diagnosis annually. We screened 733 records of adult patients who were discharged from Stony Brook University Hospital in 2016 with the diagnosis of AIS or TIA. Out of this population, patients with both a random and a fasting lipid profile obtained within 72 h of admission were included for review.

2.2. Chart Review

In this IRB-approved study, patient consent was waived since information was collected retrospectively in a coded manner, with individual patients being assigned a study ID number to preserve confidentiality. Information was extracted from the electronic medical record by 2 residents (DS, US), a research assistant (DD) and a medical student (AT) during the years 2017-18. After screening using the criteria above, we included patients who met criteria for a cerebral ischemic event on admission and had both random LDL levels collected on admission and fasting LDL levels collected within 72 h of admission. A random LDL was defined as LDL on arrival to the hospital, and fasting LDL was performed after admission with instructions of at least 12 h of fasting. Patients who were determined to have a hemorrhagic stroke or unclear diagnosis were excluded. Additionally, patients with carotid artery disease and intracranial atherosclerosis were judged to require a statin regardless of LDL levels; these patients were also excluded from the sample (see Fig. 1).

2.3. Statistical Analysis

2.3.1. Sample Size and Power Analysis

Using a binomial sign test model, and assuming a small to moderate effect size (g) of 0.10, a sample size of 199 cases would be adequate to provide 80 % power at alpha = 0.05 (2-tailed). Power analysis was calculated using G*Power 3.1.9.2 (Dept. of Psychology, Universitaet Duesseldorf, Germany: http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/who-we-are, accessed 30-Sep-2019).

2.3.2. Agreement between Methods of Measurement

The Bland-Altman technique [8] was used to plot the difference of Fasting vs Random LDL versus the Fasting LDL value. This value was chosen since Fasting LDL is considered the gold standard, and would be more informative than plotting the difference scores versus the mean, another common practice.

2.3.3. Data Analysis

The dataset was analyzed to conform to the 2018 AHA/ACC guidelines that prescribe an LDL goal of ≤ 70 mg/dL [9]. Patients were divided into three groups based on random LDL at admission: Group A: LDL < 70 mg/dL, Group B: LDL 70 − 99 mg/dL, and Group C: LDL ≥ 100 mg/dL. We determined whether the initial decision made to initiate or increase statin dosage based on the random lipid profile, would change when the fasting lipid profile became available for each patient.

For categorical variables, these three groups were compared by likelihood ratio chi-square analysis using Monte Carlo method of probability computation, based on 10,000 samples. Continuous variables were analyzed by one-way ANOVA with *a priori* orthogonal contrasts of Groups A and C compared to Group B. Cases with missing values were omitted on a test-by-test basis. All statistical analyses were conducted with IBM SPSS v.24, with $p < 0.05$ taken as the significance level.

3. Results

3.1. Patient Cohort

In the year 2016, 733 patients were discharged from Stony Brook with a diagnosis of ischemic stroke, TIA or non-traumatic ICH. Of these patients, 206 (111 M, 95 F) were included in the study sample (see Fig. 1). The cohort had a median age of 70 years (range 26–97). The baseline characteristics of these patients are shown in Table 1. Our data show no difference in the incidence of diabetes between the three groups. Group C had significantly more patients under 65 years of age (44.1 %, $\chi^2 = 23.860$, 2 df, $P < 0.001$), and significantly fewer patients with hypertension (59.8 %, $\chi^2 = 14.808$, 2 df, $P = 0.001$) or who were taking statins at admission (28.4 %, $\chi^2 = 25.858$, 2 df, $P = 0.001$), compared to the rest of the sample. By the time of discharge, a comparable number of patients in all groups were being treated with statins (> 75 %, $\chi^2 = 2.275$, 2 df, $P = 0.344$). Patients with TIA or AIS did not differ significantly in resting or fasting LDL, nor in the incidence of patients where management would change based on a fasting LDL (7.4 % versus 5.6 %, respectively).

Table 2 presents the means and one-way ANOVA comparisons of Groups A, B and C on continuous variables for these 206 patients. The three groups differed significantly ($P < 0.001$) in both Random and Fasting LDL, and the difference between the two LDL measures (see Fig. 2).

3.2. Comparison of Methods by Bland-Altman analysis

Due to some outlier data points, this data was not normally distributed (Shapiro-Wilk test = 0.810, 206 df, $P < 0.001$). In this situation the data may be log transformed to achieve normality. The authors felt that log transformation would defeat the purpose of the comparison, so here the data is presented in the original units.

Fig. 3 shows the difference between Fasting and Random LDL values plotted against Fasting LDL. The mean difference is -8.34, indicating that Random LDL tends to be higher than Fasting LDL. This difference indicates a significant bias ($P < 0.05$) between LDL measures, since the line of equality (zero difference) does not fall within the 95 % sampling error of the mean (dotted lines). 95 % confidence intervals (dashed lines) are shown for the mean difference; most of the data points fall within these limits.

3.3. Analysis of Statin Management

In 206 patients, statin management was changed based on the fasting LDL level in 12 patients (see Fig. 4). Of the 206 patients, there were 55 total patients with a random LDL value between 70 and 99 (Group B). Eleven (20.0 %) of these 55 patients had a change in management based on obtaining a separate fasting LDL value in addition to the random LDL value. There were 49 patients with a random LDL value

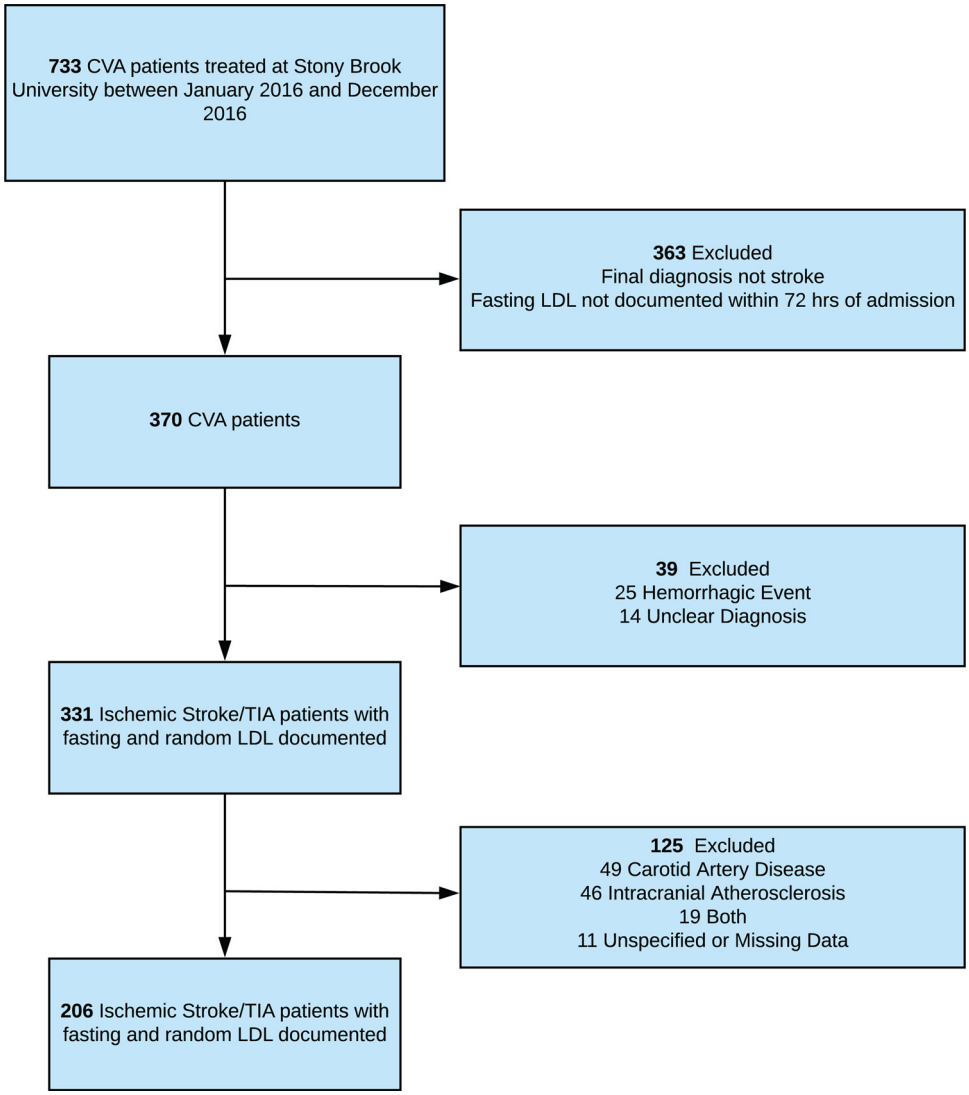

Fig. 1. Flow chart of 733 patients reviewed for inclusion in study database. N = 331 patients were diagnosed with ischemic stroke or TIA and had both fasting and random LDL documented within 72 h of admission. After exclusion of patients with carotid artery disease (n = 49), intracranial atherosclerosis (n = 46), both diagnoses (n = 19), and missing data or unspecified (n = 11), a final N of 206 patients remained for analysis of LDL values.

less than 70 (Group A). Obtaining a fasting lipid panel did not change management in any of these patients. 102 patients had a random LDL value of 100 or higher (Group C). Obtaining a fasting lipid panel changed management in only one of these patients (1.0 %). These three groups are compared, suggesting that the lipid management is more likely to change if the initial random LDL ranged between 70 and 99 as compared to an initial LDL value outside of this range (likelihood ratio $\chi^2 = 25.234$, 2 df, $P < 0.001$).

4. Discussion

4.1. Treatment Guidelines

The American Heart Association's (AHA) and American Stroke Association's (ASA) 2013 guidelines recommended statin therapy in ischemic stroke or TIA patients with an LDL-C level of 100 mg/dL or greater with or without evidence of additional arteriosclerotic

Table 1
Characteristics of the Patient Sample at Admission (N = 206). Statistics reported are 2 × 3 Likelihood Ratio χ^2 (2 df), with p-value computed by Monte Carlo simulation.

	Full Sample	Group A: Random LDL < 70 mg/dL	Group B: Random LDL 70 – 99 mg/dL	Group C: Random LDL ≥ 100 mg/dL	χ^2 (2 df)	*p*-value
Age ≥ 65 years – no. (%)	125 (60.7)	37 (75.5)	43 (78.2)	45 (44.1)	23.860	< **0.001**
Female – no. (%)	95 (46.1)	17 (34.7)	30 (54.5)	48 (47.1)	4.231	0.129
Ischemic Stroke – no. (%)	179 (86.9)	40 (81.6)	49 (89.1)	90 (88.2)	1.490	0.513
Transient Ischemic Attack – no. (%)	27 (13.1)	9 (18.4)	6 (10.9)	12 (11.8)	1.490	0.513
History of Diabetes – no. (%)	42 (21.1)	9 (18.8)	13 (24.5)	20 (20.4)	0.553	0.788
History of Hypertension – no. (%)	148 (71.8)	41 (83.7)	46 (83.6)	61 (59.8)	14.808	**0.001**
Patients taking statin at admission – no. (%)	94 (45.9)	32 (66.7)	33 (60.0)	29 (28.4)	25.858	**0.001**
Patients taking statin at discharge – no. (%)	163 (79.9)	37 (75.5)	41 (75.9)	85 (84.2)	2.275	0.344

Table 2
Results of one-way ANOVA between Groups A, B and C on selected variables. Individual groups are compared with *a priori* orthogonal contrasts (Groups A and C each compared to Group B). Groups are defined on the basis of Random LDL, so a significant difference there is expected. Note that the 3 groups differ on Fasting LDL also. Only Group C differs from Group B on the difference between the two measures of LDL.

	Group A Random LDL < 70 mg/dL Mean ± std. dev. (N = 49)	Group B Random LDL 70 – 99 mg/dL Mean ± std. dev. (N = 55)	Group C Random LDL > 99 mg/dL Mean ± std. dev. (N = 102)	F-test, df.	Omnibus *p*-value	Contrast
Random LDL (mg/dL)	56.2 ± 9.9	85.5 ± 8.1	131.5 ± 26.3	F = 268.627, df (2, 203)	$p < 0.001$	B vs A:* $p < 0.001$ B vs C:* $p < 0.001$
Fasting LDL (mg/dL)	56.9 ± 15.9	80.9 ± 11.8	116.9 ± 24.7	F = 162.804, df (2, 203)	$p < 0.001$	B vs A:* $p < 0.001$ B vs C:* $p < 0.001$
Difference (Random – Fasting LDL) mg/dL	−0.6 ± 15.5	4.6 ± 9.6	14.7 ± 19.2	F = 16.585, df (2, 203)	$p < 0.001$	B vs A: $p = 0.102$ B vs C: $p < 0.001$

* P-value reported does not assume equal variances, using Levene's Test for Homogeneity of Variances.

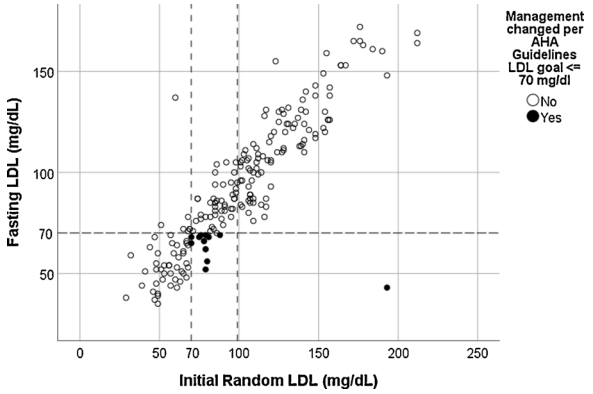

Fig. 2. Plot of initial Random LDL values against Fasting LDL values obtained within 72 h from the same patient. Dashed line on the vertical axis indicates AHA guidelines target LDL = 70 mg/dL. Dashed lines on the horizontal axis indicate random LDL range 70-99 mg/dL. Closed circles indicate cases (n = 12) where statin management changed as per AHA guidelines to treat to LDL goal < 70 mg/dL. Open circles indicate cases (n = 194) where statin management was unchanged.

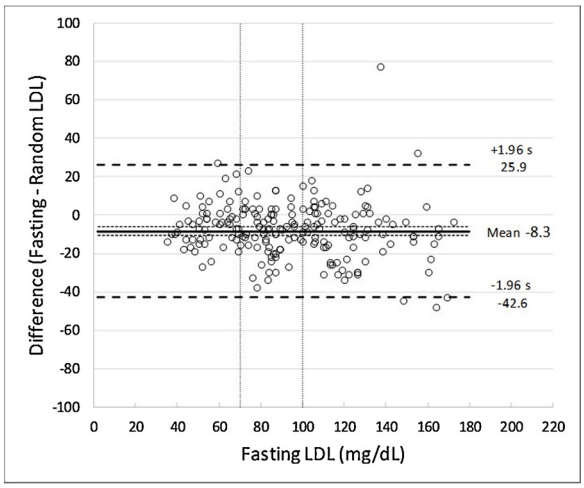

Fig. 3. Bland-Altman Plot. Differences between Fasting & Random LDL values are plotted versus the Fasting LDL score, since it is considered the gold standard. The mean difference is -8.3 mg/dL, plotted as a heavy solid line. 95 % confidence intervals (limits of agreement) are shown by the dashed lines at +25.9 and -42.6. A confidence interval for the mean is shown by dotted lines surrounding the line of mean difference, at -5.95 and -10.73. The line of equality (zero difference) does not fall within this confidence interval for the mean, indicating a significant (P < 0.05) difference between the two LDL measures.

cardiovascular disease [6,10]. The 2019 ASA Stroke guidelines do not identify a target LDL level [6], however, the latest guidelines set forth by the American College of Cardiology (ACC) and AHA call for initiating statin therapy in high-risk ASCVD patients with an LDL-C threshold of 70 mg/dL or greater [9]. This recommendation is additionally supported by the results of the Treat Stroke to Target trial [5]. While the 2019 guidelines do not require a fasting lipid panel to initiate lipid lowering therapy, they do recommend "measurement of fasting lipids" every 3–12 months to adjust therapy [6]. While 2018 AHA guidelines suggest LDL goal < 70 for patients with atherosclerotic vascular disease, it is our intention to treat with this target for all patients, especially in the acute period when a precise etiology has yet to be determined or may be difficult to ascertain. Additionally, there is growing evidence that there is benefit of statin therapy in improving functional outcomes in patients with cardioembolic stroke [11,12].

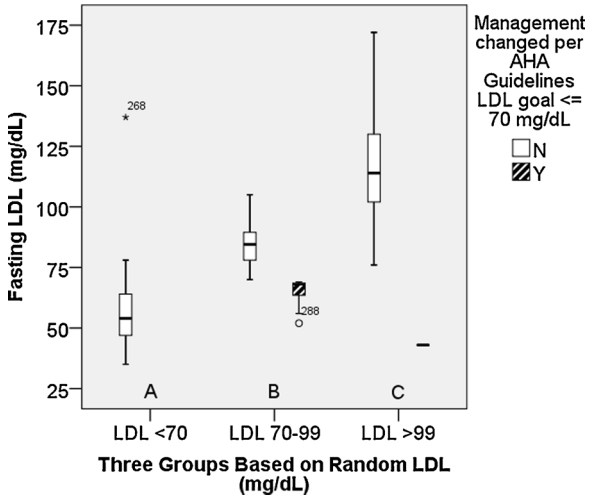

Fig. 4. Boxplot of Fasting LDL values obtained for three groups of patients (A, B, C) based on random LDL value at admission. Open boxes indicate cases where statin management would not be changed; striped box indicates cases where statin management would change per 2018 AHA guidelines. The majority of these cases are in Group B. For Group C, there is only one patient where management would change; this patient is indicated by a horizontal line. Upper and lower edges of boxes represent 75th and 25th percentiles respectively, while the horizontal line within the box represents the 50th percentile (median). Outlier data points (more than 3 interquartile ranges from the median) are indicated by a circle or asterisk and identified by case number.

4.2. Random versus Fasting LDL

While this study largely supports the decision by AHA to forgo fasting LDL testing in ischemic stroke patients, it identifies a subset of AIS patients who would benefit from further fasting LDL testing. Our results indicate that for patients presenting with AIS or TIA, the lipid panel should only be repeated in the fasting state for those patients who have random LDL levels between 70 and 99. If random level is within this range, obtaining fasting lipid level will result in a change in management in 20 % of the patients. For random LDL values that lay outside of this range, the repeat level seldom affects management. These results can be explained using two observations from our data set: 1) Random LDL levels are typically higher than fasting LDL levels. 2) They differ only by 8.76 ± 16.6 mg/dL. If the random level is < 70 mg/dL, then the fasting level is also likely to be < 70 mg/dL, therefore there is no change in management. On the other hand, if the random level is much higher than the threshold, i.e. ≥100 mg/dL, the fasting levels seldom are discordant enough to be < 70 mg/dL and prompt a change in management. It is in the 70 − 99 mg/dL range that there is a significant likelihood of the fasting value dropping below the 70 mg/dL threshold and as such negating the need for further lipid lowering therapy in a significant number of these patients (see Fig. 2).

4.3. Prior Statin Treatment

We also examined whether prior treatment with statins affected the difference between random and fasting LDL values. While overall mean values of random and fasting LDL differed ($P < 0.001$) between groups who were/were not taking statins, this difference between the two LDL measures was not significantly affected ($P = 0.443$) by statin treatment prior to hospital admission. Patients were changed to a higher intensity statin if their fasting LDL was > 70, otherwise their dose was not changed. On admission, 94 patients were receiving statin therapy (45.6 %) whereas at discharge, 163 patients (79.1 %) were prescribed statins. This represents an increase of 69 patients who were started on statin after admission.

4.4. Stroke Mechanism

While statin and lipid lowering remains a key component of secondary stroke prevention, stroke mechanism should be taken into account when making LLT decisions. It is important to note that there is a link between LDL levels and stroke risk for patients with large artery atherosclerotic stroke but not with small artery occlusion or cardioembolic stroke [13]. Thus it may not be necessary to start a lipid lowering medication in patients with cholesterol levels < 70 without large artery atherosclerosis or intracranial atherosclerosis.

4.5. Cost-Benefit Considerations

Moreover, the long term adverse effects of statin are well studied and include risk of dementia and diabetes [14] and thus it is important not to over-prescribe these medications. Therefore, it is important to strike a balance between over-prescribing and being cost effective and as such, obtaining a fasting lipid level should be reserved for the small percentage of patients in which it is likely to change medical decisions. The phenomenon of unnecessary and duplicate testing has been well studied and a recent meta-analysis revealed that an estimated 4–5 billion laboratory tests are performed in the United States each year making it the single highest-volume medical activity in this country. This often leads to more costly downstream care [15].

4.6. Proposed Algorithm for Obtaining Fasting LDL

With the aim of providing cost effective yet medically appropriate care in patients presenting with acute ischemic stroke or a TIA, we propose an algorithm to help determine if a fasting LDL value should be obtained in order to start a patient on hyperlipidemia medication or change the existing hyperlipidemia medication regimen. This algorithm is presented in Fig. 5.

4.7. Atherosclerosis

As supported by the Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS Trial), patients with intracranial atherosclerosis were started on high intensity statin regardless of their lipid level and thus were excluded from the current analysis [16]. Additionally, for the management of carotid stenosis, aggressive risk factor modification including lipid lowering drugs is recommended and thus these patients with significant vascular disease (> 50 % stenosis) were also excluded from our analysis [17–19].

Given the growing data in favor of statin therapy in strokes of non-atherosclerotic origin (i.e. cardioembolic strokes) and the difficulty in determining the stroke etiology in the acute period, it is the authors' approach to treat all ischemic stroke patients with statin therapy initially. When the stroke mechanism has been elucidated, it should be taken into account during LLT decision-making, especially when considering dose of statin therapy. As there is growing literature on the benefits of statin therapy in strokes of non-atherosclerotic etiology, it is possible these benefits may be achieved with less aggressive LDL goals or with a lower intensity statin. The authors concede that it is possible that patients of other determined etiology (i.e. dissection or endocarditis) may have been included in this study given our methodology, but given the low frequency of occurrence it is highly unlikely that they had a significant impact on this study.

4.8. Study Limitations

There are several limitations to this study, starting with its retrospective and observational design. Given the smaller number of TIA patients (N = 27), our conclusions are more relevant to the larger group of patients with AIS (N = 179); nevertheless, we found no difference between these groups. Within these limitations, we believe that our

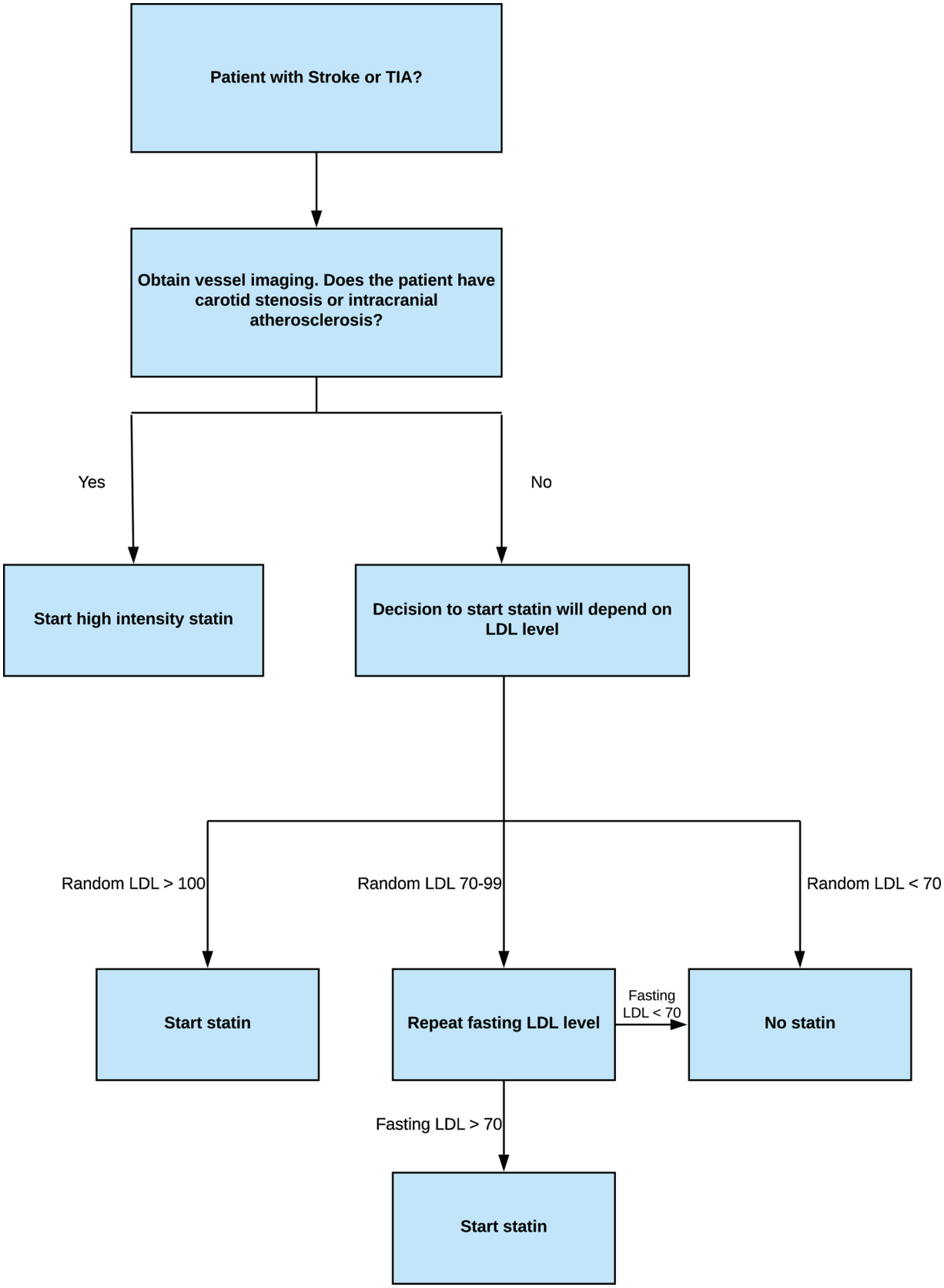

Fig. 5. Proposed algorithm for patients presenting with acute ischemic stroke or TIA, to help determine if a fasting LDL value should be obtained in order to start a patient on hyperlipidemia medication or change the existing hyperlipidemia medication regimen.

sample of over 200 patients is representative of a broad range of ischemic stroke patients seen in clinical practice. While this study looked at how patient management would be affected based on guidelines, in reality there is a variation in practice amongst neurologists in managing hyperlipidemia in stroke patients.

There were numerous differences between three groups of patients. Namely, Group C had significantly more patients under 65 years of age, and significantly fewer patients with hypertension or who were taking statins at admission compared to the rest of the sample. These differences make intuitive sense as younger patients who had stroke are likely to have uncontrolled risk factors (for example poorly controlled hyperlipidemia) and possibly poor outpatient follow-up leading to a lower past diagnosis of hypertension. To the best of our knowledge, these variations do not affect values of random or fasting lipid panels obtained and as such do not diminish the quality of our results. However, one must be mindful of other factors that are well studied and result in variation in results of the lipid panel [20]. For example, we did not take into account the time that patients had their most recent meal prior to initial lipid panel collection. Admittedly, this may have caused a misclassification error in some of our data. However, our approach reflects a more "real world" setting, where patients may present at varying times from symptoms onset and determining time of true last meal based on patient's or family's recollection may be difficult.

5. Conclusion

Within the limitations of a retrospective study, our results clearly suggest that fasting lipid panel is redundant in most but not all patients presenting with stroke. We recommend that fasting lipid profile can be foregone in most stroke patients unless they present with a random LDL level between 70 and 99, in which case, obtaining a fasting lipid level would change management in 20 % of the patients in whom unnecessary additional lipid lowering medications would be avoided. It is not clear if avoiding duplication of the lipid profile in the majority of patients per our algorithm, would lead to a significant reduction in the cost of hospital stay, or conversely an increase in patient satisfaction. These questions could be addressed in future studies.

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Not applicable.

CRediT authorship contribution statement

Usman Shehzad: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Abhinay Tumati:** Investigation, Writing - original draft, Visualization. **Ruth A. Reinsel:** Writing - original draft, Formal analysis, Visualization. **Dharampreet Singh:** Investigation. **Dazzle Dadra:** Investigation. **Archana Purushotham:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Jason Mathew:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interest

Dr. Mathew received compensation for being on a single session Advisory Panel for Portola Pharmaceuticals in February 2020.

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