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Trends in Sudden Cardiac Arrest Cases Among Individuals Aged 24-45 Years and Factors Contributing to it

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Abstract

One of the major global health concerns has been mortality due to sudden cardiac arrest (SCA/D), attributing to ~15-20% of cases of deaths across different age groups. Mortality within one hour of the commencement of the initial signs due to a cardiovascular factor or due to an unknown cause is referred to as sudden cardiac death. The heart function halts and thus not able to maintain sufficient perfusion resulting in end of life in the majority of cases. This is an emergency condition and in certain cases, resuscitation is achieved, however, the rate of resuscitation post-SCA/D remains low. Age-associated structural cardiac dysfunctionality has been a keyreasonfor sudden cardiac death. However, a growing heterogeneity and shift in the age group associated with sudden cardiac death is becoming a significant global health challenge. There has been an increase in age-adjusted mortality from 2.36 in the year 1999 to 3.16 in the year 2019 in individuals aged <45 years due to cardiac arrest. The underlying cause of sudden cardiac death, especially in the aged subjects, has been coronary artery disease in almost 75% of the cases. Ironically, different etiological factors are instrumental in developingSCA/D in young adults. Primarily, irrespective of age, coronary and non-coronary causes are responsible for SCA/D. Coronary causes include coronary heart disease, myocardial infarction, myocarditis, arteriosclerosis, atherosclerosis and arteritis while non-coronary causes include, non-ischemic heart disease (like genetically acquired arrhythmias viz., Brugada syndrome and Wolff-Parkinson-White syndrome, irregularity of the cardiac conduction system) and neurological dysfunctioning (like, intracranial haemorrhage, electrolyte, metabolic, and endocrinal irrationalities, renal malfunction, side effects of certain drugs, and substance usage. Lifestyle factors also contribute significantly to the development of fatal cardiac conditions. Athletes are also highly susceptible to developing lethal arrhythmias and hence at risk for SCA/D. In recent times, COVID-19 also seems to be an underlying cause of cardiovascular system-associated mortality. This review will focus on understanding the causative factors leading to the development of cardiac complications that can result in SCA/D and death in young adults and will briefly address the preventive measures that could be undertaken.

Keywords: Coronary heart disease, Myocarditis, Congenital cardiomyopathy, COVID-19, Athletes

1. Introduction

Abrupt and unanticipated death due to an underlying cardiovascular reason wherein the heart functioning halts within a short duration after induction of first symptoms is stated as sudden cardiac arrest/death (SCA/D). Fatal ventricular arrhythmias along with coronary heart disease have been one of the primary causes of SCA/D. SCA/D remains the foremost cause of mortality, globally amounting to 15-20% of deaths [1]. There has been an increase in age-adjusted mortality from 2.36 in the year 1999 to 3.16 in the year 2019 in individuals aged<45 years due to cardiac arrest[2]. With the advancement in medical science, resuscitation rates have improved significantly, yet, it is difficult to save the majority of the patients of SCA/D. As per an estimate, almost 3,00,000- 3,50,000 cases SCA/D are reported annually in the United States of America[3, 4]. Of that, annually 20,000 deaths,of subjects below the age of 45 years occur due to cardiovascular disease [5]. Even though the fraction of SCA/D in the young population (age range 24-45 years) remains low, the implication of such an incidence on the family and community remains huge. The occurrence of such an incidence especially in athletes symbolizes the huge vulnerability in seemingly healthy and fit persons[6]. Here it is also to clearly demark the difference between SCA/D and acute myocardial infarction /heart attack. SCA/D is the fatal outcome of an anomaly in cardiac rhythm viz., severe bradyarrhythmia, or ventricular tachycardia or ventricular fibrillation. While myocardial infarction is the disparity in the demand and supply of blood flow to the myocardium due to obstruction in the coronary artery. Although patients with myocardial infarction are at high risk of developing SCA/D[7].The abrupt nature of SCA/D demands the accessibilityto emergency healthfacilities for the survival of the subject. However, globally, there is a huge disparity in the accessibility to emergency health facilities. Hence, a preferable approach seems to be identifying the causative factors and having a better understanding of the risk factors involved, which will eventually help to develop preventive measures. Early detection of the possible threat of SCA/D seems to be a viable approach for saving lives. Even though almost 50% of cases of SCA/Din the young population occur without any prior symptoms, it is pertinent to identify and understand the associated possible risk factors and its causes. Hence, this review will focus on understanding the causative factors leading to the development of cardiac conditions that result in SCA/D in young adults and will briefly address the preventive measures that could be undertaken.

2. Epidemiology of Sudden cardiac arrest

Until recently, the frequency of SCA/D in the young population was low. However, recent years saw an increase in the cases of sudden arrest/death in the young population group. The exact estimate of the cases of SCA/D can vary depending data collection method and approach utilized. Thus, the estimates can vary significantly from country to country. However, the median global estimate is based on the incidence of utilization of emergency medical services for tending an outpatient for cardiac arrest[1]. The global estimate suggests that the incidence of SCA/D rates are less in Asian countries (i.e, 52.5/100,000 cases annually), while European countries have 86.4/100,000 cases annually, Australian continent reports to have 111.9/100,000 cases annually and Northern America has 98.1/100,000 cases annually [8]. This geographical variation in estimate, however, can be attributed to the availability of emergency medical services and its reporting as well.

The incidence of SCA/D also varies across genders as well as age groups[9]. Irrespective of age group, the incidence of SCA/D is lower amongst women as compared to men, even after normalizing their

coronary heart disease risk factors [10, 11]. This may be attributed to the lesser frequency of coronary heart disease in women. In fact, two-thirds of female cases of SCA/D have been reported to have no history of coronary heart disease or other cardiac diseases as against half of male cases [12-14]. Also, the incidence of women survivors of cardiac arrest exhibiting structurally normal cardiac conditions is higher as compared to males [15, 16]. However, reports suggest a shift in this divergence between the two genders [4, 17, 18]. The drop in the rate of SCA/D in women (~2.5% reduction in deaths) has been far less as compared to men (~3.5% reduction in deaths), especially in the young population group [17].

Some reports suggest racial disparity in the incidence of SCA/D, wherein African American men, as well as women, were found to have a more number of incidence of SCA/D at an earlier age as compared to Caucasians (relative risk of 1.3 as against 2.8)[19, 20]. Additionally, African Americans also exhibit lower rates of survival after SCA/D as compared to the white population [21]. A study carried out in Chicago reported that only 31% of African Americans survived cardiac arrest as compared to the white population [19]. The African American population also exhibit poor survival post-hospital discharge, almost 27% less than white counterparts [22]. Although, these observations are not only influenced by genetics only, infact, intersecting factors like socio-economic status also play an equally detrimental role in these findings.

The probability of SCA/D increases with an increase in age irrespective of gender and race [23]. The children are deemed to be at the lowest risk for SCA/D. Different studies have reported that in subjects below the age 20 years, the incidence of sudden cardiac death ranges between 0.7-1.7 cases per 100,000 patient-years[24-26]. Annually, 100 men per 100,000 population suffer from SCA/D as against 800 men per 100,000 population of age >75 years[19]. However, the age bracket of 75-85 years is physiologically predisposed to anamplified risk for SCA/D as with aging cardiac dysfunctionality risk increases [4, 27]. Nevertheless, studies have shown that cases of death post-SCA/D are much higher in the young population as compared to the aged population[28, 29]. Retrospective analysis of the estimates has shown that the male young population exhibitsaincreased occurrence of SCA/Dthan their female counterpart (~2:1) [30-32].

3. Aetiology of Sudden cardiac arrest

SCA/D is an abrupt halt in cardiac activity resulting in failure of cardiovascular hemodynamics often leading to death of the subject within a few hours of the appearance of the first symptom[33].Electrical imbalance in the cardiac tissue affects the cardiac systolic function which disturbs the perfusion to the body tissues. Thus, electrical imbalance in the cardiac tissue is the primary cause of SCA/D[34]. In the majority of cases, the basic cause of electrical disturbances in SCA/D is Ventricular fibrillation(~84% cases) which may be due to acute coronary ischemia. Ventricular tachycardia may also induce SCA/D, especially in patients having either cardiac structural diseases or channelopathies [35-39]. Elevated levels of reactive oxygen species due to oxidative stress and impaired metabolism in myocytes can result in electrolyte imbalance leading to ventricular tachyarrhythmias and eventually SCA/D[40].

In a substantial frequency of incidence, the exact cause of SCA/D remains undetected[41, 42]. Nevertheless, epidemiological estimates suggest that in subjects of age >35 years, coronary artery disease is the primary cause (~80% cases) of SCA/D while congenital cardiac abnormality is causative in the younger population group[43-46]. Genetic channelopathies and cardiomyopathy are significant causative factors for inducing SCA/D[47, 48]. Figure 1 gives a diagrammatic insight into the major causes of SCA/D in the young population. There is a heightened risk forthe likelihood of incidence of

SCA/D a month post-myocardial infarction. The risk tapers off after the first month, however. While subjects with ventricular remodelling and heart failure possess a significantly amplified threat of developing SCA/D[49-51].

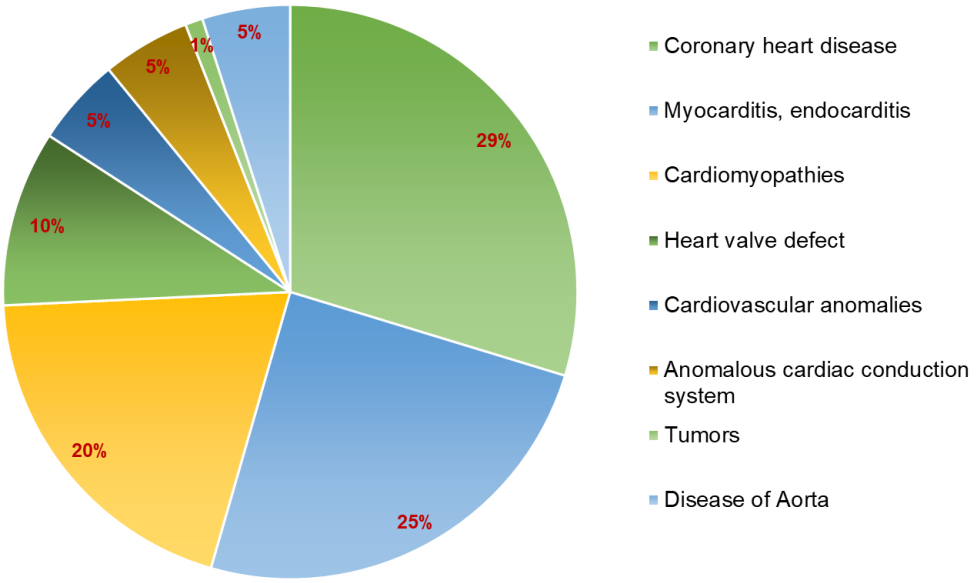

Figure 1: Major causes of SCA/D in the young population (based on data presented in [42, 52])

4. Causative factors for Sudden cardiac arrest

Regardless of age, gender, or race, the causative factors for SCA/D can be classified into two broad categories (Figure 2)[42, 53]-

- **Cardiac or coronary causes**- These include arteriosclerosis, coronary heart disease, coronary aneurysm, embolism, myocardial infarction, arteritis, dissection of arteries and deformity of the coronary arteries.
- **Non-cardiac or non-coronary causes**- These include cardiomyopathy, cardiac hypertrophy, malfunctioning heart valves, dilatative arrhythmogenic right ventricle, alcohol, viral carditis, bacterial carditis, hypertonic heart disease, irregularities in the cardiac electric conduction system and tumors.

It is difficult to diagnose cardiac/coronary causes due to the lack of identification of morphological alterations while non-cardiac/coronary factors may induce morphological alterations[42].

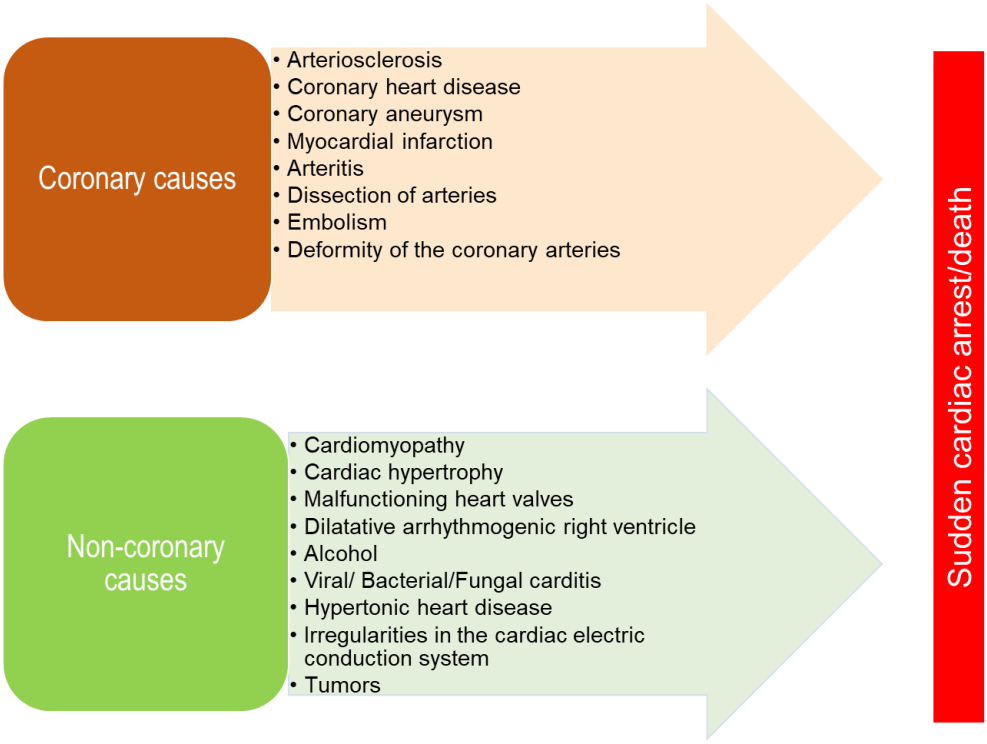

Figure 2: Coronary and Non-coronary causes of induction of SCA/D

5. Cardiac or coronary causes of sudden cardiac arrest

5.1 Interrelationship between coronary heart disease and sudden cardiac arrest

Coronary heart disease is the foremost cause of the occurrence of SCA/D in subjects aged> 35years and is the second biggest contributor to SCA/D in subjects aged<35 years[1, 54]. The findings of the autopsy reveal that atherosclerotic coronary disease is the underlying chief cause ofSCA/D in subjects aged>35 years while in subjects with age < 35 years, primary arrhythmias have been found to be the primary cause for the unexplained SCA/D[55]. In a separate comparative study, findings of the autopsy indicate that patients with coronary heart disease, aged< 36 years, exhibit a higher incidence of cardiac manifestation associated with coronary heart disease beforethe incidence of SCA/D. While subjects aged 36-49 years exhibit coronary artery blockade in association with coronary heart disease leading to the incidence of SCA/D[54].

5.2 Unexplained sudden cardiac arrest

Autopsy findings of a study show that almost 40% of the cases of SCA/D in subjects, with age <35 years, have unexplained causes as cardiac morphology was found to be normal in autopsy. Genetic analysis suggests that cardiac gene mutation might be causative for SCA/D in 27% of cases[56]. Similar findings were reported in another study carried out in the United States of America wherein 41.3% of the cases of SCA/D with age < 35 years were found to have unexplained causes.The causes for SCA/D in such cases were reported to be short QT syndrome, Wolff-Parkinson-White, Long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia [55].

5.3 Congenital structural cardiac disease

Subjects born with inherited cardiac disease are at higher risk for contracting SCA/D (~15 to 25%) as compared to normal subjects. This is due to additional risk associated with hypertrophy, fibrosis and scarring in subjects having congenital cardiac disease[42, 57, 58]. However, due to multiple subtypes of congenital cardiac disease, it is difficult to identify an exact estimate of the associated risk. Also, the risk associated with congenital cardiac disease is comparatively lower as compared to the risk associated with ischemic and dilated cardiomyopathy[42, 59].

5.4 Acquired as well as genetic cardiomyopathy

Sudden cardiac deaths in young subjects are usually associated with channelopathies, cardiomyopathies and arrhythmia disorder. Of these incidences, almost 15-30% of the cases were found to be associated with dilated, hypertrophic cardiomyopathy and right ventricular arrhythmia[1]. Similar findings were reported in a study carried out in the Australian continent wherein 16% of cases of SCA/D were found to be associated with congenital cardiomyopathy [56]. In another epidemiological study, 12% of infants and children suffering unexplained SCA/D were found to be due to hypertrophic cardiomyopathy while in 14% of cases, other subsets of cardiomyopathy were found to be the cause of SCA/D[60]. Various subsets of cardiomyopathy are associated with genetic mutations. Thus, it is important to evaluate the family history of young subjects for the incidence of SCA/D[1].

5.5 Sudden cardiac arrest associated with myocarditis

Inflammation of the myocardium which may be induced by bacteria, viruses or fungi is referred to as myocarditis[61]. Almost 15% of the incidence of SCA/D with non-cardiac reasons have been attributed to infections caused by microbes. Infections induce local damage to the cardiac tissues along with pulmonary dysfunctioning results in electrolyte and fluid imbalance, pulmonary thromboembolism, myocarditis and hypoxemia, all of which cause myocyte damage and eventually result in SCA/D[62]. Infections by microbes like, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Chlamydia pneumophila*, *Streptococcus pneumoniae* are known to cause fatal myocarditis [63, 64]. In recent times, coronavirus disease-19 has also been reported to cause SCA/D in patients with SARS-CoV-2 infection [38, 65, 66]. In one of the cases, a patient of myxedema coma contracted SARS-CoV2 infection which led to cardiac arrhythmia, pneumonia and pulmonary embolism, thereby inducing SCA/D[67]. Other viruses like, coxsackie virus, parvovirus B19, influenza virus, adenovirus and herpes simplex virus can cause cardiac complications like myocarditis [68]. Patients with meningitis are also at heightened risk for developing SCA/D. One of the studies reports that 50% of the cases of meningitis, having an age of less than 1 year and more than 60 years, develop SCA/D[62].

6. Non-cardiac or non-coronary causes of sudden cardiac arrest

6.1 SCA/D associated with adverse effects of drugs

Drug usage (like, alcohol, amphetamine, cocaine, etc), legal as well as illegal, can induce SCA/D as a drug-associated adverse event[57, 69, 70]. Many drugs that induce sympathomimetic receptors can elevate the risk of SCA/D, especially in subjects having pre-existing ion channel defects like Long QT syndrome[71]. Such sympathomimetics like cocaine, can instigate coronary arterial spasm, hypertension, myocardial ischemia, or even arteriosclerosis, which can eventually induce cardiomyopathy, cardiac arrhythmia, or even myocardial infarction[72, 73]. Consumption of such drugs can induce tachycardia

and hypertension [42].Usage of alcohol can induce alcohol-associated dilated cardiomyopathy [70]. Additionally, chronic usage of alcohol can also induce impairment in the liver and pancreas, which may further exacerbate the cardiomyopathy[74]. Various neuroleptics, diuretics, and anticonvulsants can induce myocarditis. Clozapine-induced myocarditis and cardiomyopathy is an established risk factors for SCA/D/disease [75]. Overdosage of certain drugs can induce cardiac arrhythmias. One of the classical examples of this is the usage of digoxin /digitoxin in geriatric subjects with renal insufficiency can induce bradycardic cardiac arrhythmias [76]. A study carried out in Denmark reported that a 6% incidence of SCA/D was found to have been induced due to myocarditis [61].Comparable results were reported in a study wherein a 7% incidence of SCA/D in subjects of age <35 years was induced by myocarditis[56]. US Food and Drug Administration issued a warning letter for the usage of azithromycin in patients having electrolyte imbalance, QT interval prolongation, reduced blood glucose levels, and are on therapy antiarrhythmics, as a potential risk factor for SCA/D[77].

6.2 Sudden cardiac death in athletes

In athletes, with age < 35 years, 1.3 -6.5/100,000 subjects developed SCA/D due to extensive physical activity [56, 78, 79]. This data varies in different countries, like, in the United States of America, 0.5/100,000 (in the age group of 12-24 years) and in Italy, 3.6/100,000 (in the age group 14-35 years)[80, 81]. The relative risk for SCA/D in young athletes is higher than in young non-athletes (~1.95 for males and ~2.00 for females)[82]. However, such subjects were found to have pre-existing cardiac conditions like arrhythmogenic right ventricular cardiomyopathy, premature coronary artery disease, and congenital coronary artery anomaly[82]. Amongst different sporting activities, football and basketball have aelevated risk of developing SCA/D[83-85]. Study findings show that young athletes (<30 years) with SCA/D were found to have anomalous coronary artery disease and cardiomyopathy in 50% of the cases [86]. While, in athletes with age>30 years, coronary artery disease is the impetus behind the incidence of SCA/D[78]. Additionally, the usage of banned drugs like anabolic steroids, also seems to play a role in inducing SCA/D in athletes[87, 88].

6.3 Lifestyle-associated and other causes of sudden cardiac arrest

One of the primary risk element for myocardial infarction and SCA/D is stress, physical as well as psychological[89-91]. Physical activity, misuse of drugs, and use of alcohol are some of the physical causes of stress while financial loss, death of near and dear ones, accidents, and chronic illness are some of the causes of psychological stress[92]. Stress has been found to be an inducer of cardiomyopathy, which is referred to as ‘broken heart syndrome’ or, ‘Takotsubo cardiomyopathy’ [93-95]. The broken heart cardiomyopathy is manifested as analogous to myocardial infarction with changes in ECG pattern, altered cardiac enzymatic profile and transient dysfunctional ventricular function. Although major histological alterations are not observed in this form of cardiomyopathy, necrosis of macrophages and contraction bands along with infiltration of monocytes occurs. The necrotic contraction band is considered to be the causative inducer of cardio-[96-98]adrenergic stress. It is important to note that ‘Takotsubo cardiomyopathy’ is majorly seen in menopausal women[99].

A healthy lifestyle exerts a significant effect on the cardiac health. A study shows that regular intake of fruits and vegetables in the diet, reduced consumption of red meat and alcohol, adequate exercise and sleep significantly decrease the chances of SCA/D[100]. Retrospective metanalysis establishes smoking and tobacco as a significant risk factor for cardiac complications including SCA/D. As per the estimate,

the relative risk for active smokers is 3.06 and 1.38 for subjects who gave up smoking, as against complete non-smokers [101].

Subjects having renal diseases are highly susceptible to cardiac complications including SCA/D. Renal dysfunctionality induces arrhythmic disturbances i.e., bradyarrhythmia and ventricular tachyarrhythmias. These arrhythmic disturbances are a significant causative factor for SCA/D[102]. With the advancement in the stage of renal disease, the associated risk for SCA/D also increases exponentially. As per an estimate, almost 60% of the subjects undergoing dialysis develop SCA/D[103].

7. Preventive tools for sudden cardiac arrest

SCA/D especially in the young population, is a global concern and preventive steps can help to save lives. Thus, it is essential to develop suitable and reliable screening tools. One such potential tool can be establishing suitable biomarkers. There are three classes of screening tools that are being explored extensively as screening and preventive tools for cardiac arrest viz., Electrocardiogram (ECG), Imaging, and Serum biomarkers. C-reactive protein, cardiac troponin I, B-type natriuretic peptide, low-density lipoprotein cholesterol, glucose levels, and fibrinogen are being actively explored for their effective clinical application as screening tools for cardiac complications[9, 104-106].

8. Conclusion

An increase in the occurrence of SCA/D in the young population is a cause of global concern. Conventionally, the occurrence of SCA/D increases with the increase in age. Though, recent reports suggest an increase in the incidence of SCA/D in young subjects. Coronary heart disease is the foremost cause for the induction of SCA/D in aged subjects. However, in young populations genetically inherited cardiac arrhythmias, cardiomyopathy and other cardiac abnormalities, like defects in the valve, are the primary cause of cardiac arrest. Additionally, myocarditis, which can be the outcome of bacterial or viral or fungal infection, irrational drug usage and unhealthy lifestyle are significant contributors to the induction of SCA/D in the young population. However, the absence of any structural cardiac abnormalities in young subjects makes it difficult to ascertain the definite cause of SCA/D. The unavailability of suitable screening tools makes it difficult to predict and screen the subjects for the development of SCA/D. Also, there is the absence of standardised parameters to establish the risk factor for SCA/D. Thus, future work needs to be directed to develop reliable screening tools and standardized parameters to establish risk factors for SCA/D.

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