Pre-Hospital Delay in the Diagnosis of Acute Cardiovascular Events: What Do We Know?

Sameed Ahmed M. Khatana, MD MPH

Assistant Professor of Medicine

Division of Cardiovascular Medicine, Department of Medicine

Perelman School of Medicine, University of Pennsylvania

1: Incidence and clinical course of different types of acute cardiovascular events

Cardiovascular diseases are the leading cause of death in the US and are responsible for more deaths each year than all forms of cancer and chronic lower respiratory diseases combined. A study using nationally representative National Health and Nutrition Examination Survey (NHANES) data from 2015 to 2018 estimated that 9.3% of all American adults (26.1 million individuals in 2018) experienced some form of cardiovascular disease (coronary heart disease, stroke, and heart failure).(1) In 2018 more than 30% of all deaths among adults 20 years of age and older were related to cardiovascular diseases.(1) Of these, approximately 42.1% were attributable to coronary heart disease, 17.0% to stroke, 11.0% to high blood pressure, 9.6% to heart failure, 2.9% to peripheral arterial disease, and 17.4% to other cardiovascular diseases. As of 2019, cardiovascular diseases are the leading cause of years of life lost in the US, with 14.7 million (95% CI 13.8 million to 15.3 million) years lost.(2) In addition to the high levels of mortality attributable to cardiovascular disease, in 2019, 2.4 million (95% CI 1.8 million to 3.0 million) years were lived with disability among American adults due to cardiovascular disease.(2) Many of the acute manifestations of cardiovascular disease, such as acute myocardial infarction (AMI), acute stroke, and acute aortic syndromes, not only lead to morbidity and

mortality, but also require urgent intervention. Delays in diagnosis and treatment for such conditions are therefore potentially associated with worse health outcomes.

Acute myocardial infraction:

Approximately every 40 seconds, an American adult will experience an AMI.(3) The estimated annual incidence of AMI in the US is 605,000 new events and 200,000 recurrent events. Of these, 170,000 events are silent, and do not present with typical acute symptoms. The average age at first AMI is 65.6 years for males and 72.0 years for females. The incidence of AMI varies by race and gender, with men and Black adults having a higher incidence of AMI according to one analysis of data from the ARIC registry.(1) In another analysis of AMI hospitalizations in one large health system from 2000 to 2014, hospitalization rates due to AMI were highest among White adults, followed by Black, Hispanic, and Asian/Pacific Islander adults.(4)

AMI can be classified as ST-segment elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA) based on symptoms, measurements of biomarkers, and electrocardiographic (ECG) abnormalities and typically represent progressively greater severity of disease. The proportion of individuals presenting with STEMI ranges from approximately 30% to 40% depending on the database analyzed.(5) Data from the Framingham Study from 1997 to 2005 demonstrated in-hospital case fatality rates of approximately 10% for patients presenting with either STEMI or NSTEMI.(6) One-year mortality rates were approximately 12% in patients presenting with STEMI and 25% in those presenting with NSTEMI. A meta-analysis of patients enrolled in 14 clinical trials noted a 1-year mortality rate of approximately 5% in patients presenting with NSTEMI.(7) Another study of Medicare beneficiaries noted a 10-year mortality rate of 72.7% for patients presenting with

AMI.(8) Among non-elderly adults (<65 years old), between 1999 and 2019, the overall age-adjusted AMI mortality rate was 13.4 (95% CI, 13.3–13.5) per 100,000.(9) Middle-aged adults, men, non-Hispanic Black adults, and individuals living in rural counties had higher mortality rates, in this analysis, compared to younger adults, women, non-Hispanic White adults, and individuals in urban counties, respectively. Beyond mortality, more than 20% of individuals experienced angina 1-year post-MI.(10) In the HORIZONS AMI trial, the risk of reinfarction or stroke at three years was approximately 6-7% and 1.5-2%, respectively.(11)

The primary therapeutic intervention for AMI is to restore blood flow to the affected myocardium. This is particularly important in patients presenting with STEMI which typically represents a complete, or near-complete, occlusion of blood flow in a coronary artery. Minimizing the time to treatment for a patient experiencing an AMI is crucial. Data suggest that up to half of patients with AMI experience sudden death prior to ED arrival.(12) Additionally, the degree of myocardial damage is related to length of the ischemic episode.(13) Therefore, there is a rapid diminishing benefit to reperfusion during an AMI. Restoring flow to the affected artery within 30 minutes can abort an infarction. If reperfusion occurs within 2–3 hours some preservation of myocardial function is achieved but after 6 hours there is often little or no salvage of myocardium.(14) Studies have indicated the benefit of limiting the delay between symptom onset to reperfusion when fibrinolytics and percutaneous transluminal coronary angioplasty are used.(13, 15-17) Additionally, many studies have demonstrated an association of health outcomes with the time interval between a patient's arrival to the hospital and reperfusion with the use of percutaneous coronary intervention (door-to-balloon time), with patients experiencing a door-to-balloon time ≤90 minutes having significantly better health outcomes post-MI.(18-20) Among patients presenting with NSTEMI, early risk stratification and

identification of individuals those patients at highest risk for further cardiac events who may benefit from a more aggressive therapeutic approach is also essential. Among such high risk patients an early invasive approach (ie, typically within 24 hours) is associated with improved health outcomes.(21)

Acute stroke:

Each year, approximately 800,000 people experience a new or recurrent stroke. Approximately 600,000 of these are first attacks, and 185,000 are recurrent attacks.(3) Of all strokes, 87% are ischemic, 10% are intracranial hemorrhages, and 3% are subarachnoid hemorrhages. As of 2018, an estimated 7.6 million American adults self-reported having had a stroke with an overall stroke prevalence of 2.7%. In a nationwide survey of US adults, the estimated prevalence of self-reported physician-diagnosed transient ischemic attack (TIA) increased with age and was 2.3% overall. (22) However, the prevalence of stroke TIA may be even higher, with one study reporting occurrence of self-reported stroke like symptoms in 17.8% of adults 45 years of age and older.(23) Stroke symptoms were more likely among Black than White individuals, among those with lower income and lower educational attainment, and among those with fair to poor perceived health status. A higher incidence of ischemic and hemorrhagic stroke has been noted among Mexican American compared to non-Hispanic White adults.(24, 25) In the national REGARDS cohort, in 27,744 participants followed up for 4.4 years (2003–2007), the Black participants had a significantly higher incidence of stroke compared to White participants.(26)

In 2019, on average every 3 and a half minutes, someone in the US died of a stroke and approximately 1 out of every 19 deaths in the US was attributable to stroke. When considered separately from other CVDs, stroke ranks fifth among all causes of death. In 2019 the number of

deaths with stroke as an underlying cause was approximately 150,000, with an age-adjusted death rate for stroke as an underlying cause of death of 37.0 per 100,000. The age-adjusted rate for any mention of stroke as a cause of death was 63.1 per 100, 000. Approximately 64% of all stroke deaths occurred outside of an acute care hospital. More women than men die of stroke each year because of the higher prevalence of elderly women compared with men, with women accounting for 57.1% of US stroke deaths in 2019. Stroke is also a leading cause of serious long-term disability in the US. Approximately 3% of males and 2% of females reported that they were disabled because of stroke.(27)

The goal of intervention in acute ischemic stroke is to restore perfusion to the affected area of the brain as soon as possible. The immediate goal of reperfusion therapy for acute ischemic stroke is to restore blood flow to the regions of brain that are ischemic but not yet infarcted. The long-term goal is to improve outcomes by reducing stroke-related disability and mortality. Therefore, any delay in diagnosis and eventual potential intervention is associated with worse morbidity and mortality. Options for reperfusion therapy that are proven effective include intravenous thrombolysis and mechanical thrombectomy. In individuals who qualify for intravenous thrombolysis, several studies have demonstrated the importance of initiating treatment within 4.5 hours of defined symptom onset. The benefit of intravenous thrombolysis for acute ischemic stroke decreases continuously over time from symptom onset.(28-31) A registry based study of over 58,000 patients noted that each 15-minute reduction in the time to treatment initiation was associated with lower rates of morbidity and mortality.(32) Mechanical thrombectomy is indicated for patients with acute ischemic stroke due to a large artery occlusion in the anterior circulation who meet eligibility criteria and can be treated within 24 hours of the time last known to be well. This therefore also requires minimal delay in recognition of stroke to

arrange for transfer to the appropriate center. Even very minor delays between symptom onset and initiation of stroke treatment are associated with a significant loss of disability-fee life.(33) Management of intracerebral hemorrhage and subarachnoid hemorrhage also requires rapid recognition and determination of severity to triage patients to the appropriate level of care and determine the need for surgical management and the initiation of blood pressure control, ideally within the first hour of presentation.(34)

Acute aortic syndromes:

Acute aortic syndromes encompass acute aortic dissection and other acute presentation such as aortic intramural hematoma, penetrating aortic ulcer, and periaortic hematoma. Acute aortic dissection is defined as a separation of the layers of the aortic wall due to an intimal tear and comprises the majority of acute aortic syndromes. Aortic dissections are typically classified as type A dissections which involve the ascending aorta and comprise about two-thirds of cases or type B dissections involving the descending aorta.(35) Type A aortic dissection constitutes a medical emergency, is associated with the highest initial mortality, and is usually fatal if undiagnosed.(36) Despite immediate surgical repair, type A aortic dissection harbors a 20% to 50% in-hospital mortality rate.(35) Type B aortic dissection is typically treated medically, but can also result in significant morbidity and mortality with an in-hospital mortality rate of approximately 12%.(37)

High-risk conditions commonly associated with aortic dissection include hypertension, connective tissues disorders (e.g. Marfan syndrome, Ehlers-Danlos syndrome), preexisting aortic aneurysm, bicuspid aortic valve, and family history of aortic disease. Estimating the prevalence of thoracic aortic aneurysm is difficult due to the asymptomatic nature of the disease and scarcity of screening in the general population. The prevalence of thoracic aortic aneurysm >5 cm

incidentally identified by community-based screening chest CT was estimated to be between 0.16% and 0.34% from studies performed between 1995 and 2003 in Japan and Germany.(38, 39) The annual incidence of thoracic aortic aneurysm is estimated to be 5.6 to 10.4 cases per 100,000 patient years.(40, 41) The annual incidence of acute aortic dissection in the general population is estimated to be around 2.5 to 3.5 per 100,000 person-years.(42, 43) In a review of 4,428 patients from the International Registry of Acute Aortic Dissection, 66% were male and the mean age was 63 years.(44) Females presenting with aortic dissection are generally older than males and have a more delayed presentation.(44, 45)

Given the high risk of morbidity and mortality, particularly with type A aortic dissection, urgent diagnosis, and transfer to a center able to manage such patients is crucial. Delays in diagnosis therefore can lead to significant morbidity and mortality. Greater delay in treatment for acute aortic dissection is associated with higher mortality.(46) Most patients with acute type A aortic dissection are managed using open surgical techniques with a limited role for endovascular repair depending upon the extent of the dissection. Additionally, patients require intense monitoring and management of blood pressure and heart rate. The risk of mortality due to aortic dissection increases at a rate of 1-2% per hour from symptom onset based on studies of untreated individuals.(47-49)

2: <u>Extent, causes and context for delays</u>

Understanding and documenting the extent, nature, and cause of pre-hospital delays in diagnosis is challenging due to the lack of centralized, representative, datasets in the US that capture patient behaviors and experiences prior to their interface with healthcare. As understanding pre-diagnostic delays relies on patient recall, or observation, of onset of

symptoms, this is subject to various biases. Nevertheless, there is substantial evidence of delays in various stages of the process between symptom onset and diagnosis of an acute cardiovascular event.

Delays can occur at many points in the interval between the onset of symptoms and diagnosis and eventual intervention. There may be delays:

- From symptom onset to realization that something may be wrong
- From realization of something being wrong to decision to seek medical attention
- From decision to seek medical attention to being able to contact appropriate provider or service
- From contacting appropriate provider or service to either arrival of emergency medical services (EMS) to patient or of patient arrival to emergency department/hospital/clinic
- Delays in processing
- Delays in diagnosis by medical provider

All acute conditions likely have some component of delay in each of the previous categories with certain delays more related to patient behavior and others to aspects of the healthcare system.

Acute myocardial infarction:

In one study of 104,622 patients with NSTEMI in the US between 2001 and 2006, the median delay time from symptom onset to hospital presentation was 2.6 hours with 25% of patients having more than a 6 hour delay.(50) The study also noted significantly greater in-patient mortality for individuals experiencing greater amount of delay. The geometric mean for delay between symptom onset and hospital presentation for 482,327 patients presenting with STEMI between 1995 and 2004 was 114 minutes.(51) Longer delay times were noted among

older adults (>60 years of age), women, Black, and Hispanic adults, as well as patients who were uninsured or on government funded health insurance (Medicare or Medicaid). Two other studies noted significantly greater delay from symptom onset to hospital presentation for Hispanic compared to non-Hispanic White patients presenting with STEMI and between Black compared to White patients presenting with AMI.(52, 53)

The interval between symptom onset to hospital presentation is likely the largest source of delay between symptom onset and eventual treatment in patients presenting with AMI. In one study of 188 patients presenting with STEMI presenting to hospital in Montreal, Quebec in 2002 the median symptom onset to treatment time was 200 minutes (IQR 134 to 436).(54) Of this delay, the median symptom onset to hospital arrival time was 120 minutes (IQR 60 to 290) and the median hospital arrival to treatment time was 93 minutes (IQR 54 to 155).

Acute stroke:

The delay from symptom onset to hospital presentation for patients with acute stroke varies between a median of 1.5 to 16 hours and between a mean of 4.5 to 27.5 hours.(55) In one study of 553 patients presenting with acute stroke symptoms to the emergency department, more than half presented with a delay of 3 hours or more and 39% with a delay of 6 hours or more since onset of symptoms.(56) Younger patients, men, Black patients, and patients not transported by ambulance were more likely to have a delayed presentation.

Acute aortic dissection:

The extent of pre-diagnosis delay in acute aortic syndrome is largely unknown. One study of 894 patients noted a median time from presentation to the emergency department/hospital to diagnosis of 4.5 hours (IQR 1.6 to 28.1).(57) Another study of 92 patients presenting with type A

aortic dissection noted that residents of more economically distressed areas have a greater delay in diagnosis.(58)

- **Delays in recognition of symptoms/decision to seek medical care**

For acute cardiovascular conditions, one major source of delay is the interval between symptom onset and recognition that symptoms may be due to a serious medical condition and eventual decision to seek medical care. This is likely due to several reasons including the sometimes stuttering or intermittent nature of symptoms at onset. In both patients with AMI and acute stroke, the intensity, nature, and duration of symptoms are all associated with the decision to seek medical care. Although most individuals may associate a heart attack with crushing chest pain based on representations in media, patients may not recognize symptoms to be due to an AMI if symptoms do not fit their expectations. One study of 88 patients admitted with their first AMI in the UK noted that although the most common expected symptom of an MI was central chest pain with radiation down the arm, the most common symptom actually experienced by patients was diaphoresis and subjective fever followed by chest pain.(59) A mismatch between expected and experienced symptoms was associated with a significant delay in presentation with patients not experiencing chest pain reporting a mean delay of 11.5 hours (SD=20.2) between symptoms onset and presentation. Other studies have noted that approximately one-third of patients with AMI had atypical manifestations or no chest pain, with a greater prevalence among women, older patients, and patients who were other than non-Hispanic White.(60, 61) Patients with chronic medical conditions as well as those with atypical presentations of AMI, may also be more likely to attribute their symptoms to a non-cardiac source and therefore delay their recognition of the symptoms as being from an AMI.(62)

This delay between onset of symptoms and recognition of these symptoms as being attributable to a serious cardiovascular condition has also been noted in patients experiencing acute stroke symptoms. In one study of 366 patients presenting with acute ischemic stroke in Switzerland, 62% of patients were not aware that their initial symptoms were due to stroke.(63) These patients were more likely to initially contact and visit an outpatient primary care provider and were more likely to present to the hospital with a >4.5 hour delay. Having a personal history of stroke in the past or a family member with history of stroke is associated with shorter pre-hospital delay suggestive that individuals with a prior knowledge of stroke are more likely to recognize its onset.(64)

The awareness of the general public in the US of all symptoms of a heart attack and the need to call for EMS was only 11% as of 2001.(65) An analysis of National Health Interview Survey data for 2008, 2014, and 2017 however noted that knowledge of five common signs and symptoms of a heart attack increased from 40% to 50% and the proportion who knew to call for EMS increased from 92% to 95%.(66) However, as of 2017, knowledge of the five heart attack symptoms was lower among men, younger age groups, racial/ethnic minorities (especially non-Hispanic Asians and Hispanics), and persons with lower levels of educational attainment. Similarly, as of 2014, around 35% of individuals from the general public in the US did not have knowledge of all stroke symptoms, time importance of calling EMS, and other recommended knowledge.(67) However, awareness of symptoms did increase by approximately 15 percentage points from 2009 to 2014. Knowledge of all stroke symptoms and the importance of contacting EMS was significantly lower among men compared to women, among racial and ethnic minorities, and individuals with lower educational attainment.(68)

Once individuals attribute their symptoms to an acute cardiovascular condition, possible delays may also occur in the decision to seek medical care. Additionally, patients may choose to contact friends and family or a family physician rather than EMS. Patients, even after attributing their symptoms to an acute medical issue, may delay seeking care for various reasons. Individuals who may experience embarrassment related to the perception of lack of seriousness and susceptibility to AMI typically delay seeking care.(69-71) Similarly, concern for troubling family members and significant others was also associated with prehospital delay in patients with AMI.(69, 71, 72) The role of social networks however can be complicated. Although some studies have noted that the sooner a family member or a coworker was informed about symptoms in patients experiencing an AMI, the faster the decision was made to seek professional help with contacting EMS often associated with advice from a family member or friend.(62, 73) However, other studies have suggested that individuals having an AMI while around coworkers or nonrelatives are less likely to experience a delay than those with family members or spouses at the time of their event.(74) Another study of 175 individuals presenting with stroke that small and close-knit personal networks of highly familiar contacts were associated with a greater delay.(75)

- **Delays in transportation to hospital**

Once an individual recognizes that their symptoms may be due to serious medical condition and decide to seek medical attention, there may be delays in finally reaching the hospital. Many patients choose to contact a primary care provider first, rather than EMS. In one study of patients with acute ischemic stroke, approximately 1 in 3 patients contacted a family physician first.(63) However, the decision to call or visit a primary care provider first is also associated with greater delays in patients with AMI or acute stroke.(73, 76) Contacting EMS

immediately is associated with a significantly lower rate of prehospital delay in patients AMI.(73, 77) Similarly, patients with acute stroke presenting via ambulance are more likely to receive the correct diagnosis prior to hospital arrival and are more likely to arrive at the hospital sooner.(56, 78) Patients are typically more likely to consider using an ambulance if symptoms seem more severe to them.(79)

As EMS providers not only provide rapid transportation but can diagnosis, triage, and sometimes treat acute cardiovascular conditions, their involvement can be crucial. In patients with AMI, the use of prehospital ECG can play an important role in determining whether a STEMI is occurring and therefore the necessity to triage to a health center with the ability to perform percutaneous coronary intervention for revascularization. Several studies have demonstrated the association between prehospital ECG and reduced door-to-balloon time and is recommended in guidelines by the American Heart Association.(80-83) In addition to diagnosis, prehospital treatment with medications such as aspirin and nitroglycerin is also typically done. Additionally, some studies have also examined the use of intravenous anticoagulation in the prehospital setting for individuals diagnosed with STEMI and found an increase in favorable outcomes.(84, 85) Prehospital diagnosis of the severity of stroke is also important, particularly in identifying individuals who may potentially benefit from interventions such as mechanical thrombectomy. While there is significant variation in the performance of prehospital stroke scales, there is some evidence demonstrating the feasibility in identifying such patients using certain scales.(86)

One potential area of delay is related to the dispatching of an ambulance and EMS crew with the appropriate level of medical capabilities. An EMS dispatcher, upon being called, may dispatch a basic life support (BLS) or advanced life support (ALS) ambulance. ALS ambulances

are typically dispatched for individuals experiencing acute cardiovascular events like AMI or stroke. ALS ambulance crews consist of paramedics in addition to emergency medical technicians and are equipped with airway and cardiac monitoring equipment and are able to provide basic treatments including use of intravenous medications and fluids. However, whether the use of ALS, rather than BLS, ambulances is associated with better outcomes for patients with acute cardiovascular events is not completely clear. One study of Medicare beneficiaries suggested that some outcomes after AMI for patients initially transported by ALS ambulance may be better than those transported via BLS ambulance.(87) However survival after stroke was higher among those transported by BLS ambulance. Although ALS ambulance crews are able to provide more intensive care in the prehospital setting, there is also evidence that this may delay arrival to a hospital setting where more definitive clinical management can be done. In one study from Ontario, Canada, the median time to arrival for patients experiencing cardiac arrest was 13 minutes for patients transported by BLS ambulance but 27 minutes for patients transported by ALS ambulance.(88)

The use of EMS in the setting of acute cardiovascular events, however, is not uniform across different demographic subgroups. In a cross-sectional study of 25,271 US adults, 4.5% participants responded that they would not call EMS in the setting of a perceived AMI.(89) Being older and the lack of health insurance had the strongest association with choosing not to call EMS. Another study noted that men were less likely to use an ambulance to get to the hospital in the setting of a possible MI.(90) There also differences in use of EMS in patients with acute stroke. One study of approximately 400,000 patients with stroke between 2011 and 2014 noted that Hispanic and Asian men and women had a lower odds of using EMS versus their white counterparts and Black women were less likely than white women to use EMS.(91)

Another factor that may influence prehospital delays is the physical distance to the nearest hospital, particularly one that is capable of definitively diagnosing and treating the acute cardiovascular condition. This is primarily an issue for individuals living in rural areas. In rural areas in the US, average travel time by car to the nearest hospital is 17 minutes compared to 10.4 minutes in urban areas.(92) One recent study noted a greater travel distance travelled to reach a stroke center for non-urban residents.(93) Additionally, due to the differences in the demographic profiles of rural and urban residents, this study also noted a greater distance to a stroke center in areas with a greater proportion of American Indian residents and individuals without health insurance.

- **Financial barriers/health insurance**

Financial barriers and access to health insurance play a major role at all stages of the prehospital delay process. Individuals without health insurance (around 11% of adults in 2020) are more likely to delay or forgo care due to financial costs.(94) Among people experiencing an AMI, those without health insurance and those who have financial concerns were more likely to delay presenting to the hospital.(95) There were prehospital delays of greater than 6 hours among 48.6% of uninsured patients and 44.6% of insured patients with financial concerns compared to 39.3% of insured patients without financial concerns. In a survey of 364 adults living in Chicago, individuals living in predominantly non-White neighborhoods, were more likely to state that they would not call 911 in the setting of a stroke due to concern for financial costs.(96) In a study from central Texas, among patients presenting with stroke, patients with Medicaid had a significantly higher odds of having a delayed presentation.(97) Uninsured patients had a non-significant trend towards delayed presentation.

- **Language barriers**

Individuals whose primary language is not English face many barriers accessing healthcare in the US, including in the setting of an acute cardiovascular event. As of 2020, approximately 21.5% of Americans speak a language other than English at home. In one study of calls received by two large calls centers in Washington state, 911 calls where the caller had language barriers were associated with a longer time to EMS dispatch as well as a lower accuracy in determining the level of aid required.(98) Additionally, among Hispanic Americans, lack of English proficiency is associated with lower heart attack and stroke knowledge among.(99) Several studies have noted lower English proficiency as being a barrier to calling EMS, and some have noted that the use of interpreters may lower these barriers.(100-103)

- **Immigration status**

Immigration status may also play a related, but distinct role, in prehospital delays to English proficiency. As of 2020, there were 22.1 million noncitizens in the US, accounting for approximately 7% of the population, including lawfully present and undocumented immigrants.(104) Non-US citizens are significantly more likely to be uninsured with 26% of lawfully present immigrants and 42% of undocumented immigrants without health insurance (compared to 8% of US citizens). There is also evidence that US government policies in the recent past that created new barriers to achieving permanent resident status for those immigrants who accessed programs such as Medicaid was associated with reductions in Medicaid enrollment and healthcare utilization among immigrant patients.(105) One cross-sectional study of undocumented Latino immigrants presenting to the ED in California noted that 1 in 8 expressed fear of discovery and consequent deportation.(106) Another study of Spanish-speaking adults noted that exposure of an individual’s immigration status was a barrier for contacting EMS.(107)

Although studies of how immigration status impacts prehospital delay in the setting of an acute cardiovascular event are not as common, one study from Denmark noted that immigrants with acute ischemic stroke had a significantly greater prehospital delay and a lower rate of receiving reperfusion therapy.(108)

- **Racial discrimination/structural racism**

As noted above, many racial and ethnic minority patients experience worse delays, have lower access to the recommended treatments, and have worse health outcomes after an acute cardiovascular event compared to non-Hispanic White adults. Some of these disparities are related to racial discrimination and structural racism. Among adults living in Chicago, individuals living in predominantly non-White neighborhoods, when asked about stroke knowledge, were more likely to believe that physicians treated Black patients differently than White patients and had negative opinions about hospitals.(96) There is evidence of racial bias among EMS providers in non-cardiac care. In one study of EMS providers in Oregon, Black patients were less likely to receive pain medications than White patients and Black, Hispanic and Asian patients were less likely to receive pain medication from EMS for blunt traumatic injuries than White patients.(109) Another study of Medicare beneficiaries noted that EMS providers were more likely to transport Black and Hispanic patients to a safety-net hospital ED compared with White patients living in the same zip code.(110) Additionally, individuals who reported being treated or judged unfairly because of their race or ethnicity in a medical setting are more likely to delay care in the future.(111)

- **Interventions**

Most efforts around reducing time to diagnosis and then eventual treatment focus on the interval between a patient's arrival to the ED or hospital and eventual diagnosis. However, given

that most of the delay between symptom onset and eventual diagnosis occurs in the prehospital setting, there has been some interest in reducing sources of delay in the prehospital setting. As some of the delay in the prehospital setting occurs due to either the lack of recognition of the symptoms being possibly due to an acute cardiovascular event or not knowing that contacting EMS is necessary. To combat this, several awareness campaigns aimed at the general public have been undertaken. In Australia the Heart Foundation launched the Warning Signs of Heart Attack Strategy from 2009 to 2013.(112) This included social marketing campaigns to increase awareness of the risk of heart attack, improve knowledge of warning signs and symptoms, improve confidence to know what to do when experiencing the warning signs, and to make it more likely that people would call an ambulance as a first-line response. Awareness of this campaign was associated with a shorter prehospital delay time. Another study of an awareness campaign in France noted an increase in the proportion of individuals experiencing a STEMI contacting EMS after the campaign.(113) However, another study of a campaign in the US called "Make The Call, Don't Miss a Beat" that relied on TV advertisements was not associated with increased EMS use in women with symptoms of a possible heart attack.(114) Another study of an awareness campaign for stroke symptoms in France noted an increase in EMS calls for stroke suspicion in areas that were targeted by the campaign.(115) Another study of a peer-led, workshop-based, health behavior intervention to increase stroke preparedness among African Americans in Michigan noted an increase in stroke recognition and knowledge of appropriate stroke response after receiving the intervention.(116)

There also have been some interventions targeted at the delay that may occur related to transportation to the hospital by EMS. The importance of prehospital ECG and stroke scales has been noted above. However, once the diagnosis of an acute cardiovascular event is suspected,

transporting a patient to the appropriate type of hospital for a definitive diagnosis and intervention is crucial. Programs to improve coordination between EMS providers and hospitals aim to facilitate this process. In rural areas, where distance to hospitals is greater, this may be especially important. One such program is the Reperfusion of Acute Myocardial Infarction in Carolina Emergency Departments (RACE) project in North Carolina which currently involves coordination between EMS providers, hospitals, and health insurance companies in 6 regions of the state. In an analysis of this program involving 1164 patients with STEMI, the program was associated with lower median reperfusion times and lower time involved in transfer between hospitals.(117) Coordination between EMS providers and hospital staff for stroke patients is also crucial in reducing diagnosis and intervention delays. One study examined data from the North Carolina Stroke Care Collaborative from 2008 to 2009 which included 52 participating hospitals.(118) Prehospital notification of potential stroke by EMS was associated with a higher likelihood of receiving brain imaging and receiving a definitive diagnosis in a timely manner.

Another source of delay can be due to prolonged on-scene time by EMS providers due to factors such as obtaining an ECG and intravenous access. Implementation of an EMS training program that aimed to reduce prehospital delays for patients with stroke by increasing general time awareness and limiting the number of emergency on-scene procedures was associated with reduced on-scene times by EMS.(119)

3: <u>Important research questions to be answered to reduce pre-hospital delays</u>

- **Extent of delay**

One of the primary unanswered questions of prehospital delays is understanding its true extent. Since most US data sources, such as administrative claims data, are based on an

individual's interactions with the healthcare systems, understanding delays in the prehospital setting are challenging. Patients may have difficulty recalling exact time of onset, especially if symptoms are stuttering or intermittent in nature. Some studies have identified discrepancies in symptom onset times reported by patients and those recorded in health records for patients presenting with AMI.(120, 121) Additionally, it has been shown that reported symptom onset time varies when recorded near the time of onset compared to a later time.(122) Additionally, individuals who may have symptoms of an MI but choose never to go to the hospital are almost completely absent from any large healthcare database. Large community based surveys may identify such individuals, but it may be difficult to understand the extent of delays if individuals are queried days or months after the onset of symptoms.

Certain vulnerable populations such as homeless and undocumented individuals may be particularly vulnerable to prehospital delays given some of the issues discussed above. However, given their limited access or reluctance to contact the healthcare system, the gaps in knowledge regarding prehospital delays are likely to be even greater in such populations.

There is also evidence that the severity of symptoms is associated with lesser prehospital delay. However, the extent of prehospital delay in different MI types (STEMI vs. NSTEMI), coronary artery territory affected, or different cerebral territory affected is unclear.

- **Role of outpatient providers**

In the setting of acute cardiovascular events, contacting a primary care provider first is associated with prehospital delays. However, it is possible that outpatient providers may play a role in education for high risk individuals that could potentially lower prehospital delays. What role providers play in the decision making process is not clear.

- **Role of community health workers**

The role of community health workers (CHWs) in connecting historically marginalised populations with the healthcare system is increasingly being acknowledged. The role of CHWs in management of hypertension has been demonstrated in some previous studies.(123, 124) However, whether CHWs can play a role in reducing prehospital delays is unclear. CHWs could potentially play a role in educating individuals at a high risk for cardiovascular events about potential symptoms and what is needed in case of their occurrence. The specific model of CHW based interventions and outreach that would be most effective in different populations also needs to be evaluated.

- **Health insurance/financial concerns**

Several studies have noted greater prehospital delays in individuals without health insurance or those with financial concerns. However, whether expansion of health insurance coverage (e.g., Medicaid expansion through the Affordable Care Act) can lower prehospital delays has not been studied. Additionally, how different levels of cost sharing (e.g., for individuals with high-deductible health plans) can influence prehospital delays for individuals with health insurance is also not well studied.

Similarly, among lower socioeconomic status individuals, is receipt of certain types of public assistance (e.g., food assistance, housing assistance) associated with smaller delays?

- **Caregiving**

What role does caregiving play in pre-hospital delays? Individuals who are caregivers to others may be reluctant to present to the hospital. There is evidence that individuals, when experiencing symptoms, may be concerned about burdening family and friends, leading to

delays. Additionally, individuals who rely on caregiving by others may also experience a greater degree of delay.

- **Provider biases**

Disparities in prehospital delays based on race/ethnicity, age, and gender are very well documented. Additionally, studies have noted bias in the diagnosis and treatment of acute cardiovascular disease among women and racial and ethnic minorities once they arrive at the ED or hospital.(125-127) However, how much of the disparities in prehospital delay is due to bias at various points of contact with the health system is not well studied. As noted above, there is evidence of bias in non-cardiac care by EMS providers for individuals who are racial and ethnic minorities. Whether that is the case for acute cardiovascular disease and how much it contributes to disparities in prehospital delays is unclear. Additionally, if such biases do exist, it would be important to study whether interventions such as implicit biases training can mitigate them.

- **Emergency medical services**

Use of EMS, rather than self-transportation, is associated with shorter prehospital delays for patients experiencing acute cardiovascular events. However, longer on-scene times can lead delays.(128) Some studies have documented greater delays when an ALS (compared to BLS) ambulance is utilized due to greater on-scene treatment, event after adjusting for potential differences in disease severity. However, other measures such as prehospital ECG may be invaluable in lessening delays between symptom onset and eventual treatment time in patients experiencing a STEMI. How EMS providers can balance necessary on-scene diagnostic and treatment interventions, along with the need to lessen the time between symptom onset and reaching the appropriate medical setting for definitive diagnosis and treatment should be studied further. Additionally, how this is influenced by the density of EMS providers in an area,

availability of different transportation modalities, and other EMS provider level factors is unclear.

- **Metrics/measurement**

Much of STEMI quality improvement focuses on the door-to-balloon time, which is the time from a patient's arrival to the ED or hospital balloon is inflated in the occluded, culprit coronary artery. A similar metric in stroke care is door-to-needle time which is the time from patient arrival to initiation of intravenous tissue plasminogen activator. Other metrics include door-in to door-out for patients experiencing a STEMI, which is the time that a patient spends in one ED before being transferred to another hospital. However, all of these measures focus exclusively on the time a patient spends in the hospital/ED rather in the pre-hospital setting where the majority of the delay from symptom onset to treatment occurs. Some data sources such as the Get With The Guidelines (GWTG) registry (a hospital-based quality improvement initiative created by the American Heart Association and the American Stroke Association), does measure symptom onset to arrival and treatment times. However, the focus of most quality improvement initiatives remains on the hospital setting. By expanding such measures to the time EMS is initially contacted can allow a greater understanding of sources of delay for individuals who contact EMS. Such measurement may also encourage greater coordination between EMS and local hospitals.

- **Telemedicine**

The use of telemedicine by EMS providers when communicating with a hospital prior to arrival has been associated with better health outcomes in some studies of patients with AMI and has been noted to be feasible in patients experiencing acute stroke.(129-131) However, the role of telemedicine in other aspects of the prehospital delay process is unclear. Whether the use of

telemedicine as a way for patients to remotely communicate with EMS, ED providers, or other healthcare providers prior to arrival would lengthen or shorten delay times is unclear.

- **Wearable devices**

With the growing use of wearable devices that can track certain medical parameters such as rudimentary ECGs and oxygen saturation, whether such devices can alert the wearer to the presence of certain acute cardiovascular conditions like AMI could be a potential way to reduce prehospital delays.

- **The role of education/awareness efforts**

As noted above, several campaigns to raise the public's awareness and knowledge levels about symptoms of stroke and AMI, and the appropriate response have been conducted. These, however, typically involve using mass media campaigns whether on TV, social media, radio, or print media to reach audiences. However, given that there are significant variations in awareness or knowledge of symptoms as well as the response people may have after symptom onset among people of different demographic subgroups, whether more targeted campaigns that tailor messages to these different groups are more effective needs to be studied. Since social networks play a crucial role in the prehospital delay process, campaigns also try to raise awareness about what bystanders and friends or family should do if someone may be experiencing such an event. Whether campaigns conducted in partnership with social organization such as religious or charitable groups can improve prehospital delays is worth studying further.

Additionally, it is possible that the focus of education campaigns on typical presentations of acute events could worsen pre-hospital delays for people experiencing atypical symptoms. Previous studies have noted that individuals that having more typical symptoms of AMI (crushing chest pain) or certain symptoms of stroke (loss of consciousness or difficulty speaking)

have been associated with shorter pre-hospital delays in presentation.(132, 133) Therefore, individuals with atypical symptoms have longer delays and a potential focus on typical symptoms could prolong such delays.

- **COVID-19**

Fewer patients presented to US hospitals with acute cardiovascular events during the COVID-19 pandemic and there were greater pre-hospital delays.(134-136) What impact this had on non-COVID related cardiovascular morbidity and mortality is unclear and whether local COVID-19 policies impacted these trends is also unknown.

- **Other acute cardiovascular conditions**

Although the extent of prehospital delays in AMI and acute stroke has been studied previously, the nature and reasons for prehospital delays among individuals with other acute cardiovascular conditions such as acute aortic syndromes or acute pulmonary embolism is not well known.

4: <u>Approaches and data that could be used to answer</u>

- **Internet search data**

As with many other acute and chronic medical conditions, individuals experiencing possible acute cardiovascular conditions also turn to the internet to understand the nature and seriousness of their symptoms.(137-139) However, such search data could also be used to potentially identify, to a greater degree, the extent of delay between symptom onset and eventual diagnosis. Additionally, it is possible that targeted awareness campaigns on online platforms triggered by such searches may also play a role in reduced delays.

- **Wearable technology data**

The growing use of wearable technology devices such as smartwatches and smart glasses could provide additional sources of data for identifying individuals having AMI or stroke. This could be useful in understanding the extent of delays as well as potential warning sources for an individual or their family members about a potential acute cardiovascular event.

- **Cognitive, psychological, and behavioural barriers**

Many qualitative studies have aimed to understand the cognitive, psychological, and behavioral barriers between patients experiencing symptoms, recognizing that there is an issue, and deciding to seek healthcare. Individuals experiencing depression prior to the onset of symptoms of AMI have also been noted to have greater prehospital delay.(140) As much of the prehospital delay occurs before any medical service is contacted, exploring how these barriers interface with other known barriers such as discrimination, financial resources, and health insurance will require a qualitative approach to identify dominant themes. Additionally, much work needs to be done on whether any mental health approaches can lessen prehospital delays, particularly in vulnerable groups.

- **Use of health network data**

Once EMS is contacted, there are several sources of delay as detailed previously. To fully understand the process from EMS contact, dispatch, on-scene arrival, diagnosis, treatment and triage, transfer to initial health setting and possible transfer to another facility for definitive treatment requires data sources that encompass that entire process. Regional networks that include EMS providers, payers, and health systems exist in certain areas in the US, such as in North Carolina. Use of data from such networks may help more fully elucidate extent of delays, as well as specific points where delays are more likely to occur.

References:

1. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. Circulation. 2021 Feb 23;143(8):e254-e743.

2. 2019 Global Burden of Disease (GBD) study. [cited 2022 August 30]; Available from: https://vizhub.healthdata.org/gbd-results?params=gbd-api-2019-permalink/6985d856ddd6f21be3dcde426e187f38.

3. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation. 2022 Feb 22;145(8):e153-e639.

4. Chi GC, Kanter MH, Li BH, Qian L, Reading SR, Harrison TN, et al. Trends in Acute Myocardial Infarction by Race and Ethnicity. J Am Heart Assoc. 2020 Mar 3;9(5):e013542.

5. Kushner FG, Bates ER. Chapter 10 - ST-Segment Elevation Myocardial Infarction. In: Antman EM, Sabatine MS, editors. Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease (Fourth Edition). Philadelphia: W.B. Saunders; 2013. p. 178-213.

6. McManus DD, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg RJ. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. Am J Med. 2011 Jan;124(1):40-7.

7. Berg DD, Wiviott SD, Braunwald E, Guo J, Im K, Kashani A, et al. Modes and timing of death in 66 252 patients with non-ST-segment elevation acute coronary syndromes enrolled in 14 TIMI trials. Eur Heart J. 2018 Nov 7;39(42):3810-20.

8. Wang Y, Leifheit EC, Krumholz HM. Trends in 10-Year Outcomes Among Medicare Beneficiaries Who Survived an Acute Myocardial Infarction. JAMA Cardiol. 2022 Jun 1;7(6):613-22.

9. Dani SS, Lone AN, Javed Z, Khan MS, Zia Khan M, Kaluski E, et al. Trends in Premature Mortality From Acute Myocardial Infarction in the United States, 1999 to 2019. J Am Heart Assoc. 2022 Jan 4;11(1):e021682.

10. Maddox TM, Reid KJ, Spertus JA, Mittleman M, Krumholz HM, Parashar S, et al. Angina at 1 year after myocardial infarction: prevalence and associated findings. Arch Intern Med. 2008 Jun 23;168(12):1310-6.

11. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet. 2011 Jun 25;377(9784):2193-204.

12. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008 Jan 29;117(4):e25-146.

13. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet. 1996 Sep 21;348(9030):771-5.

14. Giugliano RP, Braunwald E, Group TS. Selecting the best reperfusion strategy in ST-elevation myocardial infarction: it's all a matter of time. Circulation. 2003 Dec 9;108(23):2828-30.

15. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet. 1994 Feb 5;343(8893):311-22.

16. Brodie BR, Stuckey TD, Wall TC, Kissling G, Hansen CJ, Muncy DB, et al. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol. 1998 Nov;32(5):1312-9.

17. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation. 2004 Mar 16;109(10):1223-5.

18. McNamara RL, Wang Y, Herrin J, Curtis JP, Bradley EH, Magid DJ, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2006 Jun 6;47(11):2180-6.

19. Lambert L, Brown K, Segal E, Brophy J, Rodes-Cabau J, Bogaty P. Association between timeliness of reperfusion therapy and clinical outcomes in ST-elevation myocardial infarction. JAMA. 2010 Jun 2;303(21):2148-55.

20. Brodie BR, Gersh BJ, Stuckey T, Witzenbichler B, Guagliumi G, Peruga JZ, et al. When is door-to-balloon time critical? Analysis from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trials. J Am Coll Cardiol. 2010 Jul 27;56(5):407-13.

21. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes:

a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation. 2007 May 15;115(19):2549-69.

22. Johnston SC, Fayad PB, Gorelick PB, Hanley DF, Shwayder P, van Husen D, et al. Prevalence and knowledge of transient ischemic attack among US adults. Neurology. 2003 May 13;60(9):1429-34.

23. Howard VJ, McClure LA, Meschia JF, Pulley L, Orr SC, Friday GH. High prevalence of stroke symptoms among persons without a diagnosis of stroke or transient ischemic attack in a general population: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Arch Intern Med. 2006 Oct 9;166(18):1952-8.

24. Morgenstern LB, Smith MA, Sanchez BN, Brown DL, Zahuranec DB, Garcia N, et al. Persistent ischemic stroke disparities despite declining incidence in Mexican Americans. Ann Neurol. 2013 Dec;74(6):778-85.

25. Morgenstern LB, Smith MA, Lisabeth LD, Risser JM, Uchino K, Garcia N, et al. Excess stroke in Mexican Americans compared with non-Hispanic Whites: the Brain Attack Surveillance in Corpus Christi Project. Am J Epidemiol. 2004 Aug 15;160(4):376-83.

26. Howard VJ, Kleindorfer DO, Judd SE, McClure LA, Safford MM, Rhodes JD, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. Ann Neurol. 2011 Apr;69(4):619-27.

27. Centers for Disease C, Prevention. Prevalence and most common causes of disability among adults--United States, 2005. MMWR Morb Mortal Wkly Rep. 2009 May 1;58(16):421-6.

28. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 2010 May 15;375(9727):1695-703.

29. Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet. 2012 Jun 23;379(9834):2364-72.

30. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014 Nov 29;384(9958):1929-35.

31. Goyal M, Almekhlafi M, Dippel DW, Campbell BCV, Muir K, Demchuk AM, et al. Rapid Alteplase Administration Improves Functional Outcomes in Patients With Stroke due to Large Vessel Occlusions. Stroke. 2019 Mar;50(3):645-51.

32. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA. 2013 Jun 19;309(23):2480-8.

33. Almekhlafi MA, Goyal M, Dippel DWJ, Majoie C, Campbell BCV, Muir KW, et al. Healthy Life-Year Costs of Treatment Speed From Arrival to Endovascular Thrombectomy in Patients With Ischemic Stroke: A Meta-analysis of Individual Patient Data From 7 Randomized Clinical Trials. JAMA Neurol. 2021 Jun 1;78(6):709-17.

34. Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, et al. 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A

Guideline From the American Heart Association/American Stroke Association. Stroke. 2022 Jul;53(7):e282-e361.

35. Kabbani LS, Wasilenko S, Nypaver TJ, Weaver MR, Taylor AR, Abdul-Nour K, et al. Socioeconomic disparities affect survival after aortic dissection. J Vasc Surg. 2016 Nov;64(5):1239-45.

36. Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, et al. Presentation, Diagnosis, and Outcomes of Acute Aortic Dissection: 17-Year Trends From the International Registry of Acute Aortic Dissection. J Am Coll Cardiol. 2015 Jul 28;66(4):350-8.

37. Booher AM, Isselbacher EM, Nienaber CA, Trimarchi S, Evangelista A, Montgomery DG, et al. The IRAD classification system for characterizing survival after aortic dissection. Am J Med. 2013 Aug;126(8):730 e19-24.

38. Itani Y, Watanabe S, Masuda Y, Hanamura K, Asakura K, Sone S, et al. Measurement of aortic diameters and detection of asymptomatic aortic aneurysms in a mass screening program using a mobile helical computed tomography unit. Heart Vessels. 2002 Jan;16(2):42-5.

39. Kalsch H, Lehmann N, Mohlenkamp S, Becker A, Moebus S, Schmermund A, et al. Body-surface adjusted aortic reference diameters for improved identification of patients with thoracic aortic aneurysms: results from the population-based Heinz Nixdorf Recall study. Int J Cardiol. 2013 Feb 10;163(1):72-8.

40. Bickerstaff LK, Pairolero PC, Hollier LH, Melton LJ, Van Peenen HJ, Cherry KJ, et al. Thoracic aortic aneurysms: a population-based study. Surgery. 1982 Dec;92(6):1103-8.

41. Clouse WD, Hallett JW, Jr., Schaff HV, Gayari MM, Ilstrup DM, Melton LJ, 3rd. Improved prognosis of thoracic aortic aneurysms: a population-based study. JAMA. 1998 Dec 9;280(22):1926-9.

42. Clouse WD, Hallett JW, Jr., Schaff HV, Spittell PC, Rowland CM, Ilstrup DM, et al. Acute aortic dissection: population-based incidence compared with degenerative aortic aneurysm rupture. Mayo Clin Proc. 2004 Feb;79(2):176-80.

43. Melvinsdottir IH, Lund SH, Agnarsson BA, Sigvaldason K, Gudbjartsson T, Geirsson A. The incidence and mortality of acute thoracic aortic dissection: results from a whole nation study. Eur J Cardiothorac Surg. 2016 Dec;50(6):1111-7.

44. Evangelista A, Isselbacher EM, Bossone E, Gleason TG, Eusanio MD, Sechtem U, et al. Insights From the International Registry of Acute Aortic Dissection: A 20-Year Experience of Collaborative Clinical Research. Circulation. 2018 Apr 24;137(17):1846-60.

45. Nienaber CA, Fattori R, Mehta RH, Richartz BM, Evangelista A, Petzsch M, et al. Gender-related differences in acute aortic dissection. Circulation. 2004 Jun 22;109(24):3014-21.

46. Matthews CR, Madison M, Timsina LR, Namburi N, Faiza Z, Lee LS. Impact of time between diagnosis to treatment in Acute Type A Aortic Dissection. Sci Rep. 2021 Feb 10;11(1):3519.

47. Hirst AE, Jr., Johns VJ, Jr., Kime SW, Jr. Dissecting aneurysm of the aorta: a review of 505 cases. Medicine (Baltimore). 1958 Sep;37(3):217-79.

48. Meszaros I, Morocz J, Szlavi J, Schmidt J, Tornoci L, Nagy L, et al. Epidemiology and clinicopathology of aortic dissection. Chest. 2000 May;117(5):1271-8.

49. Tsai TT, Nienaber CA, Eagle KA. Acute aortic syndromes. Circulation. 2005 Dec 13;112(24):3802-13.

50. Ting HH, Chen AY, Roe MT, Chan PS, Spertus JA, Nallamothu BK, et al. Delay from symptom onset to hospital presentation for patients with non-ST-segment elevation myocardial infarction. Arch Intern Med. 2010 Nov 8;170(20):1834-41.

51. Ting HH, Bradley EH, Wang Y, Lichtman JH, Nallamothu BK, Sullivan MD, et al. Factors associated with longer time from symptom onset to hospital presentation for patients with ST-elevation myocardial infarction. Arch Intern Med. 2008 May 12;168(9):959-68.

52. Guzman LA, Li S, Wang TY, Daviglus ML, Exaire J, Rodriguez CJ, et al. Differences in treatment patterns and outcomes between Hispanics and non-Hispanic Whites treated for ST-segment elevation myocardial infarction: results from the NCDR ACTION Registry-GWTG. J Am Coll Cardiol. 2012 Feb 7;59(6):630-1.

53. Miller AL, Simon D, Roe MT, Kontos MC, Diercks D, Amsterdam E, et al. Comparison of Delay Times from Symptom Onset to Medical Contact in Blacks Versus Whites With Acute Myocardial Infarction. Am J Cardiol. 2017 Apr 15;119(8):1127-34.

54. Afilalo J, Piazza N, Tremblay S, Soucy N, Huynh T. Symptom-to-door time in ST segment elevation myocardial infarction: overemphasized or overlooked? Results from the AMI-McGill study. Can J Cardiol. 2008 Mar;24(3):213-6.

55. Teuschl Y, Brainin M. Stroke education: discrepancies among factors influencing prehospital delay and stroke knowledge. Int J Stroke. 2010 Jun;5(3):187-208.

56. Lacy CR, Suh DC, Bueno M, Kostis JB. Delay in presentation and evaluation for acute stroke: Stroke Time Registry for Outcomes Knowledge and Epidemiology (S.T.R.O.K.E.). Stroke. 2001 Jan;32(1):63-9.

57. Harris KM, Strauss CE, Eagle KA, Hirsch AT, Isselbacher EM, Tsai TT, et al. Correlates of delayed recognition and treatment of acute type A aortic dissection: the International Registry of Acute Aortic Dissection (IRAD). Circulation. 2011 Nov 1;124(18):1911-8.

58. Lim B, Chauhan D, Schultz ML, Levine D, Loumiotis I, Friedmann P, et al. Relation of Community-Level Socioeconomic Status to Delayed Diagnosis of Acute Type A Aortic Dissection. Am J Cardiol. 2022 May 1;170:147-54.

59. Horne R, James D, Petrie K, Weinman J, Vincent R. Patients' interpretation of symptoms as a cause of delay in reaching hospital during acute myocardial infarction. Heart. 2000 Apr;83(4):388-93.

60. Canto JG, Shlipak MG, Rogers WJ, Malmgren JA, Frederick PD, Lambrew CT, et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. JAMA. 2000 Jun 28;283(24):3223-9.

61. Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ, et al. Symptom presentation of women with acute coronary syndromes: myth vs reality. Arch Intern Med. 2007 Dec 10;167(22):2405-13.

62. Dempsey SJ, Dracup K, Moser DK. Women's decision to seek care for symptoms of acute myocardial infarction. Heart Lung. 1995 Nov-Dec;24(6):444-56.

63. Fladt J, Meier N, Thilemann S, Polymeris A, Traenka C, Seiffge DJ, et al. Reasons for Prehospital Delay in Acute Ischemic Stroke. J Am Heart Assoc. 2019 Oct 15;8(20):e013101.

64. Garcia Ruiz R, Silva Fernandez J, Garcia Ruiz RM, Recio Bermejo M, Arias Arias A, Del Saz Saucedo P, et al. Response to Symptoms and Prehospital Delay in Stroke Patients. Is It Time to Reconsider Stroke Awareness Campaigns? J Stroke Cerebrovasc Dis. 2018 Mar;27(3):625-32.

65. Greenlund KJ, Keenan NL, Giles WH, Zheng ZJ, Neff LJ, Croft JB, et al. Public recognition of major signs and symptoms of heart attack: seventeen states and the US Virgin Islands, 2001. Am Heart J. 2004 Jun;147(6):1010-6.

66. Fang J, Luncheon C, Ayala C, Odom E, Loustalot F. Awareness of Heart Attack Symptoms and Response Among Adults - United States, 2008, 2014, and 2017. MMWR Morb Mortal Wkly Rep. 2019 Feb 8;68(5):101-6.

67. Patel A, Fang J, Gillespie C, Odom E, King SC, Luncheon C, et al. Awareness of Stroke Signs and Symptoms and Calling 9-1-1 Among US Adults: National Health Interview Survey, 2009 and 2014. Prev Chronic Dis. 2019 Jun 20;16:E78.

68. Jackson SL, Legvold B, Vahratian A, Blackwell DL, Fang J, Gillespie C, et al. Sociodemographic and Geographic Variation in Awareness of Stroke Signs and Symptoms Among Adults - United States, 2017. MMWR Morb Mortal Wkly Rep. 2020 Nov 6;69(44):1617-21.

69. Fukuoka Y, Dracup K, Rankin SH, Froelicher ES, Kobayashi F, Hirayama H, et al. Prehospital delay and independent/interdependent construal of self among Japanese patients with acute myocardial infarction. Soc Sci Med. 2005 May;60(9):2025-34.

70. McKinley S, Dracup K, Moser DK, Ball C, Yamasaki K, Kim CJ, et al. International comparison of factors associated with delay in presentation for AMI treatment. Eur J Cardiovasc Nurs. 2004 Sep;3(3):225-30.

71. McKinley S, Moser DK, Dracup K. Treatment-seeking behavior for acute myocardial infarction symptoms in North America and Australia. Heart Lung. 2000 Jul-Aug;29(4):237-47.

72. Dracup K, Moser DK. Beyond sociodemographics: factors influencing the decision to seek treatment for symptoms of acute myocardial infarction. Heart Lung. 1997 Jul-Aug;26(4):253-62.

73. Johansson I, Stromberg A, Swahn E. Factors related to delay times in patients with suspected acute myocardial infarction. Heart Lung. 2004 Sep-Oct;33(5):291-300.

74. Alonzo AA. The impact of the family and lay others on care-seeking during life-threatening episodes of suspected coronary artery disease. Soc Sci Med. 1986;22(12):1297-311.

75. Dhand A, Luke D, Lang C, Tsiaklides M, Feske S, Lee JM. Social networks and risk of delayed hospital arrival after acute stroke. Nat Commun. 2019 Mar 14;10(1):1206.

76. Alonzo AA. The effect of health care provider consultation on acute coronary syndrome care-seeking delay. Heart Lung. 2007 Sep-Oct;36(5):307-18.

77. Johansson I, Stromberg A, Swahn E. Ambulance use in patients with acute myocardial infarction. J Cardiovasc Nurs. 2004 Jan-Feb;19(1):5-12.

78. Sekoranja L, Griesser AC, Wagner G, Njamnshi AK, Temperli P, Herrmann FR, et al. Factors influencing emergency delays in acute stroke management. Swiss Med Wkly. 2009 Jul 11;139(27-28):393-9.

79. Johansson I, Strömberg A, Swahn E. Ambulance use in patients with acute myocardial infarction. Journal of Cardiovascular Nursing. 2004;19(1):5-12.

80. van 't Hof AW, Rasoul S, van de Wetering H, Ernst N, Suryapranata H, Hoorntje JC, et al. Feasibility and benefit of prehospital diagnosis, triage, and therapy by paramedics only in patients who are candidates for primary angioplasty for acute myocardial infarction. Am Heart J. 2006 Jun;151(6):1255 e1-5.

81. Le May MR, Dionne R, Maloney J, Poirier P. The role of paramedics in a primary PCI program for ST-elevation myocardial infarction. Prog Cardiovasc Dis. 2010 Nov-Dec;53(3):183-7.

82. Afolabi BA, Novaro GM, Pinski SL, Fromkin KR, Bush HS. Use of the prehospital ECG improves door-to-balloon times in ST segment elevation myocardial infarction irrespective of time of day or day of week. Emerg Med J. 2007 Aug;24(8):588-91.

83. Ting HH, Krumholz HM, Bradley EH, Cone DC, Curtis JP, Drew BJ, et al. Implementation and integration of prehospital ECGs into systems of care for acute coronary syndrome: a scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. Circulation. 2008 Sep 2;118(10):1066-79.

84. Bloom JE, Andrew E, Nehme Z, Dinh DT, Fernando H, Shi WY, et al. Pre-hospital heparin use for ST-elevation myocardial infarction is safe and improves angiographic outcomes. Eur Heart J Acute Cardiovasc Care. 2021 Dec 18;10(10):1140-7.

85. Zijlstra F, Ernst N, de Boer MJ, Nibbering E, Suryapranata H, Hoorntje JC, et al. Influence of prehospital administration of aspirin and heparin on initial patency of the infarct-related artery in patients with acute ST elevation myocardial infarction. J Am Coll Cardiol. 2002 Jun 5;39(11):1733-7.

86. Duvekot MHC, Venema E, Rozeman AD, Moudrous W, Vermeij FH, Biekart M, et al. Comparison of eight prehospital stroke scales to detect intracranial large-vessel occlusion in suspected stroke (PRESTO): a prospective observational study. Lancet Neurol. 2021 Mar;20(3):213-21.

87. Sanghavi P, Jena AB, Newhouse JP, Zaslavsky AM. Outcomes of Basic Versus Advanced Life Support for Out-of-Hospital Medical Emergencies. Ann Intern Med. 2015 Nov 3;163(9):681-90.

88. Stiell IG, Nesbitt LP, Pickett W, Munkley D, Spaite DW, Banek J, et al. The OPALS Major Trauma Study: impact of advanced life-support on survival and morbidity. CMAJ. 2008 Apr 22;178(9):1141-52.

89. Mahajan S, Valero-Elizondo J, Khera R, Desai NR, Blankstein R, Blaha MJ, et al. Variation and Disparities in Awareness of Myocardial Infarction Symptoms Among Adults in the United States. JAMA Netw Open. 2019 Dec 2;2(12):e1917885.

90. Moser DK, McKinley S, Dracup K, Chung ML. Gender differences in reasons patients delay in seeking treatment for acute myocardial infarction symptoms. Patient Educ Couns. 2005 Jan;56(1):45-54.

91. Mochari-Greenberger H, Xian Y, Hellkamp AS, Schulte PJ, Bhatt DL, Fonarow GC, et al. Racial/Ethnic and Sex Differences in Emergency Medical Services Transport Among Hospitalized US Stroke Patients: Analysis of the National Get With The Guidelines-Stroke Registry. J Am Heart Assoc. 2015 Aug 12;4(8):e002099.

92. Lam O, Broderick B, Toor S. How far Americans live from the closest hospital differs by community type. 2018.

93. Yu CY, Blaine T, Panagos PD, Kansagra AP. Demographic Disparities in Proximity to Certified Stroke Care in the United States. Stroke. 2021 Aug;52(8):2571-9.

94. Ortaliza J, Fox L, Claxton G, Amin K. How does cost affect access to care? Peterson-Kaiser Health System Tracker [serial on the Internet]. 2022 [cited 2022 May 9]: Available from: https://www.healthsystemtracker.org/chart-collection/cost-affect-access-care/.

95. Smolderen KG, Spertus JA, Nallamothu BK, Krumholz HM, Tang F, Ross JS, et al. Health care insurance, financial concerns in accessing care, and delays to hospital presentation in acute myocardial infarction. JAMA. 2010 Apr 14;303(14):1392-400.

96. Song S, Kwon S, Wymore E, Kandula N, Brown J, Eisenstein A, et al. Neighborhood differences in stroke knowledge, self-efficacy, and barriers to calling 9-1-1 in Chicago (S40.008). Neurology. 2018;90(15 Supplement):S40.008.

97. Le SM, Copeland LA, Zeber JE, Benge JF, Allen L, Cho J, et al. Factors affecting time between symptom onset and emergency department arrival in stroke patients. eNeurologicalSci. 2020 Dec;21:100285.

98. Meischke HW, Calhoun RE, Yip MP, Tu SP, Painter IS. The effect of language barriers on dispatching EMS response. Prehosp Emerg Care. 2013 Oct-Dec;17(4):475-80.

99. DuBard CA, Garrett J, Gizlice Z. Effect of language on heart attack and stroke awareness among U.S. Hispanics. Am J Prev Med. 2006 Mar;30(3):189-96.

100. Subramaniam MR, Mahajan PV, Knazik SR, Giblin PT, Thomas R, Kannikeswaran N. Awareness and utilization of emergency medical services by limited English proficient caregivers of pediatric patients. Prehosp Emerg Care. 2010 Oct-Dec;14(4):531-6.

101. Sasson C, Haukoos JS, Ben-Youssef L, Ramirez L, Bull S, Eigel B, et al. Barriers to calling 911 and learning and performing cardiopulmonary resuscitation for residents of primarily Latino, high-risk neighborhoods in Denver, Colorado. Ann Emerg Med. 2015 May;65(5):545-52 e2.

102. Ong BN, Yip MP, Feng S, Calhoun R, Meischke HW, Tu SP. Barriers and facilitators to using 9-1-1 and emergency medical services in a limited English proficiency Chinese community. J Immigr Minor Health. 2012 Apr;14(2):307-13.

103. Yip MP, Ong BN, Meischke HW, Feng SX, Calhoun R, Painter I, et al. The role of self-efficacy in communication and emergency response in Chinese limited english proficiency (LEP) populations. Health Promot Pract. 2013 May;14(3):400-7.

104. Health Coverage of Immigrants. Kaiser Family Foundation; 2022 [updated April 6, 2022; cited 2022 September 15]; Available from: https://www.kff.org/racial-equity-and-health-policy/fact-sheet/health-coverage-of-immigrants/.

105. Tolbert J, Artiga S, Pham O. Impact of shifting immigration policy on medicaid enrollment and utilization of care among health center patients. San Francisco: Henry J Kaiser Family Foundation. 2019;500.

106. Maldonado CZ, Rodriguez RM, Torres JR, Flores YS, Lovato LM. Fear of discovery among Latino immigrants presenting to the emergency department. Acad Emerg Med. 2013 Feb;20(2):155-61.

107. Watts J, Cowden JD, Cupertino AP, Dowd MD, Kennedy C. 911 (nueve once): Spanish-speaking parents' perspectives on prehospital emergency care for children. J Immigr Minor Health. 2011 Jun;13(3):526-32.

108. Mkoma GF, Norredam M, Iversen HK, Andersen G, Johnsen SP. Use of reperfusion therapy and time delay in patients with ischaemic stroke by immigration status: A register-based cohort study in Denmark. Eur J Neurol. 2022 Jul;29(7):1952-62.

109. Soares WE, 3rd, Knowles KJ, 2nd, Friedmann PD. A Thousand Cuts: Racial and Ethnic Disparities in Emergency Medicine. Med Care. 2019 Dec;57(12):921-3.

110. Hanchate AD, Paasche-Orlow MK, Baker WE, Lin MY, Banerjee S, Feldman J. Association of Race/Ethnicity With Emergency Department Destination of Emergency Medical Services Transport. JAMA Netw Open. 2019 Sep 4;2(9):e1910816.

111. Skopec L, Gonzalez D, Kenney GM. Most Adults Who Feel Treated or Judged Unfairly by Health Care Providers Report Adverse Consequences. Washington, DC: Urban Institute. 2021.

112. Bray JE, Stub D, Ngu P, Cartledge S, Straney L, Stewart M, et al. Mass Media Campaigns' Influence on Prehospital Behavior for Acute Coronary Syndromes: An Evaluation of the Australian Heart Foundation's Warning Signs Campaign. J Am Heart Assoc. 2015 Jul 6;4(7).

113. Caltabellotta T, Magne J, Salerno B, Pradel V, Petitcolin PB, Auzemery G, et al. Characteristics associated with patient delay during the management of ST-segment elevated myocardial infarction, and the influence of awareness campaigns. Arch Cardiovasc Dis. 2021 Apr;114(4):305-15.

114. McCarthy ML, Haynes S, Li X, Mann NC, Newgard CD, Lewis JF, et al. "Make the Call, Don't Miss a Beat" Campaign: Effect on Emergency Medical Services Use in Women with Heart Attack Signs. Womens Health Issues. 2019 Sep-Oct;29(5):392-9.

115. Haesebaert J, Laude C, Termoz A, Bravant E, Perreton N, Bony T, et al. Impact of a theory-informed and user-centered stroke information campaign on the public's behaviors, attitudes, and knowledge when facing acute stroke: a controlled before-and-after study. BMC Public Health. 2020 Nov 16;20(1):1712.

116. Skolarus LE, Zimmerman MA, Bailey S, Dome M, Murphy JB, Kobrossi C, et al. Stroke Ready Intervention: Community Engagement to Decrease Prehospital Delay. J Am Heart Assoc. 2016 May 20;5(5).

117. Jollis JG, Roettig ML, Aluko AO, Anstrom KJ, Applegate RJ, Babb JD, et al. Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. Jama. 2007 Nov 28;298(20):2371-80.

118. Patel MD, Rose KM, O'Brien EC, Rosamond WD. Prehospital notification by emergency medical services reduces delays in stroke evaluation: findings from the North Carolina stroke care collaborative. Stroke. 2011 Aug;42(8):2263-8.

119. Puolakka T, Kuisma M, Länkimäki S, Puolakka J, Hallikainen J, Rantanen K, et al. Cutting the Prehospital On-Scene Time of Stroke Thrombolysis in Helsinki: A Prospective Interventional Study. Stroke. 2016 Dec;47(12):3038-40.

120. Davis LL. Determining Time of Symptom Onset in Patients With Acute Coronary Syndromes: Agreement Between Medical Record and Interview Data. Dimens Crit Care Nurs. 2015 Jul-Aug;34(4):222-31.

121. Fukuoka Y, Dracup K, Ohno M, Kobayashi F, Hirayama H. Symptom severity as a predictor of reported differences of prehospital delay between medical records and structured interviews among patients with AMI. Eur J Cardiovasc Nurs. 2005 Jun;4(2):171-6.

122. Davis LL, McCoy TP, Riegel B, McKinley S, Doering LV, Dracup K, et al. Congruence of the Medical Record and Subject Interview on Time of Symptom Onset in Patients Diagnosed With Acute Coronary Syndrome. Dimens Crit Care Nurs. 2016 Nov/Dec;35(6):332-8.

123. Brownstein JN, Chowdhury FM, Norris SL, Horsley T, Jack L, Jr., Zhang X, et al. Effectiveness of community health workers in the care of people with hypertension. Am J Prev Med. 2007 May;32(5):435-47.

124. Brownstein JN, Bone LR, Dennison CR, Hill MN, Kim MT, Levine DM. Community health workers as interventionists in the prevention and control of heart disease and stroke. Am J Prev Med. 2005 Dec;29(5 Suppl 1):128-33.

125. Maserejian NN, Link CL, Lutfey KL, Marceau LD, McKinlay JB. Disparities in physicians' interpretations of heart disease symptoms by patient gender: results of a video vignette factorial experiment. J Womens Health (Larchmt). 2009 Oct;18(10):1661-7.

126. Rashid M, Timmis A, Kinnaird T, Curzen N, Zaman A, Shoaib A, et al. Racial differences in management and outcomes of acute myocardial infarction during COVID-19 pandemic. Heart. 2021 May;107(9):734-40.

127. Miller TD, Roger VL, Hodge DO, Hopfenspirger MR, Bailey KR, Gibbons RJ. Gender differences and temporal trends in clinical characteristics, stress test results and use of invasive

procedures in patients undergoing evaluation for coronary artery disease. J Am Coll Cardiol. 2001 Sep;38(3):690-7.

128. Alrawashdeh A, Nehme Z, Williams B, Smith K, Brennan A, Dinh DT, et al. Impact of emergency medical service delays on time to reperfusion and mortality in STEMI. Open Heart. 2021 May;8(1).

129. Marcolino MS, Maia LM, Oliveira JAQ, Melo LDR, Pereira BLD, Andrade-Junior DF, et al. Impact of telemedicine interventions on mortality in patients with acute myocardial infarction: a systematic review and meta-analysis. Heart. 2019 Oct;105(19):1479-86.

130. Itrat A, Taqui A, Cerejo R, Briggs F, Cho SM, Organek N, et al. Telemedicine in Prehospital Stroke Evaluation and Thrombolysis: Taking Stroke Treatment to the Doorstep. JAMA Neurol. 2016 Feb;73(2):162-8.

131. Al Kasab S, Almallouhi E, Grant C, Hewitt D, Hewitt J, Baki M, et al. Telestroke Consultation in the Emergency Medical Services Unit: A Novel Approach to Improve Thrombolysis Times. J Stroke Cerebrovasc Dis. 2021 May;30(5):105710.

132. Thuresson M, Jarlov MB, Lindahl B, Svensson L, Zedigh C, Herlitz J. Symptoms and type of symptom onset in acute coronary syndrome in relation to ST elevation, sex, age, and a history of diabetes. Am Heart J. 2005 Aug;150(2):234-42.

133. Gargano JW, Wehner S, Reeves MJ. Do presenting symptoms explain sex differences in emergency department delays among patients with acute stroke? Stroke. 2009 Apr;40(4):1114-20.

134. Janke AT, Gettel CJ, Haimovich A, Kocher KE, Krumholz HM, Venkatesh AK. Changes in Emergency Department Arrival Times for Acute Myocardial Infarction During the COVID-19

Pandemic Suggest Delays in Care Seeking. Circ Cardiovasc Qual Outcomes. 2022 Feb;15(2):e008402.

135. Siegler JE, Heslin ME, Thau L, Smith A, Jovin TG. Falling stroke rates during COVID-19 pandemic at a comprehensive stroke center. J Stroke Cerebrovasc Dis. 2020 Aug;29(8):104953.

136. Bhatt AS, Moscone A, McElrath EE, Varshney AS, Claggett BL, Bhatt DL, et al. Fewer Hospitalizations for Acute Cardiovascular Conditions During the COVID-19 Pandemic. J Am Coll Cardiol. 2020 Jul 21;76(3):280-8.

137. Kaminski M, Borger M, Bogdanski P. The Retrospective Analysis of Google Queries Related to Cardiovascular Diseases Symptoms in the Years 2004-2019. Int J Angiol. 2022 Mar;31(1):27-33.

138. Senecal C, Gulati R, Lerman A. Google Trends Insights Into Reduced Acute Coronary Syndrome Admissions During the COVID-19 Pandemic: Infodemiology Study. JMIR Cardio. 2020 Aug 24;4(1):e20426.

139. Walcott BP, Nahed BV, Kahle KT, Redjal N, Coumans JV. Determination of geographic variance in stroke prevalence using Internet search engine analytics. Neurosurg Focus. 2011 Jun;30(6):E19.

140. Bunde J, Martin R. Depression and prehospital delay in the context of myocardial infarction. Psychosom Med. 2006 Jan-Feb;68(1):51-7.