The Humble Relation of Hypersensitivity-Associated Acute Coronary Syndrome (Kounis Syndrome) and Acute and Sub-Acute Triggers of Cardiovascular Events

In the very interesting paper published in *The American Journal of Cardiology,*[1] several acute and subacute triggers of cardiovascular events were described including physical, emotional and/or mental, community and/or wide events, and toxins. Although air pollution and takotsubo (stress) cardiomyopathy were included in this list, the authors have omitted to refer to the Kounis hypersensitivity-associated acute coronary syndrome that includes endothelial dysfunction leading to coronary vasospastic angina,[2] atheromatous plaque erosion or disruption inducing coronary thrombosis,[3] and hypersensitivity events associated with stent thrombosis.[4] Indeed, in a recent report,[5] it was found that the above 3 types of the disease can lead to cardiac arrest (6.3%), death (2.9%), cardiogenic shock (2.3%), and ventricular fibrillation (1.1%). Kounis syndrome as cardiovascular event trigger. In 2 Japanese hospitals the annual incidence of Kounis syndrome at the emergency department from 2012 to 2017 was 2% (2 of 100) in the first and from 2013 to 2017 2.2% (3 of 138) in the second.[6]

Furthermore, disproportionality analysis of the FDA Adverse Event Reporting System (2004 to June 2016), which constitutes a consolidated pharmacovigilance source to monitor rare but serious adverse triggers such as Kounis syndrome, has shown that out of 499 spontaneous reports of drug-induced Kounis syndrome, 236 cases (47%) were attributed to a single trigger drug.[7] The authors of the above report were referred to air pollution and takotsubo (stress) cardiomyopathy as triggers of cardiovascular events. Indeed, air pollution as antigen carrier and takotsubo as stress cardiomyopathy have been already associated with Kounis syndrome.[8,9]

Therefore, searching, recognizing, diagnosing, and discovering new acute and subacute triggers of cardiovascular disease would have important implications for prevention, protection, and therapy of these so dangerous types of diseases.

Conflict of interest

None

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National Trends of Percutaneous Coronary Intervention in Patients ≥70 Years of Age

Over the past few decades, there has been an increase in life expectancy and elderly have been constituting a bigger subset of patients with coronary artery disease (CAD).[1] Coronary arteries involvement in elderly has a peculiar pathophysiology, with increased calcification, left main coronary involvement and more diffuse disease.[2,3] In addition to the increased burden of co-morbidities, elderly patients with CAD tend to present late.[4] Available data on the trend and outcomes of PCI in elderly patients with CAD are limited, and comes mainly from single centered or small multicentered registries.[1,2] In this study, we examined the largest national administrative database to evaluate the temporal trends in the utility of PCI in the older patients as well their in-hospital mortality.

We queried the Nationwide Inpatient Sample (NIS) database from 1998 to 2013 to identify hospitalizations of patients aged ≥70 years with International Classification of Diseases, Ninth Edition procedure code for PCI, either with bare-metal (36.06) or drug-eluting stents (36.07). We aimed at evaluating the temporal trends of PCI procedures as well as all-cause in-hospital mortality in patients aged ≥70 years. Statistical analyses were performed using SPSS Statistics 22. We analyzed data from the national estimates using the new trend weights provided by the NIS.[10] Time series analyses were performed in R 3.1.3[5] using the nlme package.[6]

Over a 16-year period (1998 to 2013), a total of 3,597,119 patients with age ≥70 years underwent PCI across the United States. In those, 2,435,203 were 70 to 79 years, 1,089,789 were 80 to 89 years and 72,127 were ≥90 years. From 1998 to 2013, there was an increase in comorbidities burden in elderly receiving PCI. Baseline characteristics are described in Table 1. Overall, the number of PCIs performed in patients aged ≥70 in 1998 was 151,752 compared with 165,260 cases in 2013. From 1998

Table 1
Comparison of baseline characteristics in elderly ≥70 years who had PCI during the period from 1998 to 2013

Baseline characteristics	1998-2003 (number of PCI = 1,290,595)	2004-2007 (number of PCI = 1,362,700)	2008-2013 (number of PCI = 943,824)
Women	577,946 (44.8%)	594,857(43.7%)	400,291 (42.4%)
Hypertension	292,158(62.0%)	961,285 (70.5%)	731,441 (77.5%)
Diabetes mellitus	113,477 (24.1%)	366,894 (26.9%)	291,215 (30.9%)
Obesity*	6,038 (0.5%)	12,268 (0.9%)	17,452 (1.8%)
Smoking	55,882 (4.3%)	77,048 (5.7%)	69,845 (7.4%)
Chronic kidney disease	16,871 (3.6%)	126,693 (9.3%)	183,039 (19.4%)
Chronic lung disease	71,054 (15.1%)	221,152 (16.2%)	180,808 (19.2%)
Peripheral vascular disease	51,086 (4.0%)	180,920 (13.3%)	145,638 (15.4%)
Anemia	100,785 (7.8%)	131,413 (9.6%)	129,826 (13.8%)

* Obesity defined as body mass index ≥30.

to 2006 there was a significant yearly increase of 18,329 PCI procedures per year (95% CI 14,013 to 22,645; p <0.001). From 2006 to 2013, the trend decreased by 33,614 PCI cases per year (95% CI −41,265 to −25,964; p <0.001). Similar trends were observed in the age categories (70 to 79 years) and (80 to 89 years; Supplemental Figure 1). Among those of age ≥90 years, there was an upward trend in PCI procedures from 1998 to 2006 at an annual rate of 512 (95% confidence interval [CI] 444 to 593; p <0.001). Although during the period from 2006 to 2013, there was a slower upward trend in PCI cases with trend change of 309 (95% CI 177 to 441; p <0.001; Supplemental Table 1; Figure 1). PCI was more commonly performed in elderly with ACS in urban teaching hospitals compared with nonteaching or rural hospitals (p <0.001; Supplemental Figure 2).

In those aged ≥70 years who had any PCI, in-hospital mortality in 1998 was 26.4 per 1,000 PCI, compared with 30.4 in 2013. From 1998 to 2006, there was a steady decrease in mortality at an annual rate of 1.2 (95% CI 1.0 to 1.4; p <0.001). After 2006, there was an observed increase in in-hospital mortality at an annual rate of 3.0 per 1,000 PCI (95% CI 2.7 to 3.3; p <0.001; Figure 1). Similar trends were observed in the age categories (70 to 79 years) and (80 to 89 years). In those of age ≥90 years, in-hospital mortality in 1998 was 79.4 per 1,000 PCI, compared with 63.8 per 1,000 PCI in 2013, with no significant change in the trend (trend = −2.6;95% CI −5.9 to 0.6; p = 0.102; Supplemental Table 1).

In this observational nationwide analysis including 3,597,119 hospitalizations, we sought to describe the national trends and outcomes of PCI in the elderly. Our analysis showed an initial rise in overall PCI numbers in patients aged ≥70 years from 1998 to 2006, followed by a relative reduction from 2006 to 2013. Multiple studies utilizing the NIS database have shown a downward trend starting from 2006 in PCI volumes (21, 22). Such decline in PCI volumes was temporally related to publication of major trials such as the COURAGE trial[7] and the BARI 2D trial,[8] which failed to show a mortality benefit of PCI over optimal medical therapy in patients with stable ischemic heart disease.[7,8] Although NIS only records inpatient procedures, the shift toward more outpatient PCI procedures might have contributed to the observed downward trend after 2006.[9] Other factors which might have contributed include the adoption of appropriate use criteria for PCI and the increasing adoption of Fractional Flow Reserve guided PCI.[10,11] There was an observed shift toward intervention on elderly with more co-morbidities, which might explain the upward trend in in-hospital mortality in the later years of our study. The shift toward intervention on patients with more co-morbidities burden was demonstrated by other studies.[12−14] Interestingly, we found a

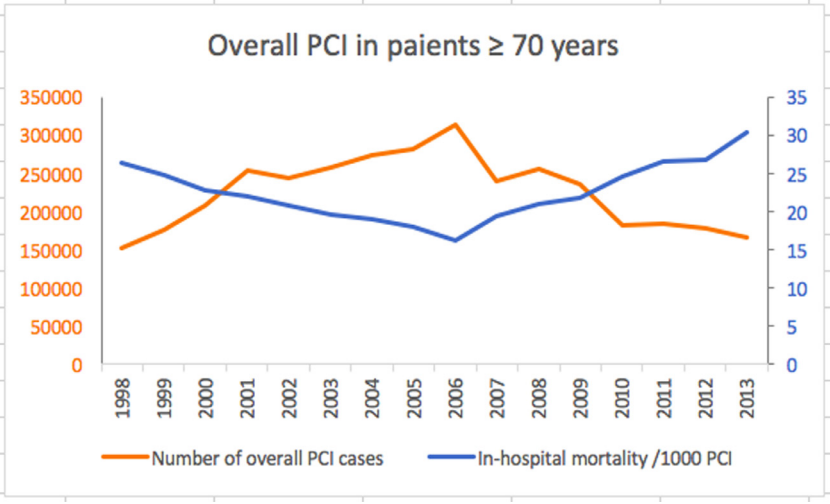

Figure 1. Temporal trend in numbers and in-hospital mortality rate of PCI procedures for elderly ≥70 years

consistent upward trend in overall PCI numbers in those aged ≥90 years, with no change in in-hospital mortality. A recent study conducted among veterans showed a significant increase in proportion of patients ≥90 years undergoing PCI from 2008 to 2014.

The current study has certain limitations. As with any administrative dataset, the NIS database is liable to coding errors and incomplete or missing documentation. The data collected for the NIS database are related to PCI procedures specifically completed in inpatients; therefore procedures performed in an outpatient setting would not be represented in our study. Many useful data for our study could not be retrieved, that include clinical variables, medications information, laboratory data and long-term outcomes. Despite these limitations, this study fills the current gap in literature regarding the true volume and outcomes of PCI in the elderly in the United States.

Disclosures

The investigators have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.11.053.

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Trends of Uptake and In-Hospital Mortality for Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Nonagenarians

Several large multicenter randomized trials have documented that transcatheter cutaneous aortic valve implantation (TAVI) is a reasonable alternative for surgical aortic valve replacement (SAVR) in intermediate to high-risk patients.[1,2] However, nonagenarians were underrepresented in these trials. As the incidence of severe aortic stenosis increases with age and the proportion of nonagenarian patients rises in the United States, we sought to investigate the temporal trends in the rates of use and in-hospital mortality of TAVI versus SAVR in this growing population.

Data were obtained from the National Inpatient Sample database from 2012 to 2015. The corresponding International Classification of Diseases procedure codes-9 and 10 were used to identify records for TAVI versus SAVR in nonagenarians. To focus on those who underwent SAVR primarily for severe aortic stenosis, we excluded records of patients with aortic insufficiency (without aortic stenosis), and those who underwent other concomitant cardiac surgery such as coronary artery bypass grafting, mitral valve, tricuspid, or pulmonary valve surgeries. The trend weights were developed to account for the stratified sampling design of the National Inpatient Sample. The trends of total TAVI and SAVR performed each year, and the rates of in-hospital mortality for TAVI