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Management of elderly patients with troponin positive chest pain in a District General Hospital

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Abstract

Background: *The number of elderly patients that present with an acute coronary syndrome (ACS) is increasing, reflecting the growing number of people in the general population in this age group. The various guidelines do not generally specify a management strategy in this elderly group and the management is often at the discretion of the treating physician. We conducted an audit within our Cardiology Department to compare our practice of management of ACS in the elderly population based on the European Society of Cardiology guidelines.*

Methods: *We conducted a retrospective analysis of the management of patients aged 80 and above that were admitted with troponin positive chest pain from 1st January to 31st December 2010. Patient information was primarily obtained from our computer data base system that includes blood results, ECHOs, diagnostic angiograms, discharge and clinic letters. If the information was inadequate we obtained patient files or contacted the relevant general practitioner.*

Results: *Octo-nonagenarians represented just over a third (35%) of all patients that were admitted with a troponin positive event during the study period. We noted a 10% mortality rate observed in our study population over a 12 month period. Atrial fibrillation was an incidental finding in 22% of patients. Nearly half of these patients (49%) were managed by the cardiologists. 68% of these patients underwent diagnostic coronary angiography, of which 32% went on to have percutaneous coronary intervention and 7% underwent surgical intervention. Majority (80%) of patients that underwent angioplasty had more than 1 stent and 74% of patients required more than one coronary vessel to be stented. The length of stay in hospital was double for patients who were under the care of the general medical teams rather than the cardiology team. This group also had a higher number of other comorbidities such as dementia, malignancy, a history of gastro intestinal bleeds and chronic renal impairment.*

Conclusions: *Octo and nonagenarians represent a significant proportion of our ACS patients. They have high mortality, greater number of comorbidities, diseased coronary vessels and if intervention was undertaken required more than one stent. Therefore, octo-nonagenarians represent a very complex group of patients. Guidelines and risk stratification are of limited value in this group as clinical trial data is currently lacking. Quality of life and risk to benefit assessments are of paramount importance in this group.* (Cardiol J 2012; 19, 4: 395–401)

Key words: acute coronary syndrome, elderly

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Introduction

The population dynamics of the UK are changing. The last 25 years has seen an increase in the number of people above the age of 65 by 1.7 million [1]. If we look at projected forecasts to 2034 then 23% of our population will be 65 or above [1]. Perhaps what is even more surprising is that the fastest population increase has been in the number of those aged 85 and over. In 1984, there were around 660,000 people in the UK aged 85 and over, by 2009 this had doubled to 1.4 million. Forecast projections put the number of this age group at 3.5 million or 5% of the UK population by 2034 [2]. The trend is also being replicated in Europe and United States [3]. In fact, the growth of the octogenarian population is estimated to triple by 2050 across Europe [1].

Heart disease remains the leading cause of death for both men and women of all ages [4]. This population shift will obviously have implications on health budgets. For example, patients aged 75 and older represent one third of those hospitalized with acute ischemic events and account for more than half of all cardiac deaths [5]. Patients over 75 years of age have twice the mortality rates than patients below 75 years of age [6]. Age has now been recognized as one of the most important risk predictors in patients admitted with a non-ST elevation myocardial infarction (NSTEMI) [7]. However due to lack of data on the management of acute coronary syndromes (ACS) in this age group some ambiguity remains in evidence based treatment of octogenarians. The current guidelines from the European Society of Cardiology strongly advice to take into consideration estimated life expectancy, co-morbidities and quality of life prior to any decisions in the management of our older NSTEMI patients [6].

We conducted an audit to investigate the management of patients aged 80 and above, who were admitted to our institution with a diagnosis of either ST elevation myocardial infarction (STEMI) or a NSTEMI or NSTE-ACS and compared our practice to the recommended guidelines for management of these conditions.

Methods

We conducted a retrospective analysis of the management of patients aged 80 and above that were admitted with troponin positive chest pain during 2010. These patients were either treated as STEMI or as NSTEMI. The list of troponin positive patients admitted between the 1st of January 2010 and the 31st of December 2010 was obtained from our medical records department. This list was further cross checked with the MINAP database and the clinical governance department. We then separated patient's that were 80 or above into our study group. Patient information thereafter was primarily obtained from our computer data base system that includes blood results, ECHOs, diagnostic angiograms, discharge and clinic letters. If the information was inadequate we obtained patient files or contacted the relevant general practitioner. This audit has been registered with our audit department.

Results

There were a total of 510 patients who were admitted with a diagnosis of a myocardial infarction (MI) (either STEMI or NSTEMI) to Good Hope Hospital during the period from 1st January 2010 to 31st December 2010. Of these, 177 were above the age of 80 representing 35% of the patients with an ACS. The male to female ratio was almost equally split at 49.7% and 50.3%, respectively. The mean and median ages were 86.2 and 86 years respectively (Fig. 1).

Table 1 summarizes the past medical history of these patients. Interestingly, more than half of the patients had no previous history of diabetes mellitus, MI, percutaneous coronary intervention (PCI) or coronary artery bypass grafts (CABG). However 78% had hypertension and 48% had previous strokes. There was also a higher prevalence of other co-morbidities (Table 1), including dementia (21%), malignancy (13%), previous gastro intestinal bleed (5%) and chronic renal impairment (12%). Figure 2 demonstrates the range of comorbidities that were present, with only 10 (6%) patients having no comorbidities, whilst 4 (2%) patients had more than 7. We also found that 106 (61%) and 8 (4%) of our patients were ex-smokers or continued to smoke respectively.

The majority of patients presented with the only symptom being chest pain (80%). However a further 15% had presented with chest pain along with another symptom (Table 2). The remaining 5% of patients denied any chest pain and presented with other complaints, the reasons for performing troponin levels were not made clear. It was considered to be an incidental finding as the patients had presented with totally non cardiac symptoms and the troponin was sent as part of routine testing. These patients were therefore excluded from the analysis.

22% (39 patients) of the patients in our study were found to be in atrial fibrillation (AF) on admission. Only 2 out of the 39 patients had complained

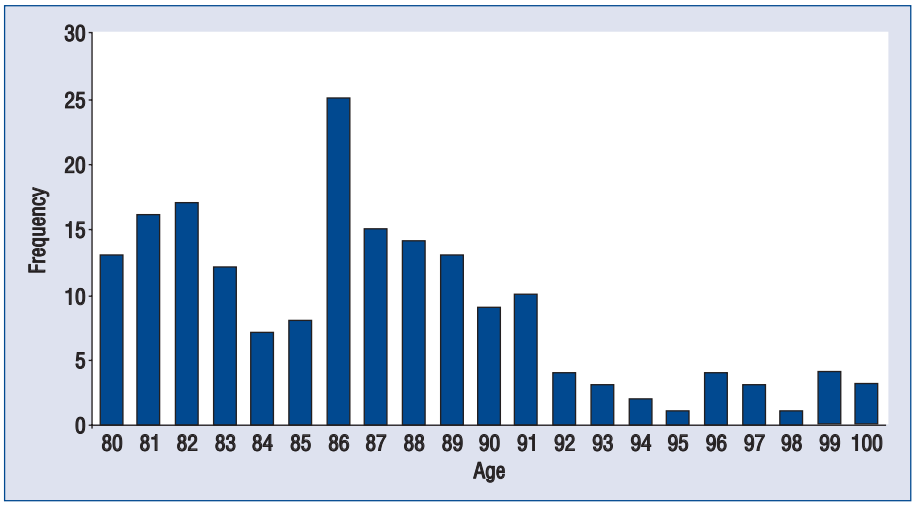

Figure 1. Age distribution of the population.

Table 1. Past medical history of significant risk factors.

	Yes (%)
Previous MI	70 (40%)
Previous PCI	12 (7%)
Previous CABG	11 (6%)
Diabetes mellitus	51 (29%)
Hypertension	138 (78%)
Stroke	43 (24%)
Dementia	23 (21%)
Arthritis	4 (4%)
Chronic kidney disease	12 (11%)
Hypothyroidism	8 (7%)
Osteoarthritis	15 (14%)
Glaucoma	4 (4%)
Chronic obstructive airway disease/asthma	16 (15%)
Malignancy	14 (13%)
Peripheral vascular disease	6 (5%)
Gastro intestinal bleeds	6 (5%)
Unknown	6 (5%)

MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass graft

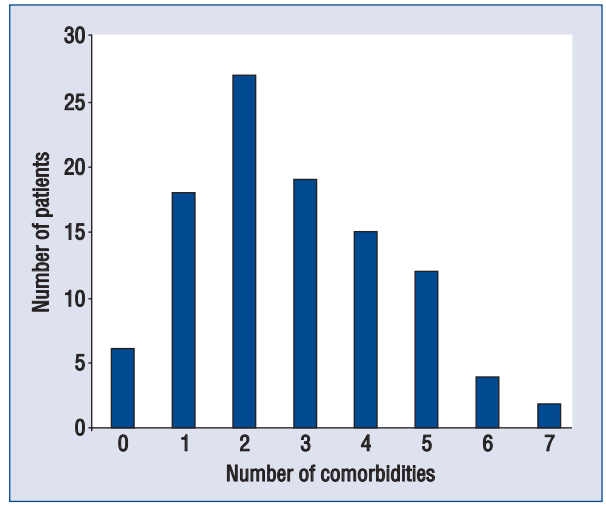

Figure 2. Distribution of the number of comorbidities among the study group.

Table 2. Presenting complaint in the patient group.

Presenting complaints	Number (%)
Chest pain only	140 (80%)
Chest pain with respiratory infection	5 (3%)
Chest pain with urosepsis	2 (1%)
Chest pain and falls	3 (2%)
Chest pain and breathlessness	10 (6%)
Chest pain and dizzy	2 (1%)
Chest pain confusion	1 (< 1%)
Incidental finding of a raised troponin	9 (5%)
Chest pain with palpitation	3 (2%)

of palpitations as the presenting complaint. Therefore AF was an incidental finding in 37 patients.

Of the total 177 patients, 86 were transferred under the care of the cardiology team with the remaining 91 staying under the care of the general medical team. Of the 91 patients that remained under the care of the general medical teams 21

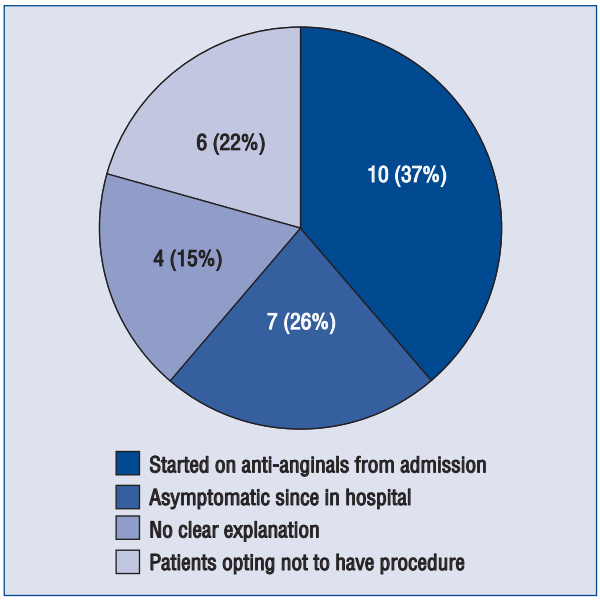

Figure 3. Explanation for patients under cardiology not undergoing diagnostic angiography.

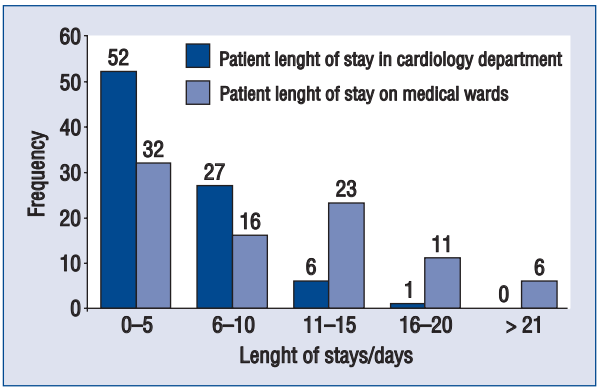

Figure 4. Comparison of lenght of stay between cardiology and general medicine.

(23%) were discussed with the cardiologist. The most common reason for the cardiology team not accepting a patient or for the medical team not referring patients to the cardiologist was the presence of significant comorbidities such as dementia or advanced malignancy (89%). Two patients had requested medical management and another 5 patients had sepsis.

We found that 59 of the 86 (69%) patients that were admitted or transferred under cardiology care had diagnostic angiography. The reasons for not performing angiography on the remaining 27 patients are listed in Figure 3. The commonest reason for 32% or 10 patients was for a trial of medical therapy in the first instance with a view to take a more invasive approach if that failed. In 4 (15%) patients of patients no clear explanation was documented as to why diagnostic coronary angiography was not performed (Fig. 3).

Of the 59 patients that underwent diagnostic angiography 34 (58%) patients were for medical management. 32 of these patients had no flow limiting disease, described as less than 75% stenosis, therefore not requiring intervention. The remaining 2 patients were deemed to be too frail for any intervention as they had extensive coronary artery disease. It is therefore not clear why they underwent any invasive test in the first place.

Out of the 25 patients with significant disease demonstrated on diagnostic coronary angiography, 19 had PCI, 4 had CABG but 2 patients opted for medical management only. The frequency of the coronary vessels stented were 5 (16%), 9 (30%), 8 (27%) and 8 (27%) for left main stem, left anterior descending, circumflex (including obtuse marginal) and right coronary, respectively. The frequency of single, double, triple and quadruple stents implanted were 4 (23%), 7 (37%), 5 (26%) and 3 (18%) respectively. Therefore in summary, of the 19 patients that underwent PCI, 15 (75%) required more than 1 stent and 15 (75%) required more than 1 coronary artery to be stented with nearly half of the patients requiring stenting of either the left main or the left anterior descending artery.

We compared patient length of in-hospital stay depending on whether they were under the general medical or cardiology team (Fig. 4). We found that the length of stay under the cardiologists was less. The mean/median lengths of stay under cardiology department and general medical departments were 5.9/5 and 10.4/10 days, respectively. 61% of patients under the cardiologists were discharged within 5 days whereas only 32% of the patients under the medical team were discharge within this time frame.

During the following year, we found that 17 (10%) patients of study population died. Six patients had out of hospital cardiac arrests and were not revived. The remaining 11 patients died whilst as inpatients. Nine of these patients died within 24 h from cardiogenic shock or aspirational pneumonia, 7 of these 9 patients were discussed with the cardiology team and were for medical/palliative treatment only. Out of the remaining 2 patients, both had prolonged admissions, ultimately dying from bronchopneumonia. No deaths were reported whilst under the care of the cardiology team

Eight patients died before being seen in the follow up clinic, 2 from cardiac causes and 6 non

cardiac causes. Of the 19 patients that had PCI 18 were alive at 12 months, 1 patient had died from a non-cardiac cause, 2 patients had recurrence of their symptoms of which 1 patient had a further NSTEMI. However both had repeat diagnostic angiogram with patent stents and without flow limiting disease.

All patients that had CABG were followed up and were alive at 12 months.

Discussion

Recent Myocardial infarction National Audit Project (MINAP) data noted the average age of patients with NSTEMI was 70 years of age and for first presentation STEMI was 65 years of age, with 52% of all myocardial infarcts occurring in patients aged 70 or above [8]. Taking into account European registries 27–34% of NSTEMI patients were 75 years or over [9, 10], however less than 20% of patients aged 75 years or more were included in clinical trials [11]. This has led to some ambiguity in the treatment of octogenarians with ACS and therefore age dependent inequalities in the management of these patients [12]. Despite this, significant reduction in hospital mortality of ACS patients in England and Wales has been seen across all age groups [12].

The management of elderly patients with an ACS is challenging. The risk of complications of an invasive strategy is high in this population group [13, 14], however these high risk patients are often those with the most to gain [15–19]. With the ageing population the decision whether to medically manage or subject patients to an interventional procedure are a common clinical dilemma.

In our study we found that around one-third of patients who were admitted with an ACS were above the age of 80. This is in keeping with other studies [5]. Around half of the patients who were admitted, however remained under the admitting medical team with 70 of the total 177 (39%) not even being discussed with the cardiology team. This is potentially a contentious point — whether the decision to investigate these patients further should be taken in conjunction with the cardiologists or whether the admitting medical team could make the decision. Currently there are no national or international guideline recommendations on who makes the decision. The ESC guidelines only recommend that any decision should be based on individual elderly patients, taking into account, "ischemic and bleeding risk, estimated life expectancy, co-morbidities, quality of life, patient wishes, and the estimated risks and benefits of revascularization" [6].

Only a third of our study group had an angiogram. It is not clear from the records whether the decision not to have any invasive testing was taken in conjunction with the patient or whether it was a medical decision. It was clearly documented only in 6 patients that the patient did not wish to have any invasive investigation done. Similarly in about 10 patients who were under the cardiologists, the plan was for medical therapy in the first instance, with a view to invasive testing if the patient failed medical therapy. This is debatable, as clinical evidence suggests that in the setting of an ACS, an early invasive strategy is far superior to a conservative strategy [12, 13]. Although not documented in the medical notes, it is possible that these patients either had significant co-morbidities or were physically frail or had other reasons for the treating clinician to make that decision. However this was not clear from the medical notes.

There was an overall mortality rate of 17 (10%) patients in our octo-nonagenarians group. Six were out patient cardiac arrests that could not be resuscitated, the remaining 11 patients died during their stay in hospital. The majority (9 of the 11) died within 24 h from cardiogenic shock. The remaining 2 died after a prolonged in patient stay in hospital with bronchopneumonia. These 2 patients had a number of comorbidities including dementia.

Patients with the greater number of comorbidities remained under the care of the medical teams and as mentioned above had no cardiac intervention. These are also the patients not surprisingly who had a longer length of stay. Within this context great care needs to be exercised and to ensure that all suitable patients are at least considered for intervention if required. This has been highlighted in some studies that found patients admitted with NSTEMI had lower mortality if under cardiac care than general medical care [20, 21]. These studies included all ages and not only octogenarians.

Patient comorbidities are a very important and integral part of the decision making process in the elderly. 94% of our patients had at least a 1 significant comorbidity, with 21% and 5% having a history of dementia and gastrointestinal bleeding respectively. Informed consent and the reasons for performing an invasive procedure that has an associated complication risk must be clearly explained with simple grammar and highlighting important points [22, 23]. We found that 22% of patients that did not have diagnostic angiograms didn't have it done at their own request. If a decision not to pursue an invasive procedure is made, then clear documentation of the reason must always be made.

If however patients agree to undergo intervention then stressing the importance of post-procedural compliance of any treatment is associated with improved patient outcomes [24, 25].

In our study 39 (22%) of the patients were found to be in AF on admission. However, only 2 out of the 39 patients had complained of palpitations as the presenting complaint. Therefore AF was an incidental finding in 37 patients as mentioned within the results. The prevalence of AF in octogenarians has been quoted as 5–15% [26]. Our results seem to suggest that ischemia could be the cause of AF in this patient group; however our numbers were too small to make such conclusions.

Elderly patients are often more passive and have a more accepting manner than younger patients [27–29]. More recently, this tide is turning with an increase in operative details being requested in all patients, however the greatest increase has been seen in the elderly [30]. If doubt remains about capacity, the patient's ability to retain and effectively communicate the risks and benefits of the intended procedure together the decision regarding the procedure should be assessed [31]. A relatively quick and straightforward test of cognition, the mini-mental state examination, should be carried out [32, 33].

Review of literature reveals that PCI procedural complication rates were higher in the elderly age group. However this was counter balanced with fewer hospital admissions and improved quality of life [16, 19, 34–36]. We also observed a positive effect after intervention in our patient group. Out of 19 patients that had PCI, 17 had no hospital admissions for angina over 12 months. The 2 patients that were readmitted had repeat angiography that failed to demonstrate any significant stenosis. Similarly, all 4 patients that had undergone CABG were symptom free for 12 months following surgery. This is in keeping with another retrospective study that has shown that the 30 day and 12 month mortality between octogenarians undergoing PCI or CABG is similar [34]. However, this data is biased as this is non-randomized with only the older patients with the least comorbidities were put forward for intervention. This does however highlight the fact that patient selection is very important in this age group and that a decision to intervene or not should be made on a case by case basis, taking into consideration the co-morbidities and the physical wellbeing, rather than on age alone.

This study is a retrospective audit of the management of elderly patients with a NSTEMI in our institution. It is therefore a purely observational study. In addition, all the information was obtained from the patient case notes and in some instances from the patient's general practitioner. Retrospective analysis of case notes has its limitations as the quality of data is related to the quality of case note documentation, which occasionally may be less than satisfactory. Another drawback of our study was the fact that we did not have many patients with STEMI in our study group. This is because all patients with STEMI are transferred directly to our regional interventional centre and do not come to our hospital.

Conclusions

Octo and nonagenarians represent a significant number of our ACS patients. They also represent a very complex group of patients as there are many other non-medical and medical issues that often make decision making difficult. Guidelines and risk stratification are of limited value in this group as clinical trial data is lacking. Therefore good communication between general medical and cardiology teams are essential in management of older patients. All patients including older patients should be presented with the various treatment options, and their views should be taken into consideration when making the decision whether or not to offer them invasive treatment strategies. Quality of life, and risk benefit assessments are of pivotal importance in our octo and nonagenarians.

Conflict of interest: none declared

References

1. Ministry for internal affairs of the Federal Republic of Germany http://www.bmi.bund.de/nn_882848/Internet/Navigation/DE/Themen/Bevoelkerungsentwicklung/bevoelkerungsentwicklung_node.html_nnn=true.
2. Mid-year population estimates. Office for National Statistics; General Register Office for Scotland; Northern Ireland Statistics and Research Agency. Population projections for 2034 are ONS National Population Projections (NPP) 2008 based.
3. U.S. Census Bureau, The 2009 Statistical Abstract, Population: Estimates and Projections by Age, Sex, Race/Ethnicity; Resident Population Projections by Sex and Age. Available on-line at: http://www.census.gov/compendia/statab/tables/09s0010.
4. Centres for Disease Control and Prevention. Health, United States, 2009. Available on-line at http://www.cdc.gov/nchs/data/hus/hus09.pdf#listfigures.
5. Goldberg RJ, Yarzebski J, Lessard D, Gore JM. Two-decades (1975–1995) long experience in the incidence in-hospital and long term case-fatality rates of acute myocardial infarction: A community-wide perspective. J Am Coll Cardiol, 1999; 33: 1533–1539.
6. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J, 2011; 32: 2999–3054.

7. Fox KA, Dabbous OH, Goldberg RJ et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: Prospective multinational observational study(GRACE). BMJ, 2006; 333: 1091.
8. Myocardial Ischaemia National Audit Project (MINAP). How the NHS cares for patients with heart attack Tenth Public Report 2011 Prepared on behalf of the MINAP Steering Group http://www.hqip.org.uk/assets/NCAPOP-Library/MINAP-public-report-2011.pdf.
9. Rosengren A, Wallentin L, Simons M et al. Age, clinical presentation, and outcome of acute coronary syndromes in the Euroheart acute coronary syndrome survey. Eur Heart J, 2006; 27: 789–795.
10. Bauer T, Koeth O, Junger C et al. Effect of an invasive strategy on in-hospital outcome in elderly patients with non-ST-elevation myocardial infarction. Eur Heart J, 2007; 28: 2873–2878.
11. Alexander KP, Newby LK, Cannon CP 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; 115: 2549–2569.
12. Gale CP, Cattle BA, Woolston A et al. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003––2010. Eur Heart J, 2012; 33: 630–639.
13. Singh M, Peterson ED, Roeet MT et al. Trends in the association between age and in-hospital mortality after percutaneous coronary intervention: National Cardiovascular Data Registry experience. Circ Cardiovasc Interv, 2009; 2: 20–26.
14. Yan BP, Gurvitch R, Duffy SJ et al An evaluation of octogenarians undergoing percutaneous coronary intervention from the Melbourne Interventional Group registry. Catheter Cardiovasc Interv, 2007; 70: 928–936.
15. Ionescu CN, Amuchastegui M, Ionescu S et al. Treatment and outcomes of nonagenarians with ST-elevation myocardial infarction. J Invasive Cardiol, 2010; 22: 474–478.
16. Bauer T, Mollmann H, Weidinger F et al. Predictors of hospital mortality in the elderly undergoing percutaneous coronary intervention for acute coronary syndromes and stable angina. Int J Cardiol, 2011; 151: 164–169.
17. Pfisterer M, Buser P, Osswals S et al.; for the TIME Investigators. Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs. optimized medical treatment strategy: One-year results of the randomized TIME trial. JAMA, 2003; 289: 1117–1123.
18. TIME Investigators. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): A randomised trial. Lancet, 2001; 358: 951–957.
19. Günal A, Aengevaeren WRM, Gehlmann HR et al. Outcome and quality of life one year after percutaneous coronary interventions in octogenarians. Neth Heart J, 2008; 16: 117–122.
20. Tang EW, Wong CK, Herbison P. Community hospital versus tertiary hospital comparison in the treatment and outcome of patients with acute coronary syndrome: A New Zealand experience. N Z Med J, 2006; 119: U2078.
21. Ho PM, Luther SA, Masoudi FA et al. Inpatient and follow-up cardiology care and mortality for acute coronary syndrome patients in the Veterans Health Administration. Am Heart J, 2007; 154: 489–494.
22. Crepeau AE, McKinney BI, Fox-Ryvicker M et al. Prospective evaluation of patient comprehension of informed consent. J Bone Joint Surg Am, 2011; 93: e114 (1–7).
23. Epstein L. Obtaining informed consent, form or substance. Arch Intern Med, 1969; 123: 682–688.
24. Calman KC. Communication of choice; choice, consent and trust. Lancet, 2002; 360: 166–168.
25. Adams AM, Smith AF. Risk perception and communication: Recent developments and implementation for anaesthesia. Anaesthesia, 2001; 56: 745–755.
26. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology. Guidelines for the management of atrial fibrillation. Eur Heart J, 2010; 31: 2369–2429.
27. Levinson W, Kao A, Kuby A et al. Not all patients want to participate in decision making. A national study in public preference. J Gen Intern Med, 2005; 20: 531–535.
28. Davis MA, Hoffman JR, Hsu J. Impact on patient acuity on preference for information and autonomy in decision making. Acad Emerg Med, 1999; 6: 781–785.
29. Ende J, Kazis L, Ash A et al. Measuring patients desire for autonomy; decision making and information seeking preference in medical patients. J Intern Med, 1994; 9: 360–361.
30. Pailland E, Ferrand E, Lejonoc JC et al. Medical information and surrogate designation; results of a prospective study in elderly hospitalised patients. Age Ageing, 2007; 36: 274–279.
31. Carol Wayne D. Assessment of capacity for medical decision making. J Gerontol Nur, 2010; 36: 47–52.
32. Warner J, McCarney, Griffin M et al. Participation in dementia research rates and correlation of capacity to give informed consent. J Med Ethics, 2008; 34: 167–170.
33. Mental capacity act UK accessed at http://www.dh.gov.uk/en//SocialCare/Deliveringsocialcare/MentalCapacity/MentalCapacityAct2005/index.htm.
34. Rajani R, Lindblom M, Dixon G et al. Evolving trends in percutaneous coronary intervention. Br J Cardiol, 2011; 18: 73–76.
35. McKellar SH, Brown ML, Frye RL et al. Comparison of coronary revascularization procedures in octogenarians: A systematic review and meta-analysis. Nat Clin Pract Cardiovasc Med, 2008; 5: 738–746.
36. Berger JS, Bhatt DL, Steg PG et al. Bleeding, mortality, and antiplatelet therapy: Results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. Am Heart J, 2011; 162: 98–105.e1.