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# Is the contemporary care of the older persons with acute coronary syndrome evidence-based?

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Globally, ischaemic heart disease is the leading cause of death, with a higher mortality burden amongst older adults. Although advancing age is associated with a higher risk of adverse outcomes following acute coronary syndrome (ACS), older patients are less likely to receive evidence-based medications and coronary angiography. Guideline recommendations for managing ACS are often based on studies that exclude older patients, and more contemporary trials have been underpowered and produced inconsistent findings. There is also limited evidence for how frailty and comorbidity should influence management decisions. This review focuses on the current evidence base for the medical and percutaneous management of ACS in older patients and highlights the distinct need to enrol older patients with ACS into well-powered, large-scale randomized trials.
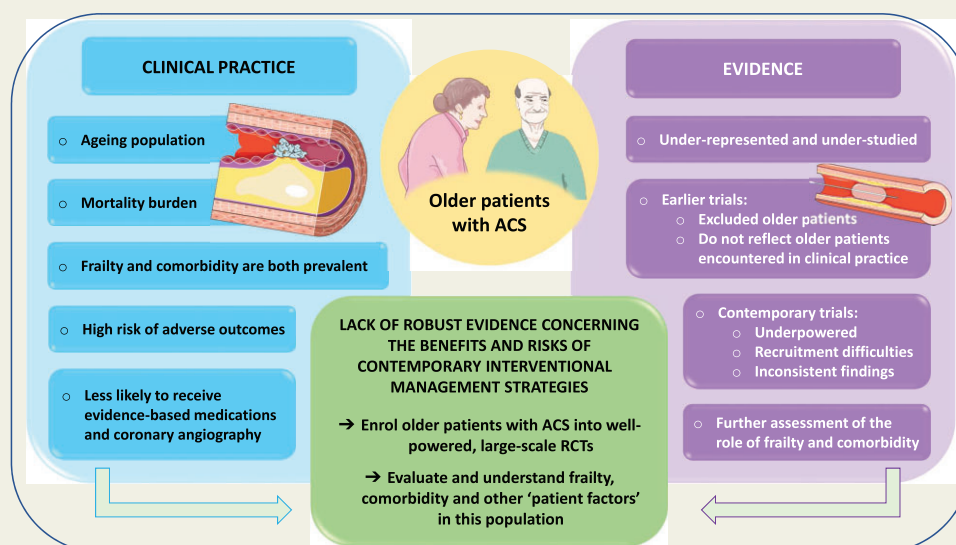
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## Graphical Abstract

# Introduction

Ischaemic heart disease is the leading cause of death worldwide, with older adults experiencing a higher mortality burden.[1] Between 2015 and 2050, the proportion of the world's population aged >60 years is set to nearly double to 22%.[2] Non-ST-elevation acute coronary syndrome (NSTEACS) is the main acute coronary syndrome (ACS) subtype in older adults aged >75 years.[3] Clinical characteristics of the older adult population are heterogeneous with frailty, comorbidity, cognitive function, and health-related quality of life (HRQoL) playing important roles in guiding clinical care and as predictors of adverse outcomes. There is, however, a lack of specific pharmacological and invasive treatment guidelines for older patients. This is due to historical under-representation of older patients with ACS in clinical trials.[4] This review focuses on the current evidence base for the medical and percutaneous management of ACS in older patients.

# Characteristics of older adults with acute coronary syndrome

The symptom characteristics in older patients with ACS are often different compared with younger patients.[4] Chest pain is not the predominant symptom whereas dyspnoea (49.3%), diaphoresis (26.2%), nausea or vomiting (24.3%), and pre-syncope or syncope (19.1%) are more common.[5,6] Worryingly, an 'atypical' presentation of ACS is associated with adverse outcomes.[6] When correctly diagnosed, older patients with ACS are less likely to receive evidence-based

medications and coronary angiography (CAG), which may contribute to an excess mortality.[7] The knowledge of the higher risk of complications to both invasive and medical treatment with increasing age can probably be a part of the explanation.[8] Current clinical practice recommendations based on the existing sparse evidence for management of older patients with ACS are summarized in *Figure 1*.

## Frailty

Frailty is common in older people, particularly in those with cardiovascular disease,[9,10] and it is associated with adverse outcomes.[11] These factors may affect any benefit derived from an invasive approach.[12] Frailty is defined as a 'state of increased vulnerability to poor resolution of homeostasis following stress, which increases the risk of adverse outcomes including falls, delirium and disability', as well as major adverse cardiac events (MACE).[13,14] Frailty assessment tools focus on either phenotype or cumulative deficit models with physicians' scaled judgement of activity, comorbidity, and dependency.[15]

Frail adults presenting with NSTEACS have more procedurally challenging angiographic characteristics, independent of age.[16,17] In age- and sex-adjusted logistic regression analysis, frailty is associated with severe culprit lesion calcification [odds ratio (OR) 5.13, 95% confidence interval (CI) 1.59–16.5, $P = 0.006$]. Frail patients had a 2.67 increased odds of being within the highest SYNTAX tertile compared with robust patients and a greater presence of high-risk lesions on virtual history intravascular ultrasound imaging, with a 2.81 increased adjusted odds (95% CI 1.06–7.48, $P = 0.039$) of presence of thin-cap fibroatheroma,
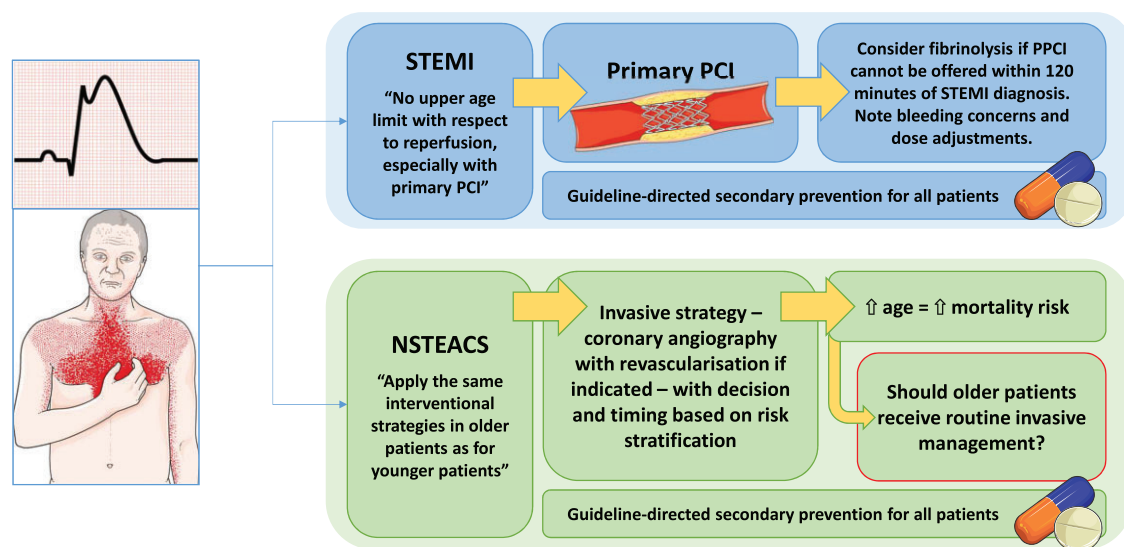
**Figure 1** Current European Society of Cardiology recommendations on the management of older patients with acute coronary syndrome. This figure use illustrations from Servier Medical Art Image Bank. These are licensed under a Creative Commons Attribution 3.0 Unported License that permits adaptation and sharing of the material for any purpose. Full license details can be found at https://creativecommons.org/licenses/by/3.0/

independent of age.[16] Frailty predicts an increase in composite of all-cause mortality, myocardial infarction (MI), stroke, unplanned revascularization, and major bleeding at 1 year among older patients with NSTEACS receiving CAG.[13] Importantly, older NSTEACS adults with frailty have poor HRQoL at baseline. One year following invasive management, modest improvements in HRQoL were most marked in frail and pre-frail patients who received a proportionally larger benefit than robust patients.[18]

## Comorbidity

The number and severity of comorbidities are inversely related to rates of CAG and percutaneous coronary intervention (PCI) in patients with ACS.[19] Comorbidity burden, as measured by the Charlson Comorbidity Index, predicts in-hospital and 1-year mortality in patients with ACS and is independently associated with adverse short- and long-term outcomes after PCI.[20] However, a recent study showed that an invasive strategy yielded a significant prognostic benefit in terms of the reduced composite endpoint of death or non-fatal MI at 16 months in patients with the greatest comorbidity burden.[21]

## Cognitive impairment

Rates of CAG and revascularization are lower in older patients with ACS and cognitive impairment compared with those with normal cognitive function, whilst cognitive impairment is associated with in-hospital mortality and death at 6 months.[22] Undiagnosed cognitive impairment is also common in older patients with NSTEACS receiving CAG and these patients are more likely to experience adverse events at 1 year.[23] However, any potential differential prognostic benefit of invasive care according to cognitive status in ACS patients has not been investigated.

## Functional decline

Decline in functional status, assessed with either HRQoL or needing assistance with activities of daily living (ADLs), is associated with all-cause mortality at 18 months.[24] Observational data have shown that the risk of functional decline in ADLs or HRQoL is lower in older patients with MI receiving revascularization compared with those receiving medical management.[25] However, selection bias limits interpretation of these findings and trial data has shown no clinically significant differences in HRQoL at 1 year between older patients with NSTEACS randomized to an invasive strategy compared with a conservative approach.[26]

# ST-elevation myocardial infarction in older adults

Older patients with ST-elevation MI (STEMI) are more likely to experience delays between symptom onset and hospital admission due to the atypical presentation and delays in seeking help.[27] When hospitalized, they are less likely to receive reperfusion therapies compared with younger patients, even in those without contraindications.[28]

## Evidence on the management of ST-elevation myocardial infarction in older adults

### Observational studies

In observational studies regarding the use of primary PCI (PPCI) vs. thrombolysis in older STEMI patients, most favours PPCI.[29,30] A comparison of selected observational studies in older patients with STEMI is summarized in Supplementary material online, S1. The

Global Registry of Acute Coronary Events (GRACE) study conducted >20 years ago (n = 1134, median age 76 years, female 40.2%) showed improved in-hospital outcomes associated with PPCI vs. thrombolysis, with lower rates of death (adjusted OR 0.62; 95% CI 0.39–0.96; *P* = 0.03) and re-infarction (OR 0.15; 95% CI 0.05–0.44; *P* < 0.001).[29] The Acute Myocardial Infarction in Switzerland (AMIS) study (n = 6877, mean age 79 years, female 39.7%) showed an increasing use of PPCI over time amongst older adults, which was translated into a significant reduction in MACE and in-hospital mortality.[31] Interestingly, an analysis from the UK Myocardial Ischaemia National Audit Project (MINAP) database (n = 68 025, mean age 69 years, female 33.6%) showed that all-cause mortality benefits associated with reperfusion strategies in comparison to conservative approaches were attenuated with advancing age.[7]

### Randomised controlled trials

Randomized clinical trials (RCTs) primarily focussing on older adults published to date have generally shown the benefits of PPCI over thrombolysis in STEMI patients, albeit in the context of underpowered studies affected by slow enrolment, particularly when recruiting patients >80 years. de Boer *et al.*[32] randomized 87 patients with STEMI aged ≥75 years to PPCI or thrombolysis and showed a reduced risk of death, re-infarction or stroke at 1 year in patients managed with PPCI. The study had small sample size, but results indicate that PPCI is likely to be safe in the older population. In the largest RCT in older STEMI patients, Senior Primary Angioplasty in Myocardial Infarction Study (SENIOR-PAMI), recruiting 483 patients ≥70 years (mean age 78 years, female 41%) receiving PPCI vs. thrombolysis, no difference was seen in the rates of primary composite endpoint of death or stroke at 30 days. Although the secondary composite endpoint of death, stroke, or re-infarction occurred less frequently in the PPCI group, driven by reduced rates of re-infarction

at 30 days.[33] Unfortunately, the study was discontinued due to slow patient recruitment and therefore definitive conclusions cannot be drawn in the >80-year olds. RCTs in older patients with STEMI are summarized in *Figure 2*.

### Meta-analyses

In a meta-analysis by de Boer *et al.*,[34] comparing PPCI and fibrinolysis, patients aged 70–80 years randomized to PPCI had reduced all-cause mortality, re-infarction, stroke, and a composite of all three endpoints, and patients >80 years randomized to PPCI experienced a lower rate of the composite endpoint. However, individual endpoints in the oldest patients were likely underpowered as only 6% (n = 410) were >80 years. Findings from contemporary RCTs and meta-analyses comparing PPCI and fibrinolysis in older patients with STEMI are summarized in *Table 1*.

## Current practice guidelines on the management of ST-elevation myocardial infarction in older adults

Treatment guidelines from the UK and European Society of Cardiology (ESC) recommend CAG with subsequent PPCI if indicated for STEMI in patients of all ages, where it can be performed within 2 h.[35,36] Beyond this time period, patients may receive fibrinolysis and those ineligible for either reperfusion strategy should be treated medically with dual antiplatelet therapy (DAPT; aspirin and a $P2Y_{12}$ inhibitor). The National Institute for Health and Care Excellence (NICE) specifically recommends that eligibility is assessed 'irrespective of age' and ESC guidance stresses 'there is no upper age limit with respect to reperfusion, especially with PPCI'.[35,36] Raised bleeding risk is widely recognized in older adults, particularly with fibrinolysis, therefore dose adjustments are recommended.[36]
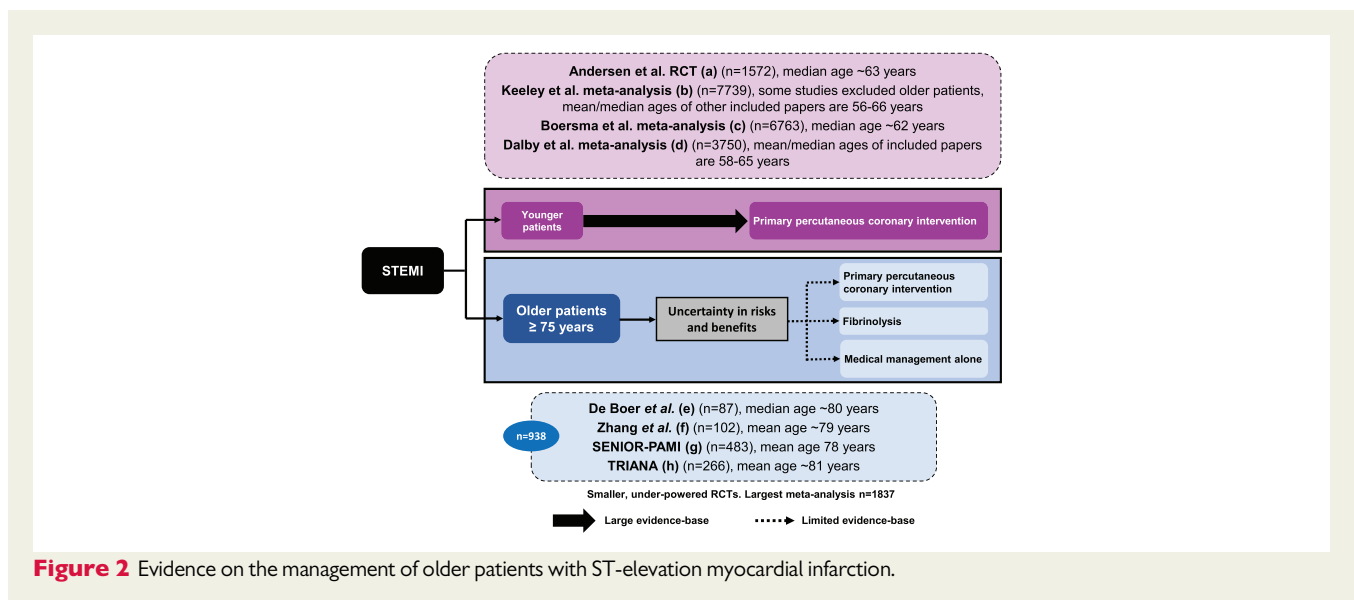


**Figure 2** Evidence on the management of older patients with ST-elevation myocardial infarction.

**Table 1** Randomized control trials and meta-analyses comparing primary percutaneous coronary intervention and fibrinolysis/thrombolysis in older patients with ST-elevation myocardial infarction

| Study | Outcome | Results | | |
|---|---|---|---|---|
| | | **PPCI (%) vs. thrombolysis (%)** | **RR, thrombolysis, vs. PPCI (95% CI)** | **P-value** |
| De Boer *et al.* RCT (2002) (e) | Primary endpoint: death, re-infarction, or stroke at 30 days | 9 vs. 29 | 4.3 (1.2–20.0) | 0.01 |
| n = 87 | Death at 30 days | 7 vs. 22 | 4.0 (0.9–24.6) | 0.04 |
| ≥75 years old | Death, re-infarction, or stroke at 1 year | 13 vs. 44 | 5.2 (1.7–18.1) | 0.001 |
| | Death at 1 year | 11 vs. 29 | 3.4 (1.0–13.5) | 0.03 |
| | | **PPCI (%) vs. conservative (%)** | **OR, PPCI, vs. conservative (95% CI)** | **P-value** |
| Zhang *et al.* RCT (2006) (f) | Primary endpoint: MACE (death, non-fatal MI, or revascularization) at 1 year | 21.3 vs. 45.2 | —a | 0.029 |
| n = 102 | In-hospital mortality | 2.0 vs. 15.4 | — | 0.04 |
| ≥75 years | MACE at 1 year | — | 0.34 (0.21–0.69) | 0.03 |
| | | **PPCI (%) vs. thrombolysis (%)** | | **P-value** |
| SENIOR-PAMI RCT (2005) (g) | Primary endpoint: death or disabling stroke at 30 days | 11.3 vs. 13.0 | | 0.57 |
| n = 483 | In-hospital major bleeding | 5.6 vs. 6.2 | | 0.79 |
| ≥70 years | Death, disabling stroke, or re-infarction at 30 days | 11.6 vs. 18.0 | | 0.05 |
| | Age 70- to 80-year subgroup: death, disabling stroke, or re-infarction at 30 days | 7.7 vs. 17.0 | | 0.009 |
| | Age >80-year subgroup: death, disabling stroke, or re-infarction at 30 days | 22.0 vs. 22.0 | | — |
| | Death at 30 days | 10.0 vs. 13.0 | | 0.48 |
| | Disabling stroke at 30 days | 0.8 vs. 2.2 | | 0.26 |
| | Re-infarction at 30 days | 1.6 vs. 5.4 | | 0.039 |
| | | **PPCI (%) vs. fibrinolysis (%)** | **OR, PPCI, vs. fibrinolysis (95% CI)** | **P-value** |
| TRIANA RCT (2011) (h) | Primary endpoint: death, re-infarction, or disabling stroke at 30 days | 18.9 vs. 25.4 | 0.69 (0.38–1.23) | 0.21 |
| n = 266 | Death at 30 days | 13.6 vs. 17.2 | 0.76 (0.39–1.49) | 0.43 |
| ≥75 years | Re-infarction at 30 days | 5.3 vs. 8.2 | 0.63 (0.24–1.67) | 0.34 |
| | Disabling stroke at 30 days | 0.8 vs. 3.0 | 0.16 (0.02–1.37) | 0.37 |
| | Major bleeding at 30 days | 3.8 vs. 4.5 | 0.84 (0.25–2.82) | 0.78 |
| | Recurrent ischaemia at 30 days | 0.8 vs. 9.7 | 0.07 (0.01–0.55) | 0.001 |
| | Death, re-infarction, or disabling stroke at 1 year | 27.3 vs. 32.1 | 0.79 (0.47–1.34) | 0.39 |
| | Death at 1 year | 21.2 vs. 23.1 | 0.90 (0.50–1.60) | 0.71 |
| | Re-infarction at 1 year | 8.3 vs. 10.4 | 0.78 (0.34–1.59) | 0.56 |
| | Disabling stroke at 1 year | 0.8 vs. 3.8 | 0.20 (0.02–1.71) | 0.37 |
| | Major bleeding at 1 year | 6.1 vs. 5.2 | 1.17 (0.41–3.33) | 0.77 |
| | Recurrent ischaemia at 1 year | 0.8 vs. 11.9 | 0.06 (0.01–0.43) | < 0.001 |

*Continued*

**Table I** Continued

| Study | Outcome | Results OR, PPCI, vs. fibrinolysis (95% CI) | P-value |
|---|---|---|---|
| Bueno *et al.* pooled analysis (2011) (i) | Risk of death, re-infarction, or disabling stroke | 0.64 (0.45–0.91) | 0.013 |
| *n* = 834 | Risk of death | 0.74 (0.49–1.13) | 0.16 |
| ≥70 years | | | |
| De Boer *et al.* meta-analysis (2010) (j) | All-cause mortality, re-infarction, or stroke in 70- to 80-year olds | 0.45 (0.34–0.59) | — |
| *n* = 6763, with 1837 ≥70 years | All-cause mortality in 70- to 80-year olds | 0.55 (0.39–0.76) | — |
| | Re-infarction in 70- to 80-year olds | 0.37 (0.23–0.62) | — |
| | Stroke in 70- to 80-year olds | 0.36 (0.20–0.68) | — |
| | All-cause mortality, re-infarction, or stroke in >80 year olds | 0.56 (0.36–0.86) | — |
| | All-cause mortality in >80 year olds | 0.62 (0.39–1.0) | — |
| | Re-infarction in >80 year olds | 0.53 (0.21–1.4) | — |
| | Stroke in >80 year olds | 0.72 (0.31–1.7) | — |

CI, confidence interval; MACE, major adverse cardiovascular events; OR, odds ratio; PPCI, primary percutaneous coronary intervention; RCT, randomized controlled trial; RR, relative risk; STEMI, ST-elevation myocardial infarction.
aA dash (—) indicates data are not available.

## Future directions on the management of ST-elevation myocardial infarction in older adults

Although there have been advances with improved stent technologies and new pharmacological agents, recommendations on the use of PPCI and fibrinolysis are based on studies enrolling small numbers of older patients and there is a lack of evidence and clinical guidance on how frailty and comorbidity should be considered. However, the superiority of PPCI over fibrinolysis appears to extend to older patients and existing literature suggests that fibrinolysis may be safe and effective if needed. But the largest study evaluating PPCI vs. thrombolysis was conducted >15 years ago.[33] Thus, there is a need for further large-scale RCTs comparing PPCI and fibrinolysis in older patients with frailty and comorbidities using contemporary care. However, such studies are likely to face challenges because of the difficulties enrolling 'very old' patients and ethical concerns, given the maintained apprehensions about bleeding risk in thrombolysis and the confidence in PPCI.

# Non-ST-elevation acute coronary syndrome in older adults

Generally, RCTs and meta-analyses of predominantly younger populations of patients with NSTEACS show that an invasive strategy results in reductions in composite endpoints (cardiovascular death or re-infarction) with no effect on mortality.[37] The greatest benefits of an invasive strategy, in terms of reduction in death or MI, have been demonstrated in high-risk patients, such as older patients or those with greater risk scores[38] even though, older patients are less likely to receive CAG.[4]

## Evidence on the management of non-ST-elevation acute coronary syndrome in older adults

### Observational studies
Observational studies may better reflect the heterogeneous older patient population and clinical practice with 'real-world' data in comparison to RCTs with restrictive entry criteria. Main findings in selected observational studies in older NSTEACS patients are summarized in Supplementary material online, *S2*.

### Randomized controlled trials
To date, only five RCTs specifically investigating an invasive strategy in older patients with NSTEACS have published results. Their main findings are summarized in *Table 2*. The After Eighty trial (*n* = 457, mean age 85 years, female 50.8%) did not find a mortality benefit for older patients with NSTEACS randomized to an invasive vs. a conservative strategy but a significantly lower incidence of the primary composite outcome (MI, need for urgent revascularization, stroke, and death) at an average of 18 months of follow-up, driven by lower rates of recurrent MI and urgent revascularization.[39] However, there were no frailty or HRQoL assessments and almost 90% of screened patients were excluded for unclear 'logistical' reasons—limiting the generalizability of findings to the real-world population. RCTs of patients with NSTEACS are summarized in *Figure 3*.

**Table 2** Randomized control trials comparing invasive and conservative approaches in older patients with non-ST-elevation acute coronary syndrome

| Study and population | Outcome | Results | | |
|---|---|---|---|---|
| | | Early invasive (%) vs. initially conservative (%) | HR, early invasive vs. initially conservative (95% CI) | *P*-value |
| Savonitto *et al.* Italian Elderly ACS (2012) (IV) *n* = 313 NSTEACS ≥75 years old | Primary endpoint: death, re-infarction, disabling stroke, repeat hospital stay for cardiovascular causes, and severe bleeding at 1 year | 27.9 vs. 34.6 | 0.80 (0.53–1.19) | 0.26 |
| | Primary endpoint in patients with elevated troponin levels | 22.1 vs. 40.0 | 0.43 (0.23–0.80) | 0.0375 |
| | Primary endpoint in patients with normal troponin levels | 37.7 vs. 26.7 | 1.67 (0.75–3.70) | —[a] |
| | Death at 1 year | 12.3 vs. 13.8 | 0.87 (0.49–1.56) | 0.65 |
| | Re-infarction at 1 year | 7.1 vs. 10.7 | 0.67 (0.33–1.36) | 0.27 |
| | Repeat hospital stay for cardiovascular causes or severe bleeding at 1 year | 11.7 vs. 13.8 | 0.81 (0.45–1.46) | 0.49 |
| | Recurrent ischaemia during hospitalization | 0.6 vs. 9.4 | — | 0.0004 |
| | | **Early invasive (%) vs. conservative (%)** | **HR, early invasive vs. conservative (95% CI)** | ***P*-value** |
| Tegn *et al.* After Eighty (2016) (V) *n* = 457 NSTEACS ≥80 years old | Primary endpoint: death, re-infarction, need for urgent revascularization, and stroke at mean follow-up of 18 months | 41 vs. 61 | 0.53 (0.41–0.69) | 0.0001 |
| | Death over follow-up | 25 vs. 27 | 0.89 (0.62–1.28) | 0.534 |
| | Re-infarction over follow-up | 17 vs. 30 | 0.52 (0.35–0.76) | 0.001 |
| | Need for urgent revascularization over follow-up | 2 vs. 11 | 0.19 (0.07–0.52) | 0.001 |
| | Stroke over follow-up | 3 vs. 6 | 0.60 (0.25–1.46) | 0.265 |
| | Major bleeding | 1.7 vs. 1.8 | — | — |
| | | **Routine invasive (%) vs. selective invasive (%)** | **IRR, routine invasive vs. selective invasive (95% CI)** | ***P*-value** |
| Sanchis *et al.* MOSCA (2016) (VI) *n* = 106 NSTEMI ≥70 years old with two comorbidities | Primary endpoint: death, re-infarction, or readmission for cardiac cause at 2.5 years | — | 0.95 (0.47–1.92) | 0.877 |
| | All-cause mortality | 42 vs. 48 | 0.69 (0.39–1.23) | 0.205 |
| | Re-infarction | — | 1.24 (0.52–2.96) | — |
| | Bleeding episodes | — | 0.45 (0.10–2.13) | 0.289 |
| | | | **HR, routine invasive vs. selective invasive (95% CI)** | ***P*-value** |
| | Primary endpoint: death, re-infarction, or readmission for cardiac cause at 2.5 years (first-event analysis) | — | 0.77 (0.48–1.24) | 0.285 |
| | Mortality at 3 months | — | 0.35 (0.12–0.99) | 0.048 |
| | Mortality at the end of follow-up | — | 0.69 (0.39–1.23) | 0.205 |
| | Mortality or ischaemic events at 3 months | — | 0.43 (0.19–0.98) | 0.046 |
| | Mortality or ischaemic events at the end of follow-up | — | 0.70 (0.42–1.19) | 0.194 |

*Continued*

**Table 2** *Continued*

| Study and population | Outcome | Results | | |
|---|---|---|---|---|
| | | **Invasive (%) vs. conservative (%)** | **HR, invasive vs. conservative (95% CI)** | **P-value** |
| Hirlekar *et al.* (2020) (VII) | Primary endpoint: all-cause mortality, re-infarction, stroke, urgent revascularization, or re-hospitalization for cardiac causes at 1 year | 34.3 vs. 37.7 | 0.90 (0.55–1.46) | 0.66 |
| *n* = 186 | | | | |
| NSTEACS | | | | |
| ≥80 years old | All-cause mortality | 11.0 vs. 15.2 | 0.70 (0.31–1.58) | 0.40 |
| | Re-infarction | 12.9 vs. 22.3 | 0.56 (0.27–1.18) | 0.13 |
| | Stroke | 3.7 vs. 2.3 | 1.35 (0.23–7.98) | 0.74 |
| | Urgent revascularization | 4.6 vs. 16.5 | 0.29 (0.10–0.85) | 0.02 |
| | Re-hospitalization for cardiac causes | 15.2 vs. 9.4 | 1.62 (0.67–3.90) | 0.28 |
| | MACCE within 1 month | 11.9 vs. 16.2 | 0.72 (0.33–1.56) | 0.40 |
| | Minor bleeding within 1 month | 4.4 vs. 2.2 | 1.81 (0.34–9.61) | 0.49 |
| | | **Routine invasive (%) vs. selective invasive (%)** | **HR, routine invasive vs. selective invasive (95% CI)** | **P-value** |
| De Belder *et al.* RINCAL (2020) (VIII) | Primary endpoint: all-cause mortality and re-infarction at 1 year | 18.5 vs. 22.2 | 0.79 (0.45–1.35) | 0.39 |
| *n* = 251 | All-cause mortality at 1 year | 10.5 vs. 11.1 | 0.94 (0.44–1.99) | 0.86 |
| NSTEMI | Non-fatal re-infarction at 1 year | 9.7 vs. 14.3 | 0.64 (0.31–1.32) | 0.23 |
| ≥80 years old | Unplanned revascularization at 1 year | 1.6 vs. 6.4 | — | 0.10 |
| | Major bleeding | 5.6 vs. 2.4 | — | 0.21 |
| | Angina symptoms[b] at 3 months | 8.8 vs. 19.0 | | < 0.001 |
| | Angina symptoms[b] at 1 year | 15.0 vs. 16.8 | | 0.25 |

ACS, acute coronary syndrome; CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; MACCE, major adverse cardiac and cerebrovascular events; NSTEACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction.
[a]A dash (—) indicates data are not available.
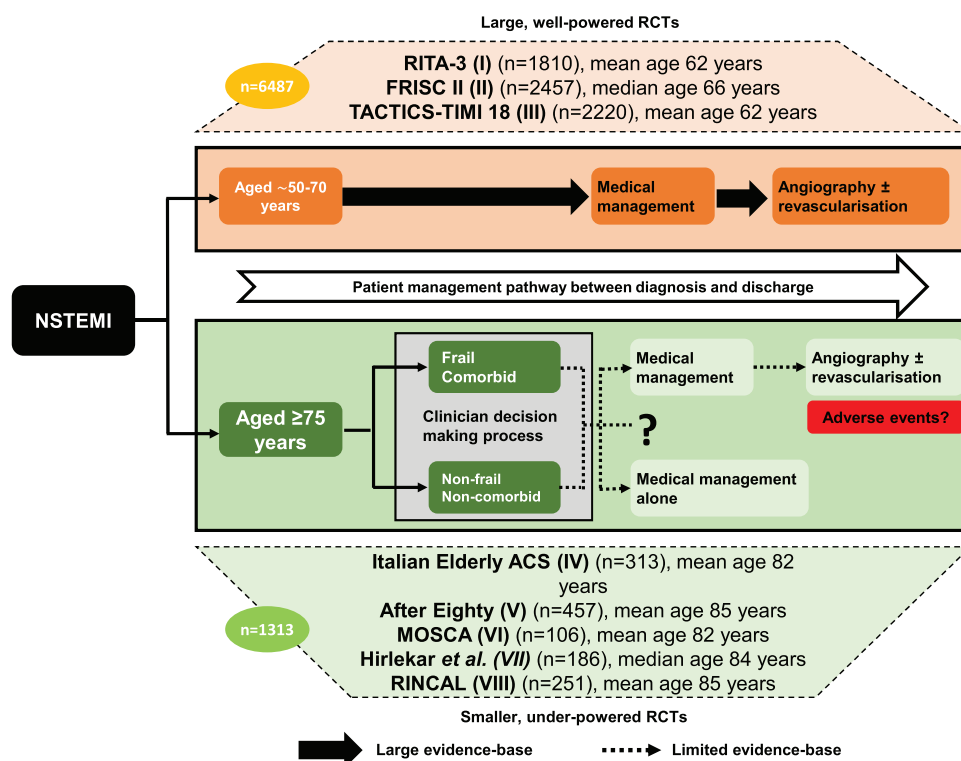[b]The rates of Canadian Cardiovascular Society (CCS) angina 'Class 1'.

**Figure 3** Evidence on the management of older patients with non-ST-elevation acute coronary syndrome.

### Meta-analyses

Ma et al.[40] analysed a large cohort of older patients with NSTEACS and found that an early invasive approach conferred a lower risk of death and secondary endpoints (including MACE, MI, and a composite of death and MI) in 5-year follow-up, although the result in favour for invasive approach regards to mortality was driven by the observational studies included in the cohort. Garg et al.[41] reviewed patients with NSTEACS aged ≥75 years with a focus on RCTs and found a lower risk of subsequent revascularization amongst those managed by a routine invasive approach. Consistent with previous studies, there was no reduction in all-cause or cardiovascular mortality. This highlights the inconsistencies between the RCTs and observational studies and the non-uniform definition of endpoints. The main findings of existing meta-analyses are summarized in Table 3.

### Current clinical guidelines on the management of non-ST-elevation acute coronary syndrome in older adults

National Institute for Health and Care Excellence, ESC, and American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend risk stratification of patients with NSTEACS of all ages, with those at intermediate or higher risk of adverse outcomes receiving a routine invasive strategy of CAG and subsequent revascularization if indicated. Older patients are seen as an important subgroup but the only 'key recommendation' is to apply the same invasive approach as for the younger patient.[35,42,43] Guidelines suggest that management decisions regarding older NSTEACS patients should be patient-centred and consideration of the risk of future cardiovascular events, comorbidities, benefits and risks of invasive revascularization (including both ischaemic and bleeding risks), HRQoL, frailty, cognitive status, functional impairment, life expectancy, and patient preferences. Given the paucity of evidence, there is a lack of consensus and specific clinical guidance on how these factors should be considered.
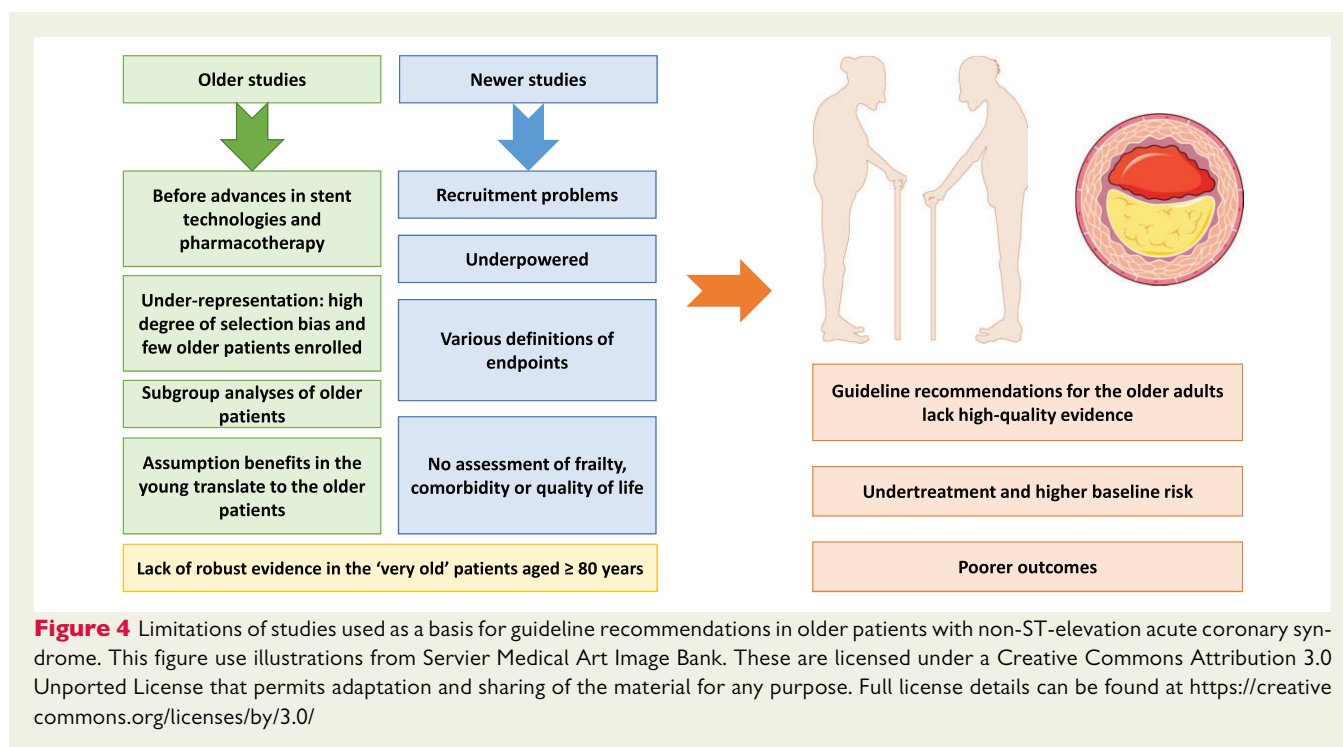
### Future directions on the management of non-ST-elevation acute coronary syndrome in older adults

The exact benefits of an invasive strategy in the management of NSTEACS in older adults are not clearly established and results from RCTs, meta-analyses, and observational studies are inconsistent. The age disparity between trial and registry populations widens as age increases.[5] The problems with RCTs of older NSTEACS patients consist of lack of power, slow enrolment, and excluding those with comorbidities, frailty, or very high procedural risk. Therefore, enrolled patients tend to have lower rates of traditional risk factors, better renal function, fewer cardiovascular comorbidities, and preferential haemodynamic measurements than the 'real world' population.[5] Furthermore, it remains challenging to compare studies, given that varying composite endpoints and invasive strategies are

**Table 3**  **Meta-analyses comparing invasive and conservative approaches in older patients with non-ST-elevation acute coronary syndrome**

| Meta-analysis | Outcome | Results | | |
|---|---|---|---|---|
| | | **OR, routine invasive vs. initial medical (95% CI)** | ***P*-value** | ***I*²(%)** |
| Gnanenthiran *et al.* (2017) (IX) | In-hospital mortality | 0.65 (0.53–0.79) | <0.0001 | 38 |
| *n* = 20 540 | Mortality | 0.67 (0.61–0.74) | <0.00001 | 0 |
| NSTEACS | Mortality, with analysis limited to RCTs | 0.84 (0.66–1.06) | 0.15 | 0 |
| ≥75 years old | | | | |
| Four RCTs and 3 observational stud- | In-hospital re-infarction | 0.43 (0.30–0.61) | <0.00001 | 0 |
| ies, with follow-up from 6 months | Re-infarction | 0.56 (0.45–0.70) | <0.00001 | 18 |
| to 5 years | Re-infarction, with analysis limited to RCTs | 0.51 (0.40–0.66) | <0.00001 | 0 |
| | Need for revascularization | 0.27 (0.13–0.56) | 0.0005 | 0 |
| | Stroke | 0.53 (0.30–0.95) | 0.03 | 0 |
| | In-hospital major bleeding | 2.37 (1.53–3.68) | 0.0001 | 30 |
| | Major bleeding at follow-up, with analysis limited to RCTs | 2.19 (1.12–4.28) | 0.02 | 0 |
| | | **RR, early invasive vs. initial conservative (95% CI)** | ***P*-value** | ***I*²(%)** |
| Ma *et al.* (2018) (X) | Primary endpoint: mortality | 0.65 (0.59–0.73) | <0.001 | 23.7 |
| *n* = 832 007 | Mortality, with analysis limited to RCTs | 0.82 (0.64–1.05) | 0.119 | 0 |
| NSTEACS | In-hospital mortality | 0.70 (0.53–0.92) | 0.011 | 49.5 |
| ≥75 years old | Re-infarction | 0.58 (0.46–0.72) | <0.001 | 0 |
| Four RCTs and 9 observational stud- | Mortality or re-infarction | 0.63 (0.50–0.79) | <0.001 | 21.8 |
| ies, with follow-up from 6 months | Stroke | 0.54 (0.30–0.97) | 0.04 | 0 |
| to 5 years | MACE | 0.60 (0.49–0.74) | <0.001 | 38.3 |
| | Re-hospitalization | 0.95 (0.75–1.21) | 0.672 | 0 |
| | Any in-hospital bleeding | 2.51 (1.53–4.11) | <0.001 | 0 |
| | In-hospital major bleeding | 1.78 (0.31–10.13) | 0.514 | 37.1 |
| | | **OR, routine invasive vs. selective invasive (95% CI)** | ***P*-value** | ***I*²(%)** |
| Garg *et al.* (2018) (XI) | All-cause death | 0.87 (0.63–1.20) | 0.38 | 0 |
| *n* = 1887 | Cardiovascular death | 0.84 (0.61–1.15) | 0.27 | 0 |
| NSTEACS | Re-infarction | 0.51 (0.40–0.66) | <0.001 | 0 |
| ≥75 years old | Death or re-infarction | 0.65 (0.51–0.83) | <0.001 | 0 |
| Six RCTs, with mean | Need for revascularization | 0.31 (0.11–0.91) | 0.03 | 51 |
| follow-up of 3 years | Major bleeding | 1.96 (0.97–3.97) | 0.06 | 7 |
| | | **RR, early invasive vs. initial conservative (95% CI)** | ***P*-value** | ***I*²(%)** |
| Reano *et al.* (2020) (XII) | All-cause mortality | 0.69 (0.39–1.23) | 0.21 | 91 |
| *n* = 3768 | Cardiovascular mortality | 0.86 (0.67–1.10) | 0.23 | 0 |
| NSTEACS | Re-infarction | 0.63 (0.39–1.04) | 0.07 | 60 |
| ≥65 years old | Stroke | 0.52 (0.26–1.03) | 0.06 | 0 |
| Six RCTs, with follow-up from | Need for revascularization | 0.29 (0.14–0.59) | 0.002 | 3 |
| 3 months to 15 years | Recurrent angina at 1 year | 0.81 (0.45–1.46) | 0.49 | — |

CI, confidence interval; MACE, major adverse cardiovascular events; NSTEACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio.

**Figure 4** Limitations of studies used as a basis for guideline recommendations in older patients with non-ST-elevation acute coronary syndrome. This figure use illustrations from Servier Medical Art Image Bank. These are licensed under a Creative Commons Attribution 3.0 Unported License that permits adaptation and sharing of the material for any purpose. Full license details can be found at https://creative commons.org/licenses/by/3.0/

investigated. Resulting in no direct impact on patient care and current management recommendations reflecting this lack of evidence (summarized in *Figure 4*). Further well-powered RCTs are required, as well as the inclusion and evaluation of comorbid and frail patients, in order to improve the generalizability of findings to the real-world population. The benefit-risk profile of invasive strategies in the older patient cohort is currently investigated in the British Heart Foundation older patients with non-ST SEgmeNt elevatIOn myocaRdial infarction Randomized Interventional TreAtment (BHF SENIOR-RITA) trial.[44] Patients ≥75 years old with NSTEMI are randomized to a routine invasive approach or a conservative strategy, with broad eligibility criteria to include a representative population, including patients with frailty and comorbidities.

# Contemporary treatment strategies in older patients

Advances in interventional techniques and technologies enable an optimal management of more complex coronary anatomy.[45] In addition to ischaemic events, older patients are at increased risk of complications due to both the medical and invasive ACS treatment, such as bleeding, which increases the mortality rates.[46] Older adults are also at higher risk of contrast-induced nephropathy following PCI. Therefore, appropriate measures should be implemented to prevent contrast-induced nephropathy.[47–49]
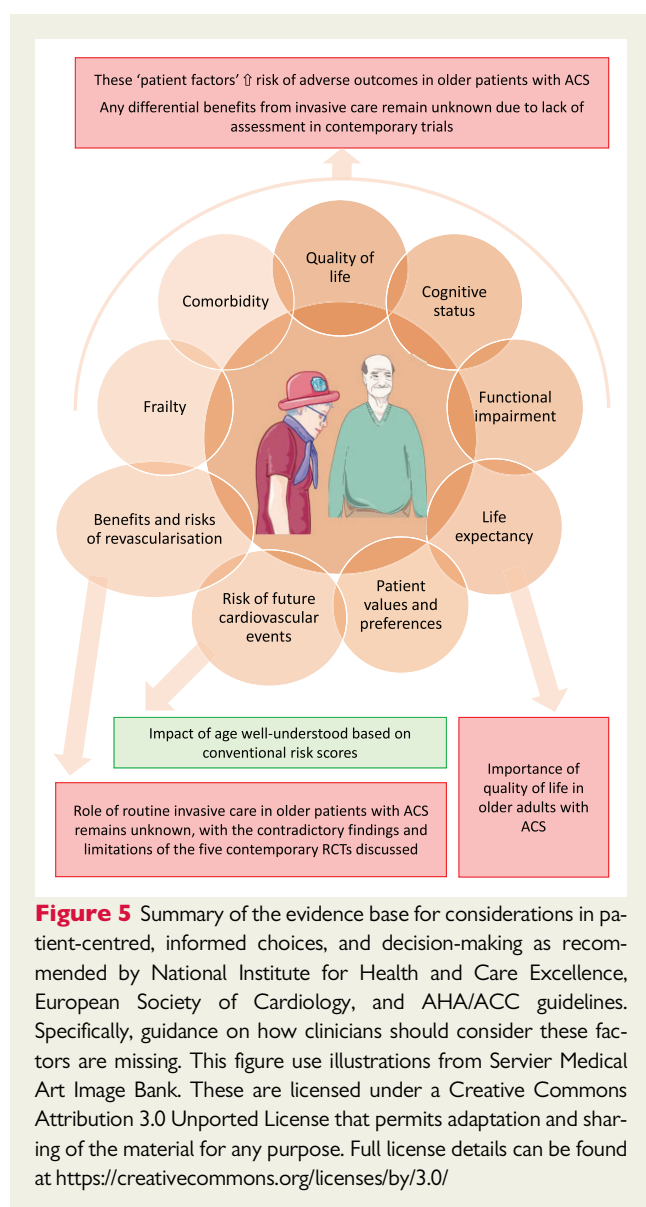
In contemporary practice, the bleeding risk, however, is reduced by the widespread use of radial access.[50] Bleeding risk is further reduced with the use of latest generation drug-eluting stents and

shorter duration of DAPT.[51–53] A strategy of ticagrelor monotherapy following 3 months of DAPT therapy significantly reduced clinically relevant bleeding compared with ticagrelor plus aspirin without an increase in ischaemic events, irrespective of age.[54]

Current guidelines recommend the same secondary prevention treatment in older adults as in younger patients regarding management of hypercholesterolaemia, hypertension, and type 2 diabetes mellitus. Although guidelines mention the importance of some considerations for older and frail patients these are only class C recommendations at present.[55] Statin treatment has been showed to decrease the risk of adverse events in older patients with ACS.[56] A recently published meta-analysis showed that blood pressure reduction should be considered as an important treatment option, regardless of age.[57] The ACCORD study showed that a slower reduction of glycaemia is favourable in older patients.[58] Similarly, for frail and older patients, a less stringent Glycated Haemoglobin (HbA1c) target should be considered.[59]

## Why are older patients less likely to be studied in clinical trials?

Although the mean age of participants in ACS trials has increased in recent years, older patients remain under-represented.[4,60,61] Reasons behind this are, in our opinion, likely multifactorial and linked to potential preconceptions in the management of older patients with ACS. It can be speculated that various unique characteristics that are more common in older patients might act as barriers to trial recruitment or participation. For example hearing or visual impairments and issues with transport if study protocols involve numerous follow-up visits. Cognitive impairment

**Figure 5** Summary of the evidence base for considerations in patient-centred, informed choices, and decision-making as recommended by National Institute for Health and Care Excellence, European Society of Cardiology, and AHA/ACC guidelines. Specifically, guidance on how clinicians should consider these factors are missing. This figure use illustrations from Servier Medical Art Image Bank. These are licensed under a Creative Commons Attribution 3.0 Unported License that permits adaptation and sharing of the material for any purpose. Full license details can be found at https://creativecommons.org/licenses/by/3.0/

is likely perceived as an absolute barrier to enrolment too and fewer older patients are probably approached for trial enrolment because of indirect ageism or bias especially with outcomes focused on mortality. Notwithstanding the paucity of specific evidence, its dissemination is often limited both among clinicians and among patients. Similarly, penetration of knowledge about CV risk and practice guidelines is suboptimal, being one of the causal factors for low adherence to treatment in older adults.

## What is missing from the current data?

In our opinion, the heterogeneity of the older adult population causes that a 'one-size-fits-all' approach is inappropriate and management decisions regarding invasive care should be individualized. However, robust evidence is needed to inform individual decision-making. Gaps in the current evidence regarding guideline-recommended factors to

consider when discussing interventional management strategies in older patients with NSTEACS are summarized in *Figure 5*. To better reflect the heterogeneous characteristics of older patients with ACS it is our belief that older patients need to be recruited into RCTs. Thus future trials need wider inclusion criteria designed to suit inclusion of older patients, which also have been stated by previous papers in this topic.[60,61]

# Conclusions/learning points

Recent pharmacological studies provide evidence that older patients should be offered the same treatment as younger patients specifically in the management of blood pressure, diabetes, and cholesterol. Several recent studies have shown that short duration of DAPT is beneficial in reducing bleeding without affecting ischaemic outcomes in high-risk ACS patients. However, there is a paucity of robust evidence regarding the benefits and risks of contemporary interventional management strategies particularly among frail, comorbid older patients with ACS. There is therefore need for well-powered, multicentre RCTs that better represent the real-world population dedicated to this patient group.

# Lead author biography

Dr Vijay Kunadian is an academic consultant interventional cardiologist based at Newcastle University and Freeman Hospital, Newcastle upon Tyne, UK. She is Chief Investigator in many multicentre clinical trials and published >150 peer-reviewed publications. She is a member of the ESC Regulatory Affairs Committee; Member of the ESC Education Committee: Director of Webinar series, Task Force Lead-Live events; She was board of the EAPCI, co-chair of the Scientific Committee of the EAPCI; Member EAPCI Women's Committee, Young Committee, Database & Registries Committee; Steering Committee member Research and Development Committee of the BCIS. She has mentored >30 postgraduates.

# Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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